ELSEVIER

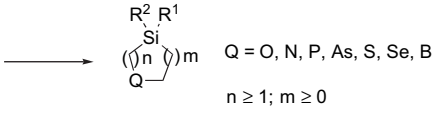
Tetrahedron

Tetrahedron Vol. 62, No. 34, 2006

# Contents

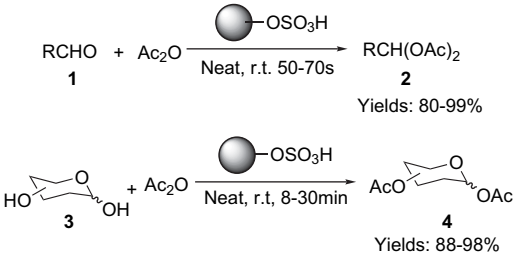
## REPORT





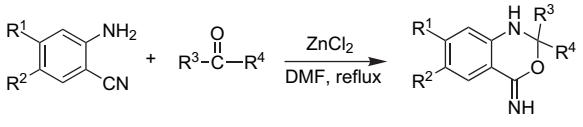

## ARTICLES

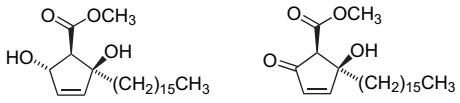




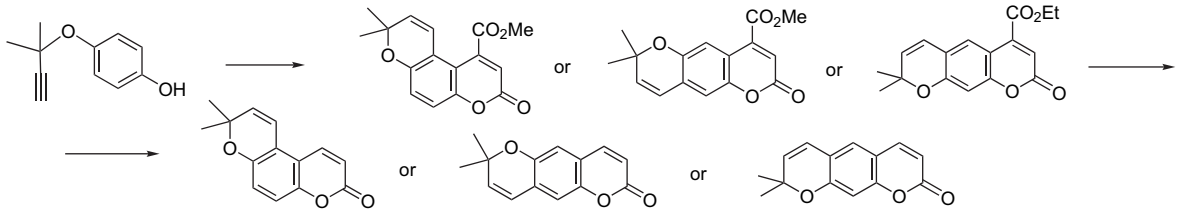

A general, simple, efficient, cost effective, and green procedure for acetylation of aldehydes and sugars has been developed by treatment with acetic anhydride at room temperature.





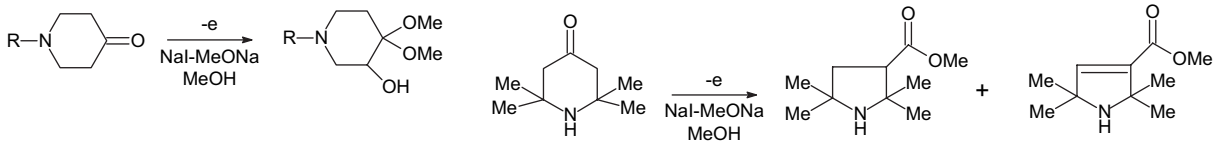




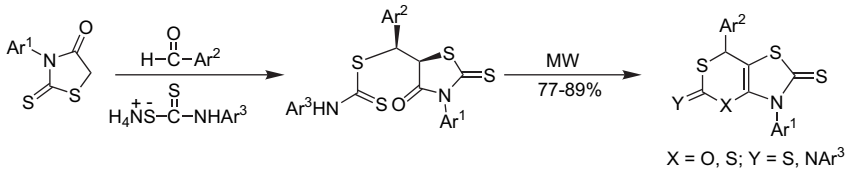



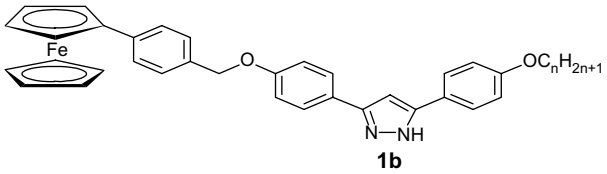

Angular and linear pyranocoumarins are easily prepared from 4-[(1,1-dimethyl-2-propynyl)oxy]phenol.



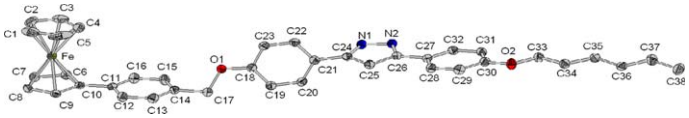




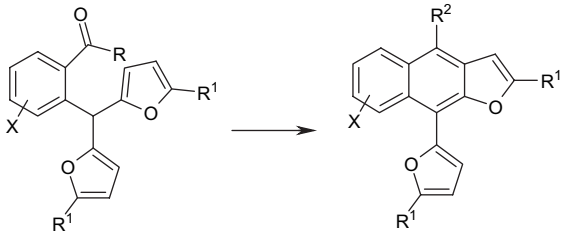





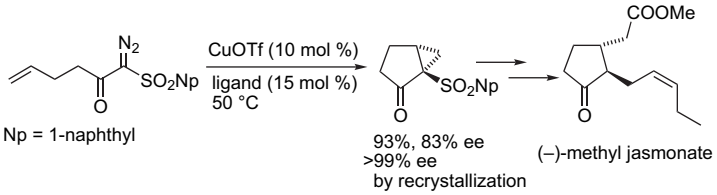

1b



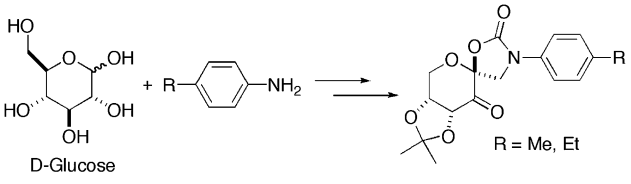


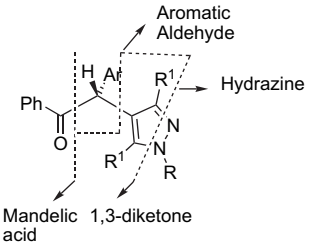




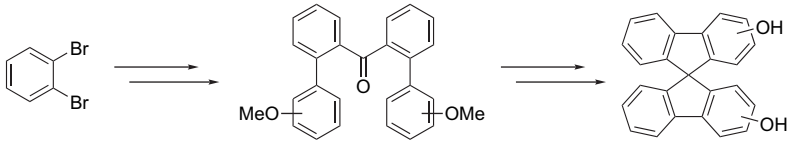





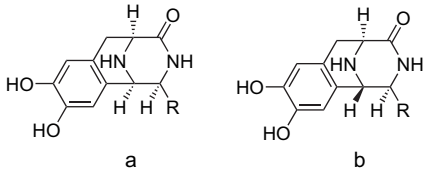





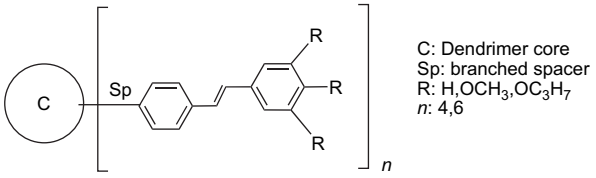


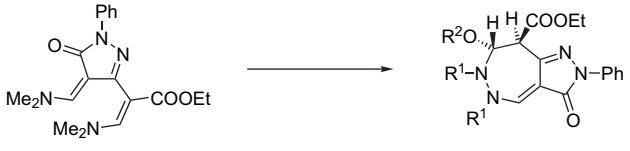





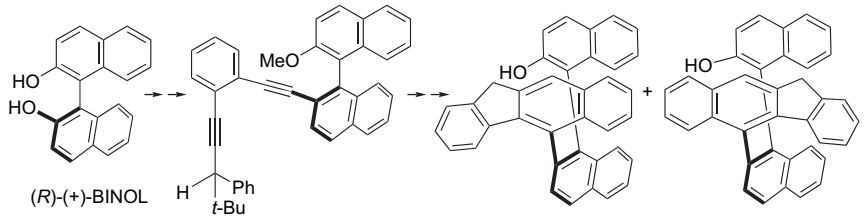


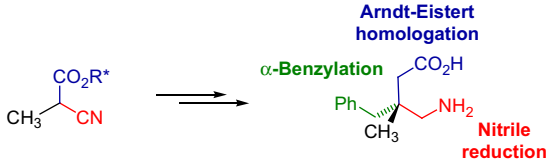



Substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates were obtained from ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate, via substitution of both dimethylamino groups with 1,2-dialkylhydrazines.

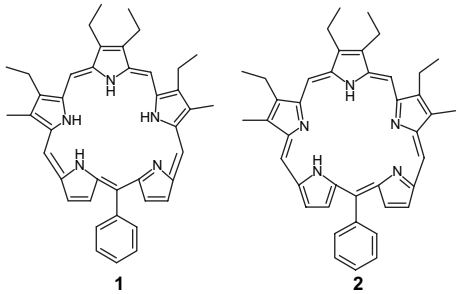


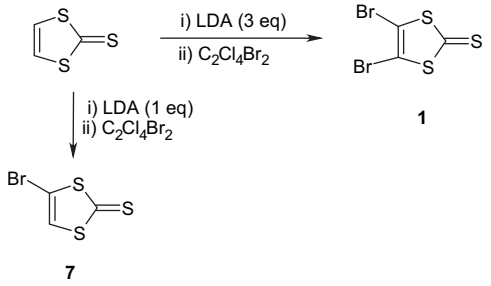




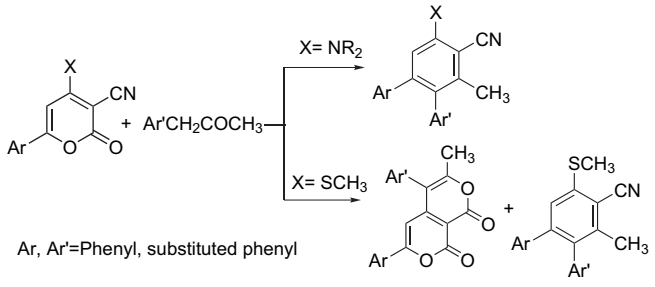





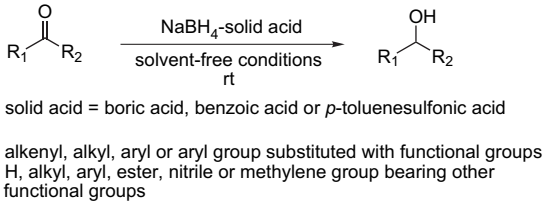





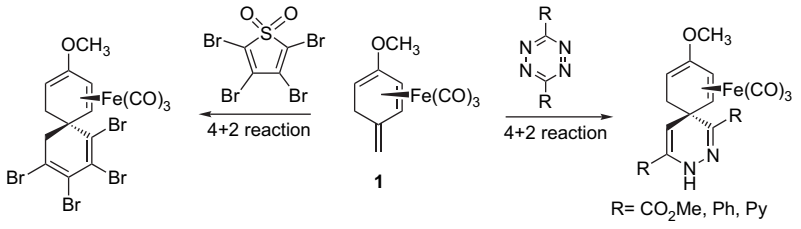


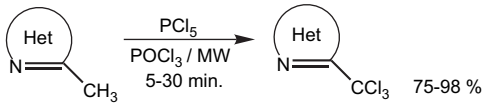





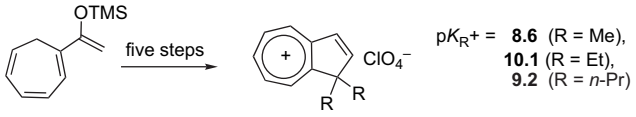





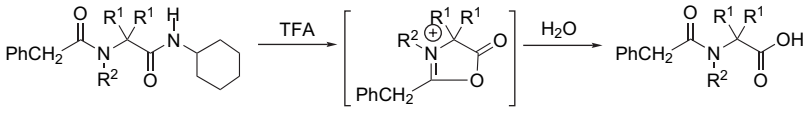







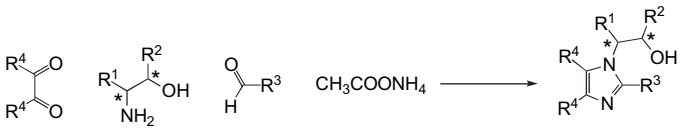



$R^1$ = Me, Bn, $R^2$ = 4-X-$C_6H_4CH_2$, X = MeO, Me, H, F, Cl, $CF_3O$, $CF_3$, $NO_2$
$R^1$ = Me, $R^2$ = 4-X-$C_6H_4$, X = MeO, H, Cl, CN, $NO_2$

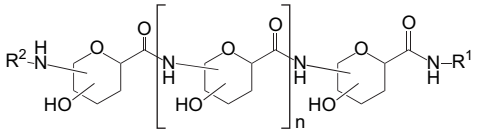
Kinetic data were collected and submitted to Hammett relationships, the results being interpreted in terms of structure/reactivity, thus allowing rationalisation of the contribution of the substituent at the nitrogen atom to the lability of the C-terminal amide bond.






***One-Step Four-Component Cyclocondensation***

R = H, alkyl, aryl
13 examples, 30–82% yields



*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect



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# Heterocyclic compounds with a silicon atom and another non-adjacent different heteroatom

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**Contents**



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## 1. Introduction

Interest in organosilicon compounds has increased considerably in the last decade. This is due to the fact that incorporation of a silicon atom in a carbon framework of molecules modifies their properties, e.g., modification of the electric properties of conducting polymers or other physical properties have been reported.[1] Similarly, modifications of physiological and biological activities are known.[2]

Numerous heterocyclic compounds possessing one or more silicon atoms have been reported.[3] The preparation of compounds in which the silicon atom and the other different heteroatom are in the 1,2-positions appears very common. Examples of compounds in which these heteroatoms are separated by one (or more) carbon atom are, however, less well known. The aim of this review is to examine such compounds. Heterocycles incorporating a metal atom in the cycle will not be discussed. We will examine, successively, the different ring sizes.

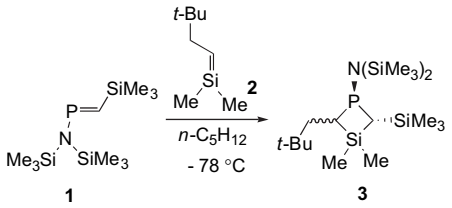
## 2. Preparation of four-membered heterocyclic compounds

For this ring size, examination of the literature shows that compounds with silicon and phosphorus, nitrogen, sulfur or oxygen atoms in the 1,3-positions are known. In Scheme 1, the IUPAC names and structures of these uncommon heterocycles have been summarized.

Two main approaches, cycloadditions and ring closures, to this ring size have been developed. In fact, very few preparations have been reported.

### 2.1. Formation by cycloaddition

The main approaches to these compounds imply [2+2] or two [2+1] cycloadditions. [2+2] Cycloadditions were reported for the formation of phosphasiletanes. Neilson and co-workers studied the reactivity of silene **2** and found that this compound can react with methylenephosphine **1** to give an 8:1 mixture of the two isomers **3**.[4] The stereochemistry of the main isomer was postulated to be the one in which the $Me_3Si$ and neopentyl substituents on the ring are both trans to the $(Me_3Si)_2N$ group. These compounds were stable enough to be distilled (Scheme 2).

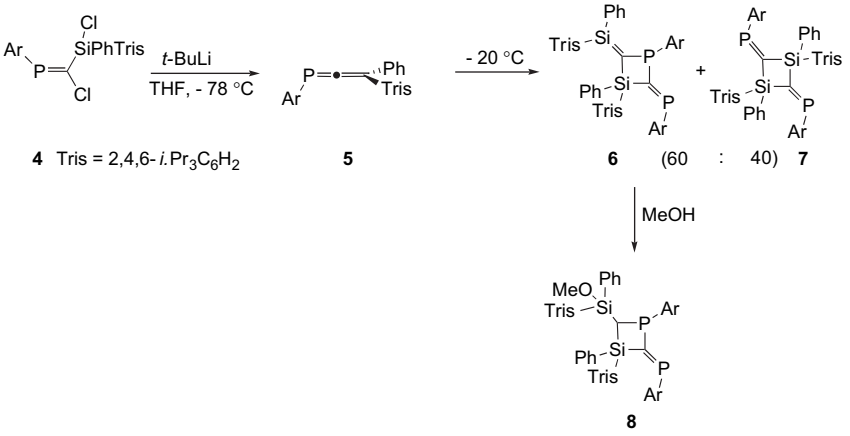



**Scheme 2**.

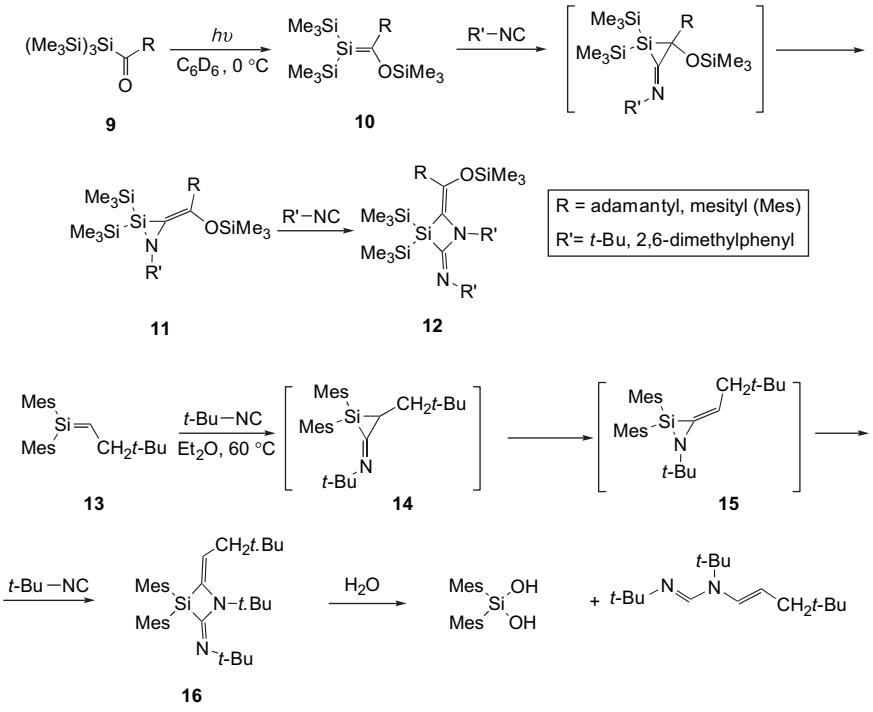
Dimerization at −30 °C of the very reactive 3-phospha-1-silaallene **5** (Ar=2,4,6-tri-*tert*-butylphenyl) formed at −78 °C by dedichlorination of (chlorosilyl)chlorophosphalkene **4**, led to a 60:40 mixture of two products **6** and **7**.[5] The major compound **6**, however, appeared to have a low stability, and its characterization was performed after transformation into compound **8** by the addition of methanol (Scheme 3). A large steric hindrance of the groups fixed at the phosphorus and silicon atoms seems to be essential for the formation of stable silaallenes **5**.[6]

Addition of isocyanides to stable silenes **10**, formed by photochemically induced isomerization from acylsilanes **9**, led to the formation of 1,3-azasiletidines by two successive [2+1] cycloadditions[7] (Scheme 4). The postulated siliaaziridines **11** were detected when the R substituent was an adamantyl group. The presence of bulky substituents seems, here also, to be crucial for the formation of silenes **10** and for the isolation of azasiletidines **12**. Similar results were reported with silene **13**.[8] Reaction of this stable compound with *tert*-butyl isocyanide in ether at 60 °C led to 1,3-azasiletidine **16**. This product was formed by the addition of


**Scheme 1**.




**Scheme 3**.




**Scheme 4**.

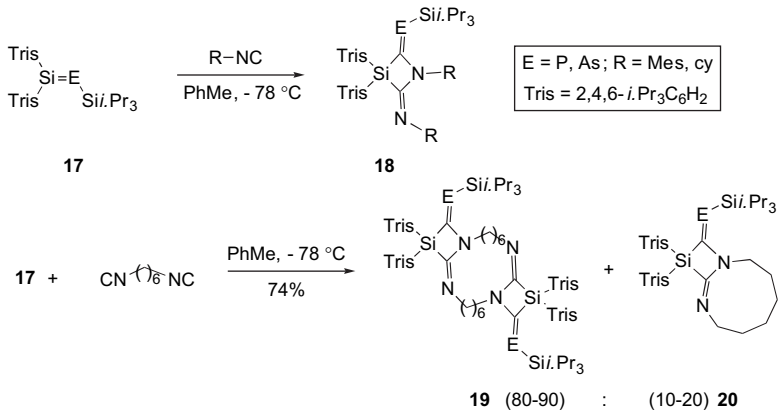
the isocyanide to silene **13**, to give silirane **14**. This latter compound rearranged into the more stable azasiliridine **15**, and addition of a second molecule of isocyanide led quantitatively to the azasiletidine **16**. This compound appeared to be water sensitive and gave rise to cleavage products.

Driess and co-workers studied the reactivity of silylidenephosphanes and arsanes **17**, and found that these compounds reacted with 2 equiv of isocyanide to lead to azasiletidines **18**,[9] as in the previous examples, by two successive [2+1] cycloadditions (Scheme 5). When the reaction was carried out with a diisocyanide, the tricyclic compounds **19** were the major products[9b] and the bicyclic derivatives **20** were the minor components.

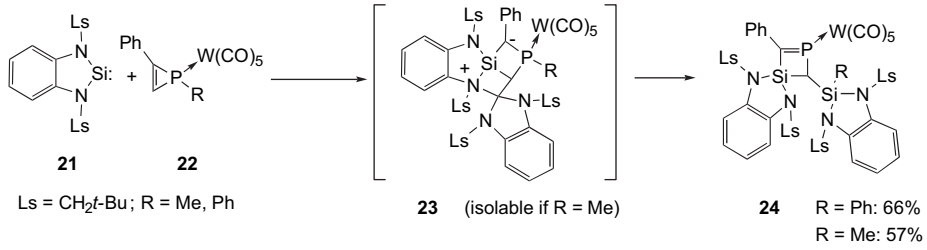
A recent report showed that stabilized phosphasiletanes can be obtained by the reaction of silylene **21** with 1-*H*-phosphirenes **22**.[10] When the substituent on the phosphorus atom was a phenyl group, the phosphasiletane was unstable and phosphasiletene **24** was isolated (Scheme 6). If, however, the phenyl moiety was replaced by a methyl group, to decrease the migration rate of the substituent from the phosphorus to the silicon atom, a phosphasiletane intermediate **23** (R=Me) was isolated, isomerization occurring upon heating at 75 °C.

## 2.2. Formation by cyclization

Voronkov's group showed that bis(chloromethyl)dimethylsilane **25** reacted with potassium hydrosulfide to give thiasiletane **26** in 55% yield (Scheme 7).[11] This cyclization was not observed with the more basic sodium salt. Ab initio and density functional theory calculations indicated that the cyclobutane ring of compound **26** is not planar.[12] These

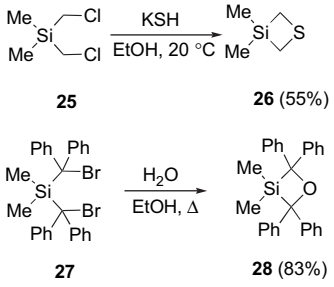



**Scheme 5**.




**Scheme 6**.

calculations showed that no electronic interactions exist between the silicon and sulfur atoms. These conclusions are in agreement with those deduced from IR or electron diffraction spectra and X-ray structure.[13]

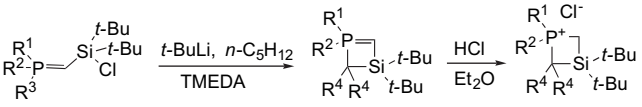



**Scheme 7**.

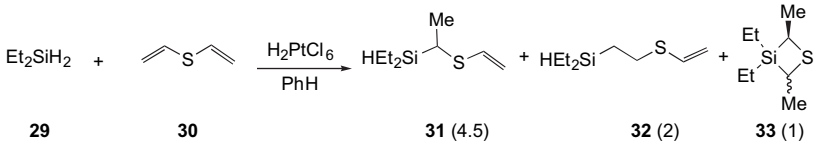
The first oxasiletane obtained using this methodology was formed by the reaction of bis(bromodiphenylmethyl)dimethylsilane **27** with water in ethanol at reflux (Scheme 7).[14] The structure of compound **28** was subsequently confirmed by X-ray diffraction. Dibromosilapropane **27** reacted similarly with $H_2S$, to lead to the corresponding thiasiletane (16% yield).[15]

The preparation of thiasiletanes is also possible by intramolecular hydrosilylation of unsaturated sulfides. Voronkov and co-workers showed that the reaction of diethylsilane **29** with divinyl sulfide **30** in the presence of $H_2PtCl_6$ at 100 °C for 12 h led to thiasiletane **33** in low yield (1:1 mixture of the two diastereomers). The major reaction products **31** and **32** resulted from a monohydrosilylation (Scheme 8).[16] Heating of the unsaturated hydrogenosilane **31** in the presence of the catalyst, under the same reaction conditions, gave rise to the exclusive formation of thiasiletane **33**. Improved results for the cyclization of silane **31** were reported using the Wilkinson catalyst (73% yield).[17]

An original preparation of phosphasiletenes **35a**,**b** (Scheme 9) was reported involving the reaction of silylmethylenephosphoranes **34a**,**b** with *tert*-butyllithium. This lithium reagent abstracted one of the acidic hydrogens of the isopropyl or methyl substituents fixed on the phosphorus atom, and intramolecular substitution of the chlorine atom on the silicon took place. The structure of the cyclic product **35a** was secured by X-ray diffraction. These phosphasiletenes easily




**Scheme 9**.

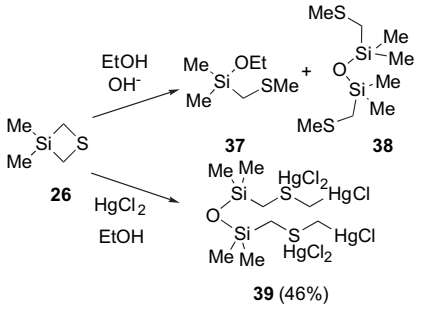



**Scheme 8**.

added HCl to give the corresponding 1,3-phosphasiletan-1-iums **36a**,**b**.[18]

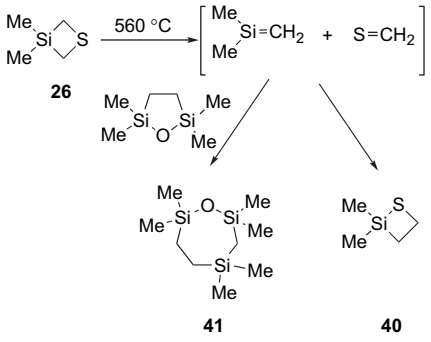
### 2.3. Reactivity and applications

The reactivity of thiasiletanes has been briefly examined and it was found that the cyclobutanic C–Si bonds in thiasiletane **26** were easily cleaved (exothermic reactions) by reaction with potassium hydroxide or mercuric chloride in ethanol, to give **37** and **38**, or **39**, respectively (Scheme 10).[11]




**Scheme 10**.

Gusel'nikov and co-workers have studied the thermal stability of this family of compounds. At temperatures between 500 and 700 °C, the compounds underwent [2+2] cycloreversions. Pyrolysis of thiasiletane **26** led to the intermediate formation of dimethylsilene, which reacted with the in situ-formed thioformaldehyde to yield 1,2-thiasiletane **40**. Co-pyrolysis in the presence of 2,2,5,5-tetramethyl-1-oxa-2,5-disilacyclopentane gave the insertion product **41** (Scheme 11).[19]




**Scheme 11**.

## 3. Preparation of five-membered heterocyclic compounds

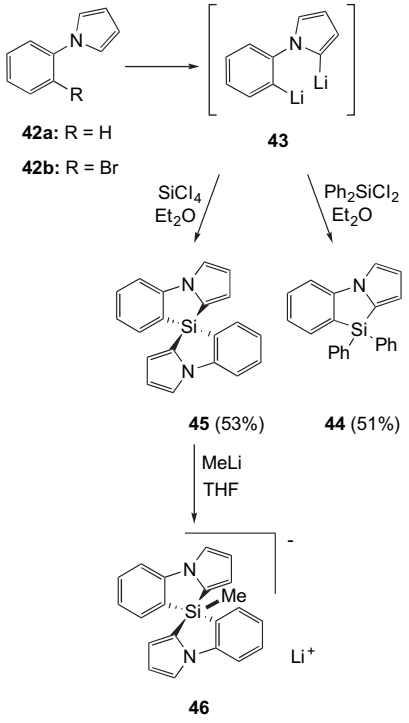
Compounds with silicon and oxygen, sulfur, nitrogen, phosphorus, selenium or boron atoms in the 1,3 positions have been reported. In Scheme 12, the IUPAC names and structures of these heterocycles have been summarized.

The different methods of preparing these heterocycles are listed by the nature of the bond formed in the cyclization step. The more studied methods imply the reaction of 1,3-dianions with dihalosilanes and these are included in the ring closures by silicon–carbon bond formation. Ring closures by the formation of heteroatom–carbon and carbon–carbon bonds have also been examined.

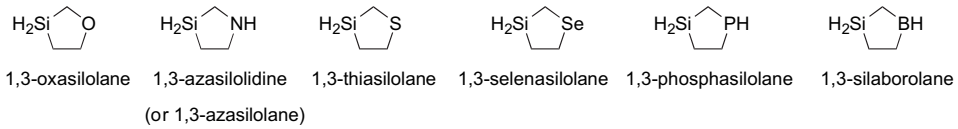
### 3.1. Preparation by formation of silicon–carbon bonds

Two strategies have been explored to obtain these five-membered heterocyclic compounds in such conditions. The first method implies the reaction of 1,1-dichlorosilanes with 1,4-dimetallic species and the second uses the intramolecular cyclization of difunctionalized linear compounds.

**3.1.1. Preparation by reaction of dihalosilanes with dianionic species.** Cheeseman and Greenberg showed that the reaction of 2,2′-dilithio-1-phenylpyrrole **43** with diphenyldichlorosilane led to the corresponding heterocyclic compound **44** in good yield (Scheme 13).[20] The dilithiated compound **43** was generated from 1-phenylpyrrole **42a** (2 equiv BuLi, TMEDA) or from 1-(2-bromophenyl)-1-*H*-pyrrole **42b** (2 equiv BuLi). By reaction with $SiCl_4$, the lithiated compound **43** led to the spiranic product **45**. After



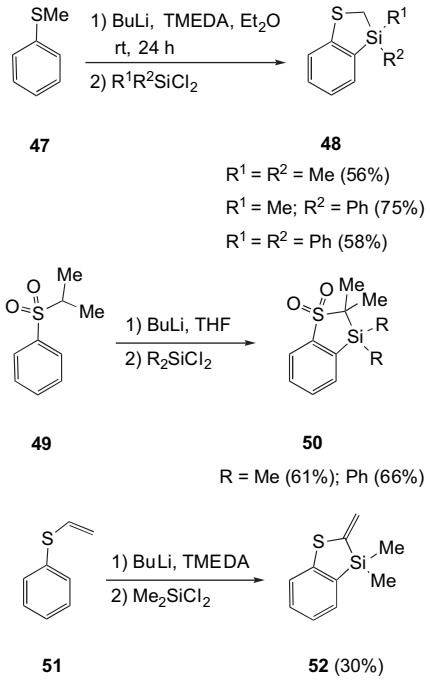

**Scheme 13**.




**Scheme 12**.

reaction with methyllithium, this latter product led to the formation of the pentacoordinate silicate **46**. Exchange of lithium by a tetrabutylammonium cation yielded a more stable compound, which was fully characterized. Dynamic equilibria of the pseudorotamers of such a silicate have been observed.[21]

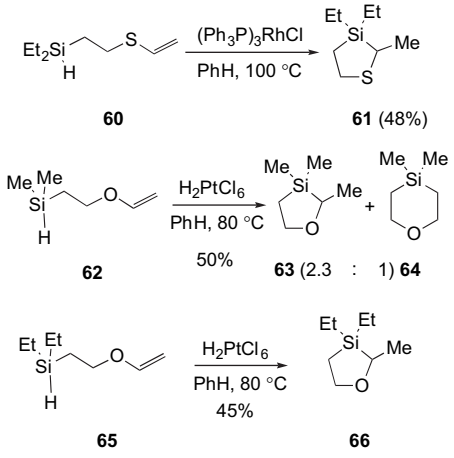
Reaction of methylphenylsulfane **47** with 2 equiv of *n*-BuLi in ether led to a 1,4-dianion. The reaction of this latter dianion with dichlorosilanes gave the corresponding thiasilolanes **48** in good yields (Scheme 14),[22] and reaction with tetrachlorosilane led to a spiro compound. A similar dianion formation was found starting from sulfone **49**, and BuLi in THF,[23] and dioxothiasilolanes **50** were obtained in good yields. The same group showed that thiasilolane **52** could be formed from vinylthiobenzene **51** using a similar strategy.[24]



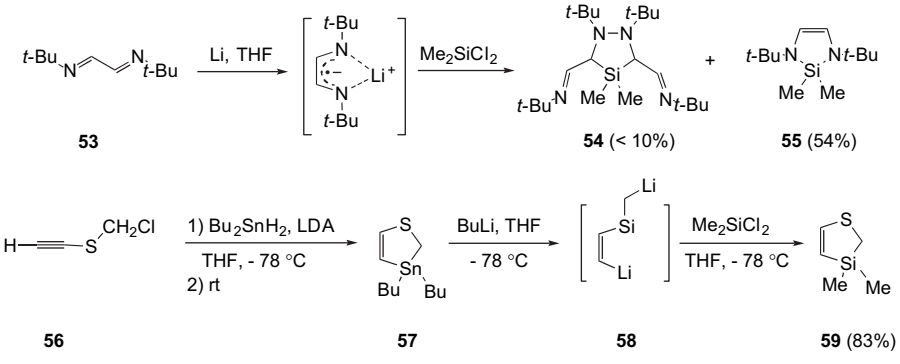

**Scheme 14**.

Reaction of *N*,*N*′-1,2-ethanediylidene-di(*tert*-butylamine) **53** with lithium followed by the addition of dichlorodimethylsilane was reported to yield products **54** and **55** via a radical cation intermediate (Scheme 15).[25] Diazasilolidine **54** (C-silylation compound) formed after dimerization of the radical cation was isolated in low yield. The major product **55** resulted from the N-silylation. This main process was exclusively observed when dichloromethylsilane[25] or trichloromethylsilane[26] was used as quenching agent or when *N*,*N*′-1,2-ethanediylidene-di(2,6-dimethylbenzeneamine) was used as substrate.[26] Thiasilolene **59** has been prepared by the reaction of dilithiated compound **58** with dichlorodimethylsilane. This intermediate **58** was obtained by cleavage of the carbon–tin bonds of the cyclic compound **57**, by reaction with butyllithium at low temperature. The stannylated compound **57** was prepared in two steps from chloromethyl ethynyl sulfide **56** by reaction with $LiHSnBu_2$ followed by intramolecular hydrostannylation (Scheme 15).[27]

**3.1.2. Preparation by formation of a carbon–silicon bond.** One of the best methods to form a carbon–silicon bond is probably the hydrosilylation reaction. The Voronkov group studied the intramolecular version of this reaction, in particular for the preparation of thiasilolane **61** from vinyl sulfide **60** (Scheme 16). The most effective catalyst to carry out these cyclizations appeared to be the Wilkinson catalyst.[16b,17] Competitive formation of six-membered compounds was not observed. When the reaction was catalyzed by chloroplatinic acid, lower yields were obtained.[16a] This hydrosilylation was also found to be possible starting from 2-vinyloxyethylsilanes **62** and **65**. In the presence of chloroplatinic acid as catalyst, intramolecular cyclizations were observed, and regioselectivity seemed to depend upon the silicon atom substituents. With diethylsilane **65**,



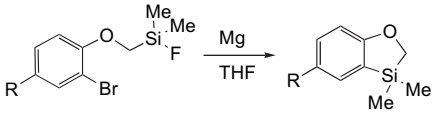

**Scheme 16**.




**Scheme 15**.

only the five-membered ring compound was obtained, while, with dimethylsilane **62**, a mixture of compounds **63** and **64** was formed, resulting from the competitive *endo* and *exo* cyclizations.[28]

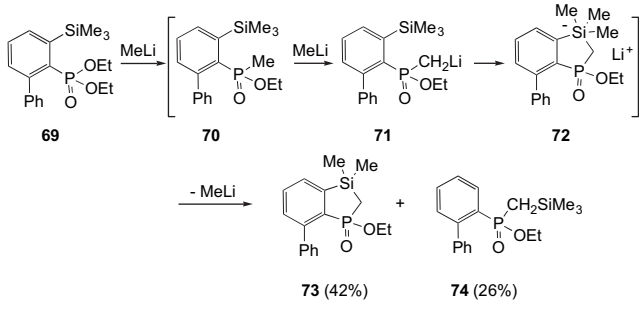
Nietzschmann and co-workers reported that benzoxasilolanes **68a**,**b** could be obtained by reaction of dihalo derivatives **67a**,**b** with magnesium (Scheme 17).[29] The scope of this very simple method, when an aryl organometallic intermediate should lead to a nucleophilic attack on the silicon atom, has never been examined.




**67a**: R = H **68a** (61%)
**67b**: R = Me **68b** (65%)

**Scheme 17**.

An original preparation of benzophosphasilolenes such as **73** was reported by Vedejs and co-workers by the reaction of 2-trimethylsilylarylphosphonate **69** with methyllithium (Scheme 18).[30] This transformation implies the substitution of one of the ethoxy groups fixed at the phosphorus atom by a methyl (intermediate **70**), followed by abstraction of one of its acidic hydrogens by methyllithium to give **71**. Subsequent nucleophilic attack of the silicon atom led to siliconate **72**. Elimination of methyllithium gave rise mainly to the heterocyclic compound **73**. In the absence of an aryl substituent in the α-position of the aromatic ring of compound **69**, this cyclization was not observed.

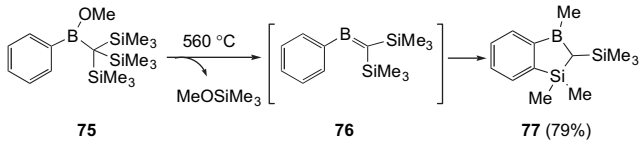



**69** **70** **71** **72**

**73** (42%) **74** (26%)

**Scheme 18**.

Flash vacuum pyrolysis (560 °C) of phenylborinate **75** led to the intermediate formation of a methylene borane **76**. This compound, later, after a 1,3-shift of one of the methyl groups fixed at the silicon atom, led to the formation of silaborolane **77** (Scheme 19).[31] When the substituent fixed on the boron




**75** **76** **77** (79%)

**Scheme 19**.

atom is a benzyl instead of a phenyl group, benzosilaborinanes were obtained (see Scheme 85).

The preparation of silaheterocycles by the formation of Si–C bonds was also reported to be possible in the case of the formation of reactive intermediates such as silenes or silylenes. The formation of an azasilole was reported by Tilley et al. during their study concerning the reactivity of a tris(trimethylsilyl)silylscandium(III) derivative **78**.[32] Its reaction with 2-isocyano-1,3-dimethylbenzene led to the formation of azasilole **80**, in which the scandium metal was complexed by two nitrogen atoms (Scheme 20).[32] The formation of the azasilole was tentatively explained by the insertion of one molecule of isocyanate into the Sc–Si bond to give, first, the isolable intermediate **79**, which, after the addition of a second equivalent of isocyanate, led to the product **80**, the structure of which secured by X-ray crystallographic analysis.

Hindered disilenes were found to be in equilibrium with silylenes by moderate heating. Reaction of disilene **81** with mesityl isocyanate resulted in the formation of the intermediate **82**. By a nucleophilic attack of the silicon atom of this intermediate at the *o*-position of the mesityl group and migration of the mesityl and methyl groups, the product **84** was formed, via the postulated intermediate **83**. The structure of **84** was confirmed by X-ray crystallographic analysis (Scheme 21).[33]

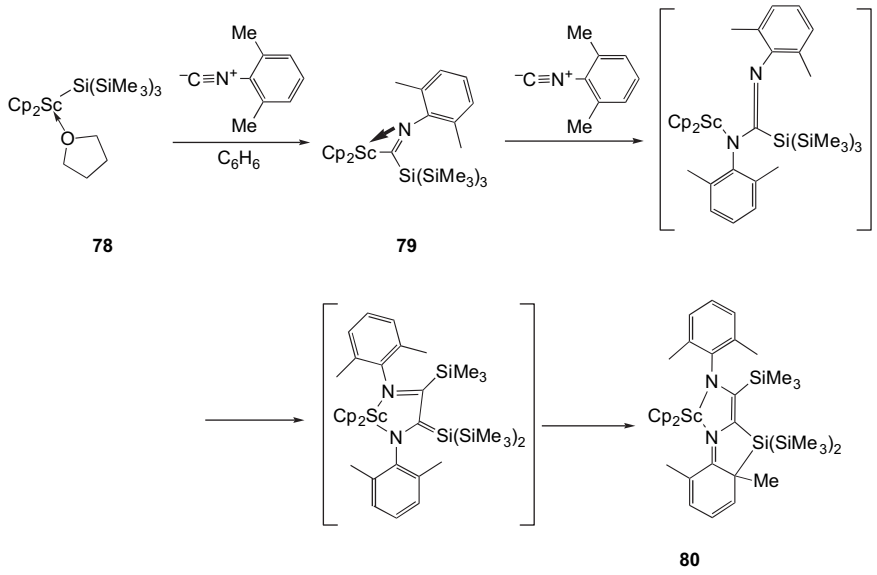
### 3.2. Preparation by formation of carbon–heteroatom bonds

Intramolecular cyclization of alcohol **85** in the presence of NaH led to oxasilolane **86** (Scheme 22).[34] The electronic diffraction spectra of this compound were determined out and compared to the ab initio calculations.

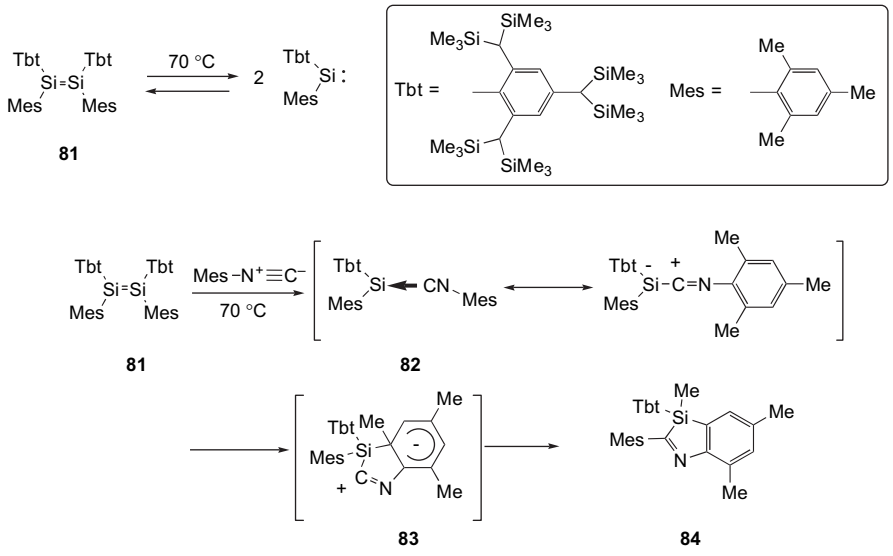
Reich and co-workers have studied the reactivity of 2,3-bis-(trimethylstannyl)-1,3-butadiene **87**.[35] By reaction with 1 equiv of MeLi, followed by silylation with a chlorosilane, they isolated compound **88**. This compound, later, after reaction with 1 equiv of methyllithium and addition of selenium, led to the bis(methylidene)selenosilolane **89**. This unstable compound was used to prepare the Diels–Alder adduct **90** (Scheme 23).

Two different groups have reported interesting syntheses of 4-silaproline derivatives. Tacke and co-workers found that the racemic silaproline ester **93** could be obtained in two steps from 2,5-dihydropyrazine **91** by metallation with butyllithium followed by alkylation using bis(chloromethyl)dimethylsilene and hydrolysis with HCl (Scheme 24).[36] Heating of alkylated compound **92** at 120 °C led to azasilolidine **94**. (*R*)-Silaproline ester **93** was also prepared by this method starting from (*R*)-2,5-dihydro-2-isopropyl-3,6-dimethoxypyrazine (Schöllkopf pyrazine **95** in Scheme 25) (overall yield: 20%).[36b]

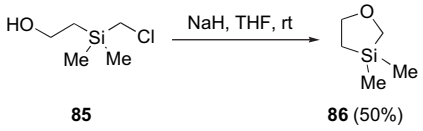
A second approach to (*R*)-silaproline esters has been reported.[37] Alkylation of Schöllkopf pyrazine **95** with bis-(iodomethyl)dimethylsilane give a mixture of the two diastereomers **96** and **97**. The major isomer was isolated and transformed into (*R*)-*N*-protected silaproline **98**



**Scheme 20**.



**Scheme 21**.

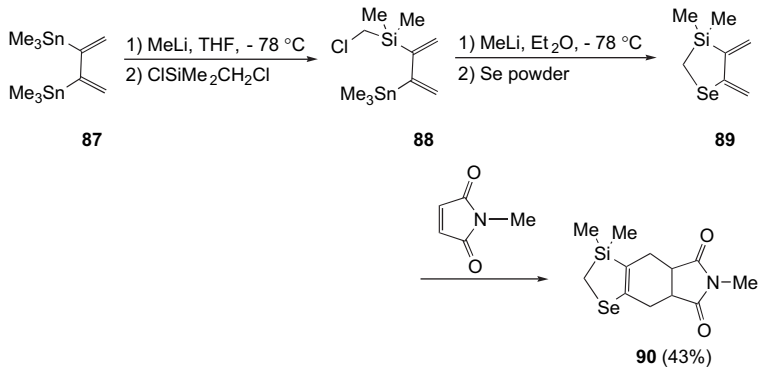


**Scheme 22**.

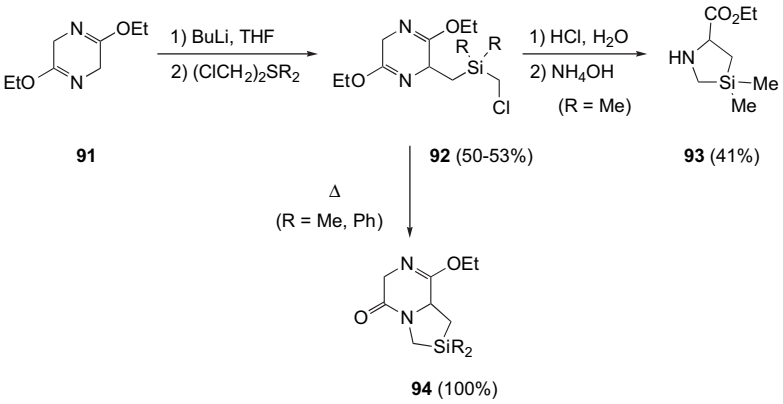
(Scheme 25). Reaction with the (*S*)-pyrazine gave similarly the silaproline with the (*S*) configuration. These silaprolines appear to be 14-fold more lipophilic than proline. Replacement of a proline unit in the C-terminal segment NT(8–13) of neurotensin by silaproline improved the resistance to biodegradation without a great modification of their biological activities.[38] Similar results were observed by incorporation of silaproline in substance P.[39]

The Voronkov group showed that the method used for the preparation of 1,3-thiasiletanes by the reaction of α,ω-dihalosilaalkanes with KSH (Scheme 7) could not be applied to the formation of 1,3-thiasilolanes. Another approach was reported to be possible in the case of sulfur compounds. Thiasilolane **101** was obtained by reaction of allyl(chloromethyl)silane **99** with alcoholic KSH solution. The intermediate thiolate anion **100** was not detected (Scheme 26).[40] The six-membered ring compound (*endo* cyclization) was not formed. This method was, however, applied to the formation of the six-membered compound by *exo* mode cyclization (see Scheme 72).

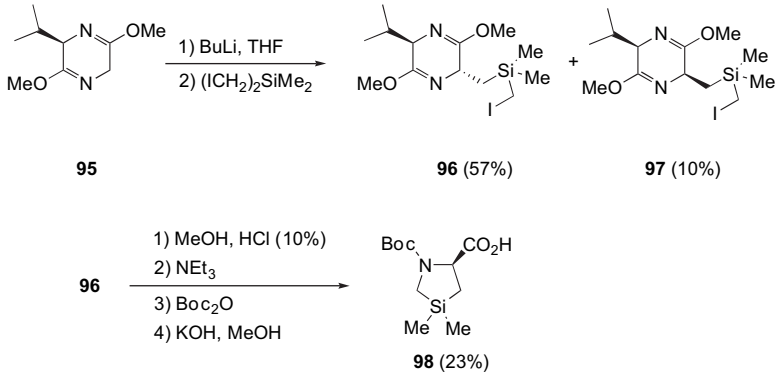
The same group has also studied the formation of thiasilolanes by radical cyclization. This method appears interesting, due to the easy formation of a thiyl radical and its propensity to add to carbon–carbon double bonds. Reaction of divinylsilane **102** with $H_2S$ under irradiation in the presence of $YCl_3$ as photocatalyst led mainly to a mixture of thiasilolane **101** and thiasililane **103** (Scheme 27).[41] In the



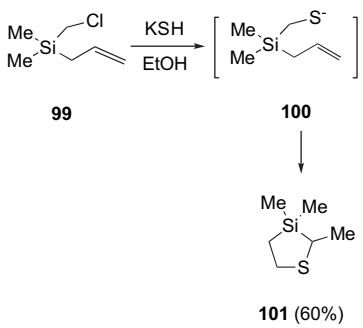

**Scheme 23**.




**Scheme 24**.



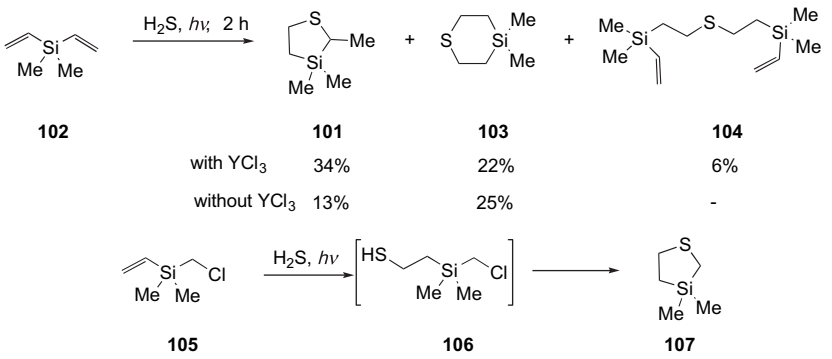

**Scheme 25**.




**Scheme 26**.

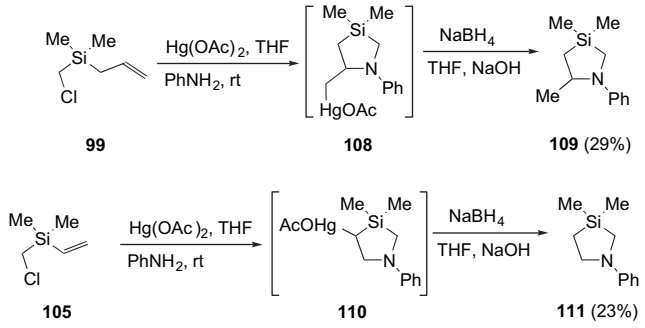
absence of $YCl_3$, the side product **104** resulting from an intermolecular reaction of the intermediate thiol was not formed, but product **101** was obtained in lower yield.[40] Irradiation of 2-[dimethyl(vinyl)silyl]ethanethiol led to the same mixture of regioisomers **101** and **103**. Another route to the thiasilolanes, e.g., **107**, briefly explored, uses the intramolecular cyclization of 2-(chloromethyldimethylsilyl)-ethanethiol **106**, postulated as an intermediate in the addition of $H_2S$ onto the carbon–carbon double bond of vinylsilane **105**.[40]

Electrophilic cyclizations have also been reported to be useful for the preparation of azasilolidines and oxasilinanes.



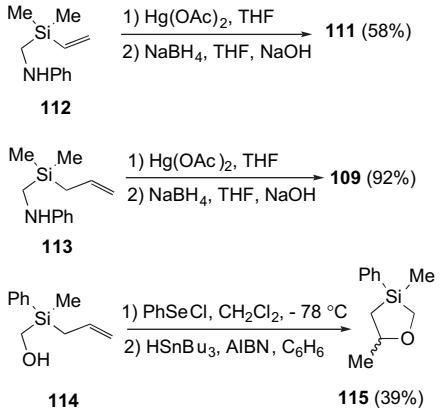

**Scheme 27**.

The Russian group showed that alkenyl(chloromethyl)-silanes **99** and **105** reacted with aniline in the presence of mercury(II) acetate to afford in low yields, after reductive elimination, the corresponding azasilolidines **109** and **111** (Scheme 28).[42] These reactions occurred by the intermediate formation of the aminoalkyl(chloromethyl)dimethylsilanes, which cyclized to the mercury derivatives **108** and **110**.




**Scheme 28**.

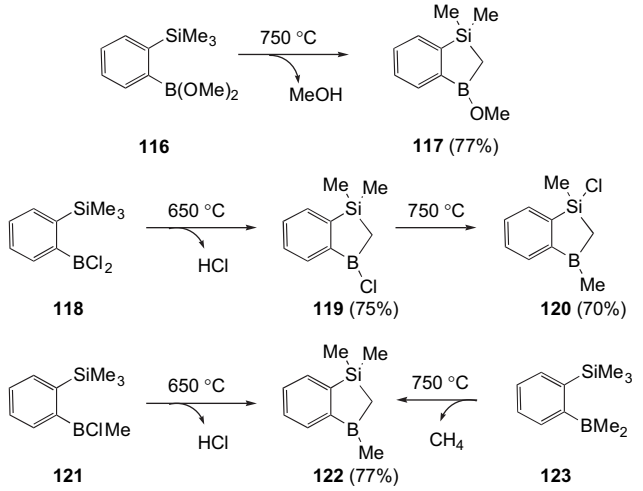
In a subsequent study, it was shown that these heterocyclic compounds could be obtained more efficiently by intramolecular aminomercuration of alkenyl(aminomethyl)silanes, e.g., aminosilanes **112** and **113** led to azosilolidines **111** and **109** in good yields (Scheme 29).[43] Higher-ring-size compounds were obtained in lower yields. The absence of the formation of azasilinanes during the cyclization of compound **113** was explained by the well-known ability of silyl




**Scheme 29**.

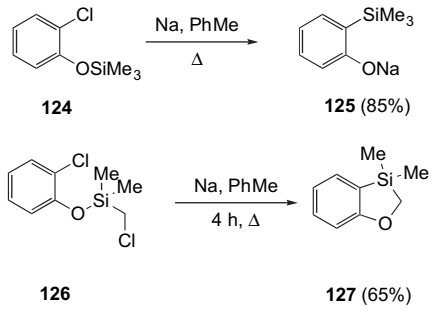
groups to stabilize a neighboring β-carbocation.[44] Seleno etherification of alcohol **114** followed by reductive elimination led to oxasilolane **115** as a 1:1 mixture of two diastereomers in moderate yield. At the present time, the potential of this reaction has not been fully explored (Scheme 29).[45]

Schacht and Kaufmann have studied the flash vacuum pyrolysis of (2-trimethylsilylphenyl)boranes, e.g., thermolysis of borane **116** led to silaborolane **117** and methanol in good yield (Scheme 30).[46] The mechanism of these reactions seems to take place by a radical pathway. Flash vacuum pyrolyses of chloroboranes **118** and **121** occurred at lower temperature than methoxyboranes to give **119** and **122**, respectively. This result is a consequence of the easier extrusion of hydrogen chloride compared to that of methanol. At higher temperature, chloroborane **119** was rearranged into chlorosilane **120**. The transformation of methylborane **123** into silaborolane **122**, by extrusion of methane, was also reported to occur at high temperature.




**Scheme 30**.

Nietzschmann and co-workers studied the reaction of 2-halophenoxysilanes such as **124** in the presence of sodium or *n*-butyllithium. A [1,3]-carbanionic rearrangement was observed, leading to the formation of 2-silylphenate **125** (Scheme 31).[47] When one of the substituents fixed at the silicon atom was a chloromethyl group, e.g., **126**, this rearrangement led to the formation of the benzooxasilolane **127**.[29,48]

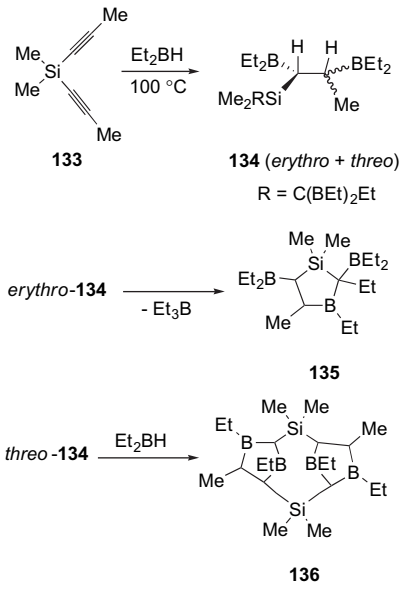



**Scheme 31**.

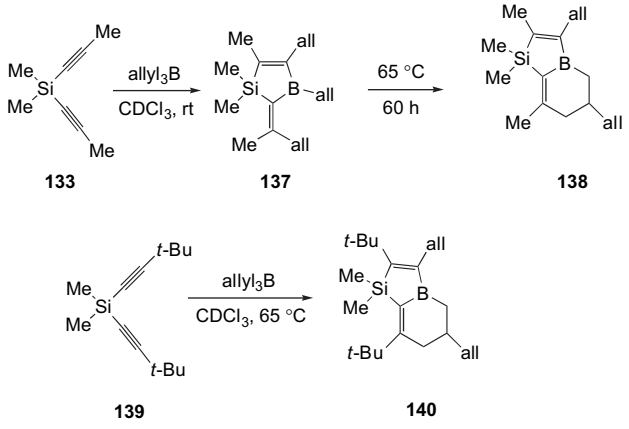
Sato and co-workers showed that azasilolines **129** were obtained in low yields, among various products, by an intermolecular reaction of trialkylsilylethylamines **128** with benzyne (Scheme 32).[49] These results prompted this group to study an intramolecular version of this reaction, to avoid the formation of numerous side reaction products. The reaction of (aminomethyl)(3-chlorophenyl)silanes **130a–c** with phenyllithium in ether led to the intermediate formation of benzyne derivatives **131a–c**, which were trapped by the nitrogen atom to give compounds **132a–c** in acceptable yields (Scheme 32).[50]

Köester and co-workers showed that siladiyne **133** reacted with an excess of diethylborane to give a mixture of *threo*- and *erythro*-3,3,5,6-tetrakis(diethylboryl)-4,4-dimethyl-4-silaheptanes **134**. The *threo* isomer reacted further with diethylborane to lead to product **136**, while elimination of triethylborane occurred leading to the formation of silaborolane **135** with the *erythro* isomer (Scheme 33).[51] The mechanism of these transformations was not clarified.

Subsequently, the same group examined the addition of diynylsilanes with triallylborane. Starting from diynylsilane **133**, methylenesilaborole **137** was obtained, which, by heating at 65 °C, was rearranged into the bicyclic silaborole **138**.[52] With the less reactive diynylsilane **139**, the methylenesilaborole was not detected, and silaborole **140** was isolated as a unique product (Scheme 34). This cycloaddition was not observed in the case of dimethylbis(2-phenylethynyl)silane. Reaction of diynylsilane **139** with 1-boraadamantane was found to lead also to the formation of a silaborolane.[53]

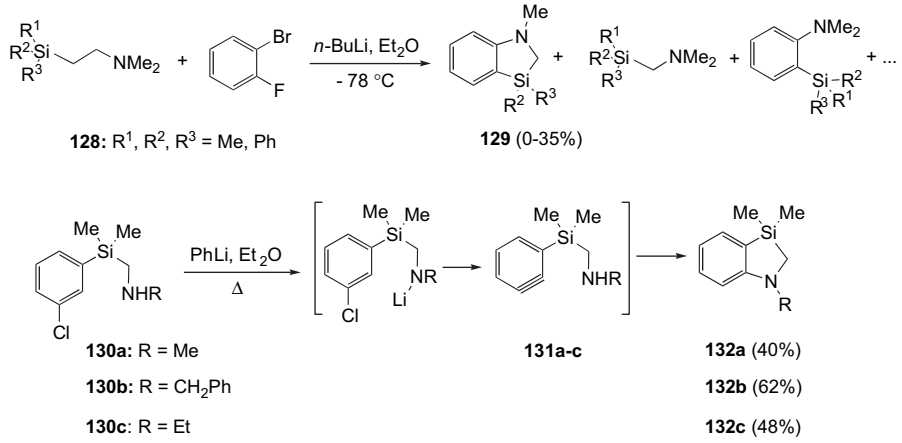



**Scheme 33**.



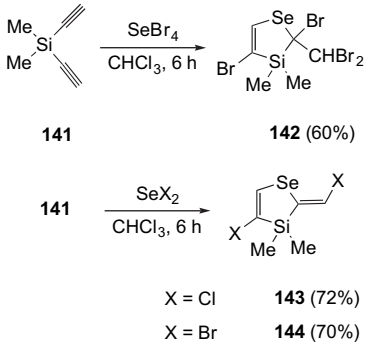

**Scheme 34**.

Electrophilic addition of $SeBr_4$, $SeCl_2$ and $SeBr_2$ and to diethynylsilane **141** was reported to lead by successive




**Scheme 32**.

electrophilic reactions to the formation of selenosilolenes **142–144** (Scheme 35).[54,55]




**Scheme 35**.

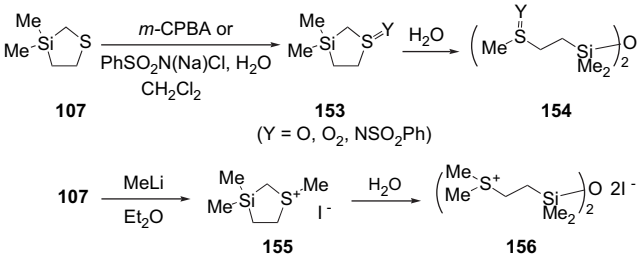
### 3.3. Preparation by formation of carbon–carbon bonds

The preparation of thiasilolene **148** was reported by intramolecular cyclization of ethynylsilane **145** initiated by tributyltin hydride in benzene. The initial radical **146** evolved by cyclization, cleavage, and further cyclization into the radical **147**. Finally, this latter radical gave rise to the formation of compound **148** (Scheme 36).[56]

Recently, Tanaka and co-workers have also reported an example of cyclization by the formation of a carbon–carbon bond. They studied the radical cyclization of nucleoside 2-sila-5-hexenyl radicals. When a methyl group was present on carbon 2′ (Scheme 37, compound **149**), they observed a competition between the 5-*exo* and 6-*endo* cyclizations. In the reaction mixture, compound **150** was the major component, compound **151** the minor component, and the glycosidic bond-rearranged product **152** was also isolated. This latter product is probably formed by rearrangement of the 5-*exo* cyclization product **150** after radical C–N bond cleavage. In the absence of this methyl group, only the product corresponding to 6-*endo* cyclization was observed (see Scheme 91).[57]

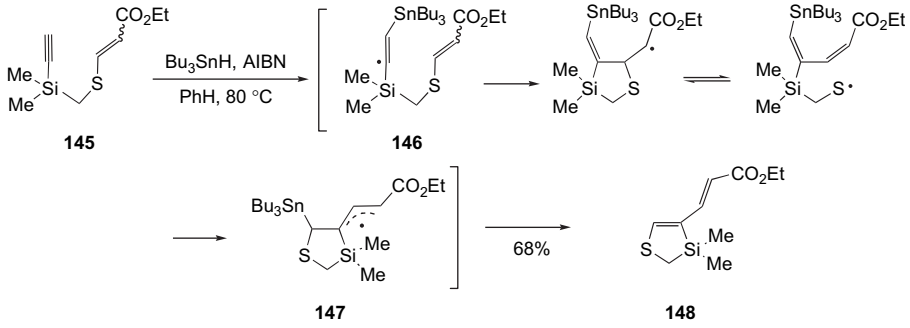
### 3.4. Reactivity and applications

Thiasilolanes reacted with *m*-chloroperbenzoic acid to give the corresponding sulfoxides and sulfones (Scheme 38, compounds **153**: Y=O and $O_2$). These sensitive compounds were cleaved to give **154** (Y=O and $O_2$) in the presence of hydrolytic solvents such as water. Similar ring openings of sulfimide **153** to **154** (Y=$NSO_2Ph$) and sulfonium salt **155** to **156** were reported.[58] The corresponding six-membered ring compounds appear to be more stable.

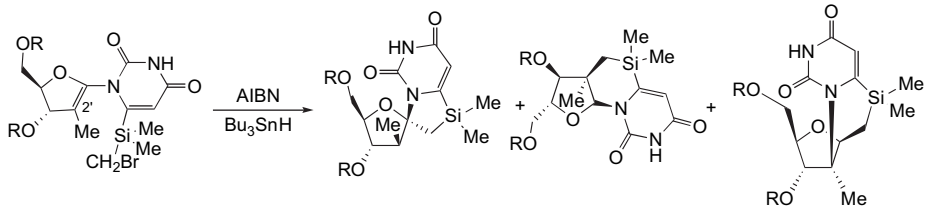



**Scheme 38**.

The reaction of benzoazasilolidines **132a**,**b** with benzyne was examined.[50] Stevens' rearrangement products **157a**,**b** were obtained when the substituents fixed at the nitrogen

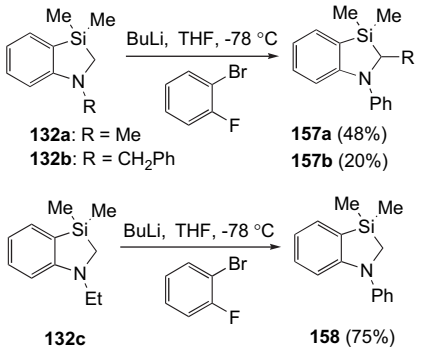



**Scheme 36**.




**Scheme 37**.

atom were benzyl or methyl groups. When the substituent was an ethyl group (compound **132c**), however, product **158** was obtained, formed by a Hoffmann elimination reaction (Scheme 39).




**Scheme 39**.

In conclusion, many approaches have been examined for the preparation of five-membered heterocyclic compounds containing a silicon atom and another heteroatom. In general, however, these methods have not been explored in detail and work seems necessary to improve the preparations and examine their scope. Contrary to the corresponding four-membered-ring heterocyclic compounds, these compounds appear to be stable enough to allow subsequent reactions and their use for the synthesis of more complex frameworks.

## 4. Preparation of six-membered heterocyclic compounds

Heterocyclic compounds with silicon and oxygen, sulfur, nitrogen, phosphorus, selenium, tellurium or boron atoms in the 1,3- or 1,4-positions are known. In Scheme 40, IUPAC representative names and structures of these heterocycles have been summarized.

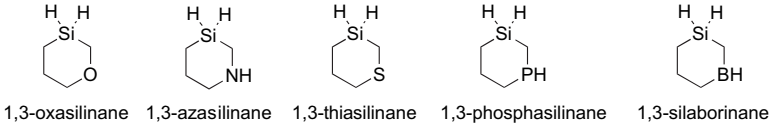
As for the synthesis of five-membered heterocycles (vide infra), different strategies have been developed to obtain this ring size, and they are subdivided by the nature of the bond formed in the cyclization step.

### 4.1. Preparation by formation of carbon–silicon bonds

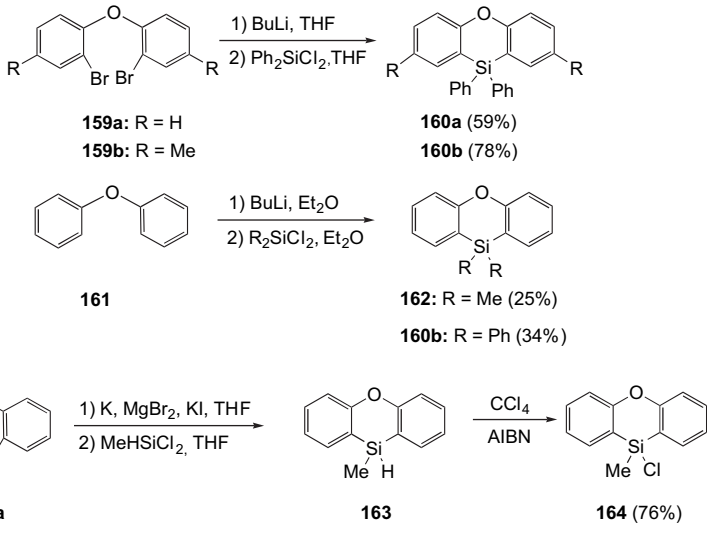
**4.1.1. Preparation by reaction of dihalosilanes with dianionic species.** This method implies the reaction of silane derivatives (mainly *gem*-dichlorosilanes) with 1,5-dianions.

**4.1.1.1. Preparation of oxasilinanes.** Different groups have simultaneously developed this method. The first oxasilinanes appear to have been synthesized by Hitchcock and co-workers.[59] Compounds **160a**,**b** were obtained by reaction of 2,2′dibromodiphenyl ethers **159a**,**b** with butyllithium followed by the addition of 1,1-dichlorosilanes (Scheme 41).

At the same time, Gilman and Oita found that lithiation of diphenyl ether **161** could give rise to the formation of products **160a** and **162** (R=Me). These reactions, carried out in ether, led to lower yields (25–40%) than those obtained by the Hitchcock approach.[60] Gilman and Miles prepared several compounds with different substituents on the silicon atom (**162**: R=benzyl, *n*-dodecyl) with the aim of obtaining synthetic lubricants of low melting point and high volatilization point.[61] These results were confirmed in two subsequent reports.[62,63] Corey and Chang have examined in detail these two approaches to oxasilinanes, and found that the halogen–metal exchange led to dilithio intermediates in better yields than the direct metallation.[64] Utilization of sodium as the




**Scheme 40**.

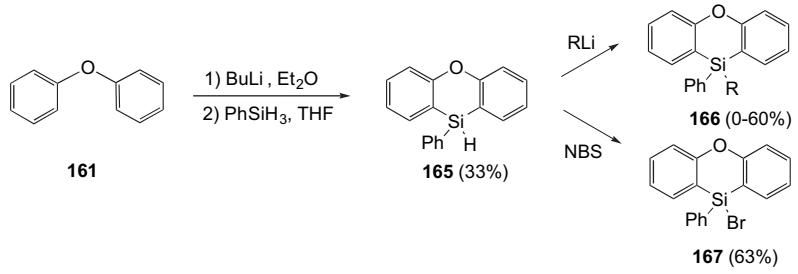



**Scheme 41**.

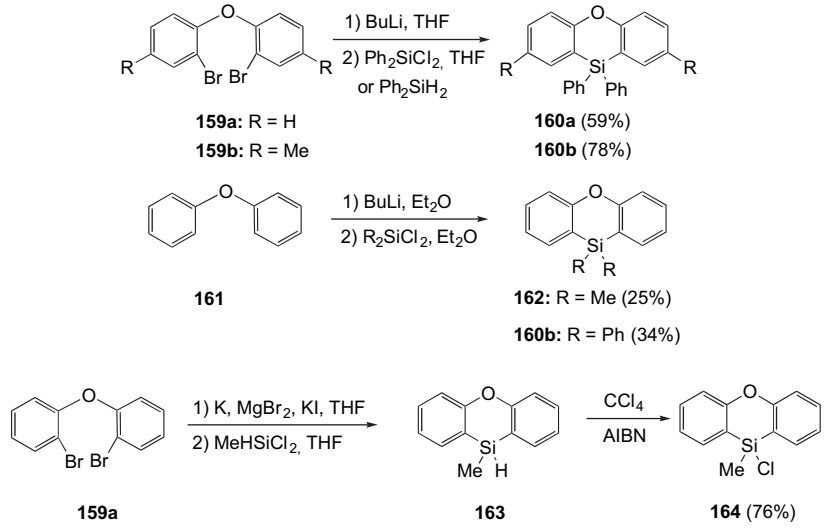
metal has been reported to be less efficient.[65] More recently, it was reported that the reaction of 2,2′-dibromophenyl ether **159a** with Riecke magnesium led, after reaction with methyldichlorosilane, to oxasilinane **163** in good yield. This latter compound reacted with $CCl_4$ in the presence of AIBN to give chlorosilane **164** (Scheme 41).[66] This method was also applied to the preparation of 10-methyl-10*H*-phenothiasiline (vide supra). Formation of oxasilinanes by this method is not limited to the reaction of dichlorosilanes, hydrogenosilanes also being used with success as quenching agents (Scheme 42).[64,67] Reaction of phenylsilane with the dilithium derivative formed from diphenyl ether **161**, led to hydrogenosilane **165**. This compound was subsequently transformed into silanes **166**, by reaction with organolithium reagents, or to bromosilane **167**, by reaction with *N*-bromosuccinimide.

**4.1.1.2. Preparation of azasilinanes.** Simultaneously with the preparation of oxasilinanes, Gilman and co-workers studied the preparation of azasilinanes using this methodology. Compounds **169** and **170a**,**b** were obtained by the reaction of the *N*-alkyl-2,2′-dilithiodiphenylamine prepared from **168** with dichlorosilanes[68] and dihydrogenosilanes[68d] (Scheme 43). Compound **169** was also obtained by the reaction of the dilithio intermediate with triphenylchlorosilane, one of the phenyl groups being expelled (42% yield).[69] Azasilinanes **170a**,**b** bearing hydrogen on the silicon atom were used for further functionalization by reaction with organolithium compounds to form **171a**,**b** (Scheme 43).

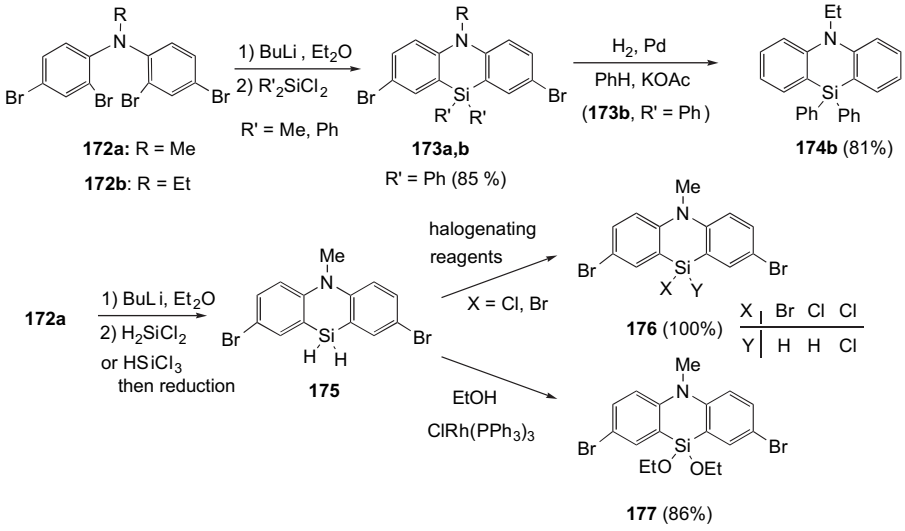
The main drawback of the work developed by Gilman et al. was the difficult preparation of the dibrominated compound **168**. Wasserman and co-workers showed that dibenzoazasilinanes could be obtained from the tetrabromodiphenylamines **172a**,**b** (Scheme 44), formed by polybromination of diphenylamine and alkylation. Reaction of amines **172a**,**b** with BuLi led to a regioselective Br–Li exchange and the resulting dilithio intermediates react with dichlorosilanes to give the cyclic compounds **173a**,**b**. Subsequent hydrogenolysis of the C–Br bonds gave rise to the azasilanes, e.g., **174b** (R′=Ph) in good overall yields.[70] The same products were obtained by the reaction of **173a**,**b** with BuLi, followed by hydrolysis. Contrary to the claim of Wasserman, substitution of the two bromine atoms was found to be difficult using BuLi.[71] The preparation of phenazasilenes was reported to be more convenient using monoalkylsilanes, instead of chlorosilanes.[72] Two different pathways were used to obtain phenazasilene **175** from tetrabromo compound **172a**. After formation of the dilithio intermediate, the quenching was carried out using $H_2SiCl_2$ (23% yield) or, better, $HSiCl_3$ followed by in situ reduction of the monochlorosilane (58% yield) (Scheme 44).[73] Reactions of compound **175** with $CCl_4$ in the presence of $ClRh(PPh_3)_3$ or NBS led to compounds **176** (X=H; Y=Br, Cl) resulting from monohalogenation, and reaction with $SOCl_2$ led easily to the dichlorosilane (**176**; X, Y=Cl). Dialkoxysilanes such as compound **177** were formed by the reaction of dihydrosilane **175** with primary alcohols in the presence of Wilkinson's catalyst.




**Scheme 42**.



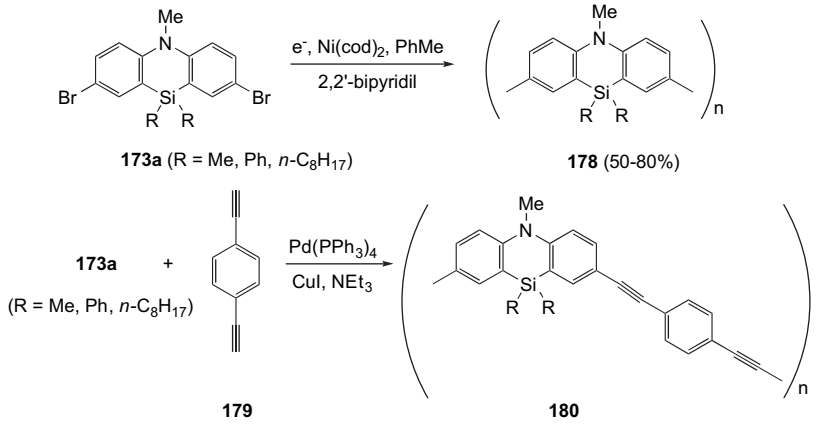

**Scheme 43**.



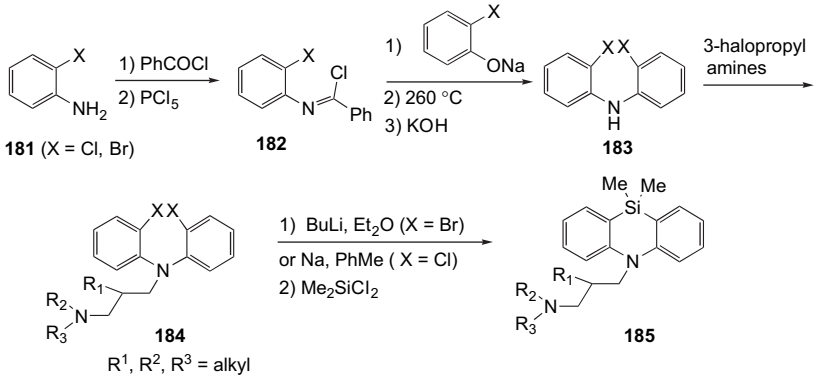

**Scheme 44**.

Electrochemical polymerization reactions of bromophenazathiasilins have been examinated.[74] Phenazasilines **173** led in the presence of nickel salts to the formation of polymers **178**. Polymerization in the presence of 1,4-diethylnylbenzene **179** was reported to give copolymers **180**. Similar polymerization was observed starting from 1,3-diethynylbenzene. These polymers show reversible electrochromic properties upon electrochemical treatment (Scheme 45).[75]

Using Gilman's method, the Wannagat group prepared azasilinanes *N*-substituted by a 3-(dialkylamino)propyl group from dibromoamines obtained by the sequence reported in Scheme 46 (75–80% yields).[76] Chloroimines **182**, synthetized from 2-haloanilines **181**, reacted with 2-halophenates to give diphenylamines **183**. Subsequent addition of 3-halopropylamines led to 1,3-diamino compounds **184**, which were transformed by Gilman's method to the desired



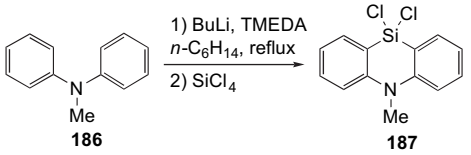

**Scheme 45**.




**Scheme 46**.

azasilinanes **185**. The authors showed that the dichloro derivatives could also be used if sodium was used as metal, but lower yields were obtained (32%). These silaacridanes have thymoleptic properties, comparable to those of their carbon analogues.[77]

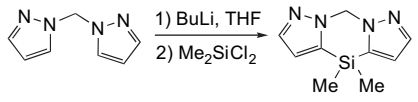
The preparation of phenazasiline **187** was also reported to be possible directly from diphenylamine **186**. To the dilithiated intermediate obtained by the reaction of amine **186** with butyllithium in the presence of TMEDA in hexane at reflux was added tetrachlorosilane in default quantity (Scheme 47).[78]




**186** **187**

**Scheme 47**.

Different 1,3,5-diazasilinanes have also been synthesized by this methodology. The reaction of butyllithium with bis(pyrazol-1-yl)methane **188**, followed by the addition of dichlorodimethylsilane, led to the tricyclic compound **189** (Scheme 48).[79] When dichlorodiphenylsilane was used as the electrophile, the yield of the silaheterocyclic product was only 10%.

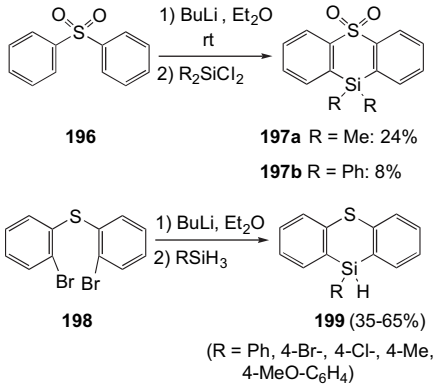



**188** **189** (63%)

**Scheme 48**.

Linear aminals led to the same reaction. Karsch and coworkers showed that treatment of bis(amino)methanes **190** with *tert*-butyllithium in pentane led to the isolable dianions **191**. These latter dianions reacted with dichlorosilanes to give the corresponding diazasilinanes **192** (Scheme 49).[80] Sieburth and Mutahi have recently reported the preparation of silanediols, which inhibit protease enzymes, in particular, HIV protease. Among these compounds, the silaheterocyclic derivative **195** was obtained in two steps from the urea derivative **193** and then **194** using the same approach (Scheme 49).[81]

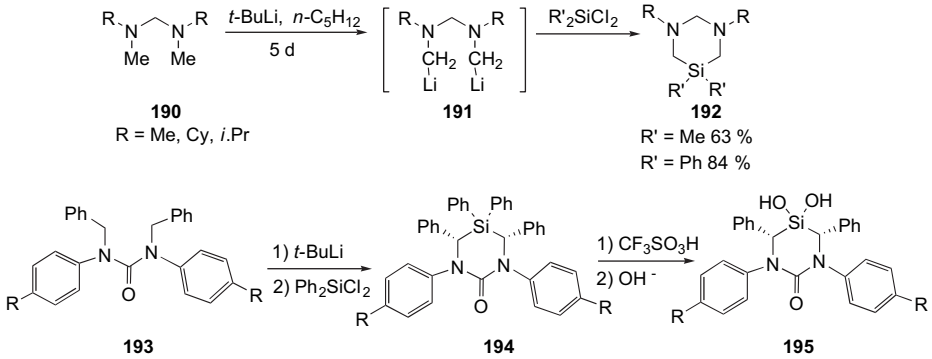
**4.1.1.3. Preparation of thia- and phosphasilinanes.** Simultaneously with the preparation of oxa- and azasilinanes, Gilman and Oita examined the formation of thiasilinanes. Reaction of diphenylsulfone **196** with butyllithium in ether led to the corresponding 2,2′-dilithiodiphenyl sulfone, which reacted with dichlorosilanes to lead to the formation of phenothiasilenes **197a**,**b** in modest yields (Scheme 50).[82] Subsequently, it was shown that utilization of lithium 2,2,6,6-tetramethylpiperidide as base in THF allowed an increase in the yield to 69% in the case of compound **197a**.[83] Reduction by $LiAlH_4$ of the sulfones to the sulfides was reported.[84] The direct formation of thiasilinanes **199** was shown to be possible starting from bis(2-bromophenyl)sulfide **198** (Scheme 50). Reaction of the dilithiated intermediate was reported with monoalkyl- or monoarylsilanes[85] and dichlorosilanes.[85,86] The main drawback of this method seems to be the difficult formation of the starting dibromide **198**.



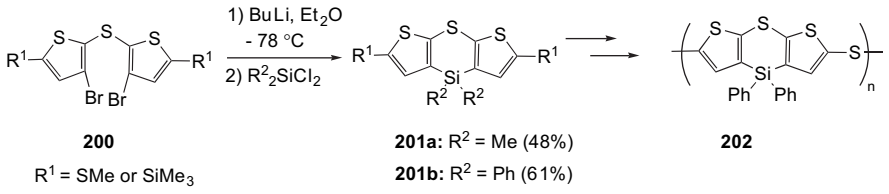

**Scheme 50**.

This method was also reported to be useful for the preparation of thiasilines **201a**,**b**. These compounds were prepared from sulfides **200** by Br–Li exchange with butyllithium followed by reaction with dichlorosilanes (Scheme 51).[87] Oxidation of compounds **201** with 1 or 2 equiv of *m*-chloroperbenzoic acid led to the corresponding mono and dioxides. Compound **201b** ($R^1$=Br) was transformed into polymer **202**, which, after doping with $FeCl_3$, showed interesting conducting properties.

The formation of 1,4-phosphasilinanes was reported by the reaction of bis(2-chlorophenyl)phosphines **203** with lithium

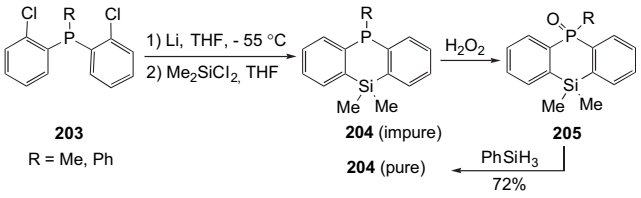



**Scheme 49**.



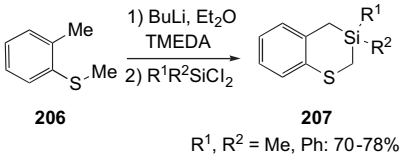

**Scheme 51**.

in THF, followed by the addition of dichlorodimethylsilane. Impure phosphasilinanes were obtained. After oxidation into the phosphine oxides **205**, subsequent reduction using phenylsilane led to pure 1,4-phosphasilinanes (Scheme 52).[88] The structures of compounds **204** were secured by X-ray crystallography.[89]



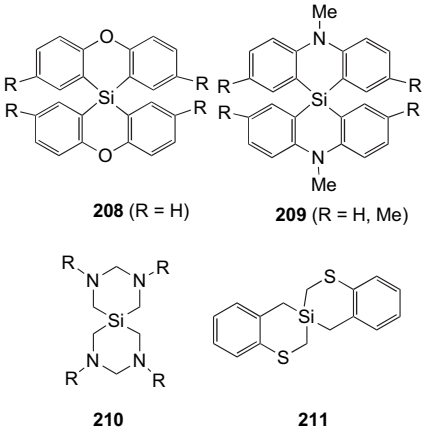

**Scheme 52**.

This methodology was not limited to the formation of 1-sila-4-heteroatomic compounds. Cabiddu and co-workers reported the first preparation of 1-sila-3-thiacyclohexane derivatives using the same approach. They showed that aromatic thio ethers such as compound **206** underwent direct dimetallation by reaction with 2 equiv of *n*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethanediamine (TMEDA). The reaction of these dianions with electrophiles was examined. 1,3-Thiasilinanes **207** were obtained when dichlorosilanes were used (Scheme 53).[90] No reaction was observed when a second methyl group was present in the *meta* or *para* position of the sulfur atom on the aromatic ring.




**Scheme 53**.

**4.1.1.4. Reactions with $SiCl_4$.** In parallel to the utilization of dichlorosilanes, different reports have indicated the utilization of $SiCl_4$ as quenching agent. Spiro compounds were, in general, obtained.[22,59,60,64,67,69,71,72,80,90,91] The first example involving this reaction was reported by Hitchcock.[59] The spiro ethers **208** substituted in the *meta* position of the silicon atom were not, however, obtained (compound **208**; R=Me), probably due to steric hindrance. This harmful aspect due to the presence of a substituent in *meta* position was not observed for the formation of azasilinanes **209**.[71] Similar formations of spiro compounds **210** and **211** (Scheme 54) have been reported using the respective dilithiated derivatives of the compounds **192**[80] and **206**.[90] An attempt to prepare 10,10′-spirodibenzothiasilin-5,5,5′,5′-tetroxide using tetrachlorosilane as a quenching agent was not successful.[82]

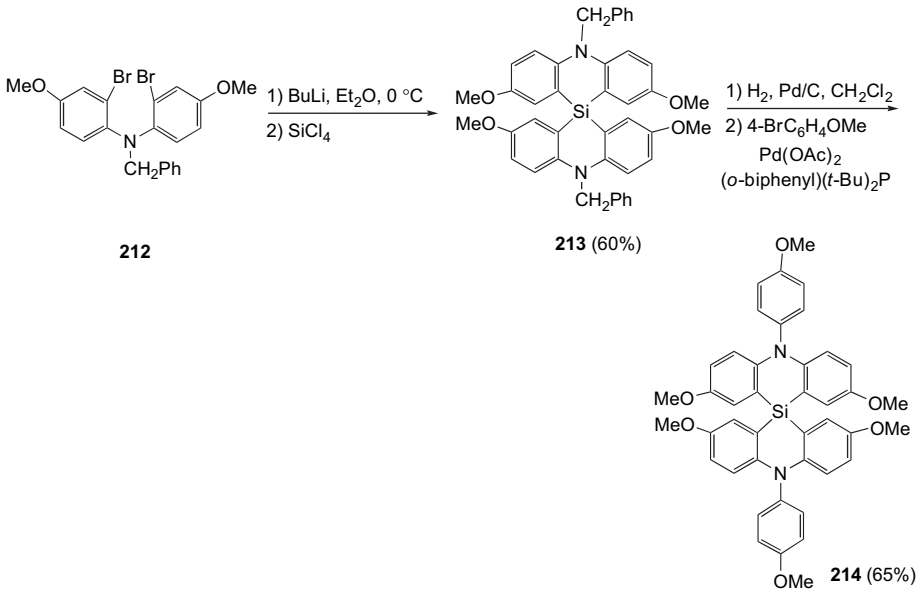



**Scheme 54**.

Access to the spiro compound **214** was recently reported. This compound was prepared via the *N*,*N*′-bis(benzyl) spiro compound **213**, which was obtained by the Gilman method by the reaction of dibromoamine **212** with butyllithium followed by the addition of tetrachlorosilane. Compound **214** reacted with $SbCl_5$ in methylene chloride to give the first stable bis-radical cation (Scheme 55).[91]

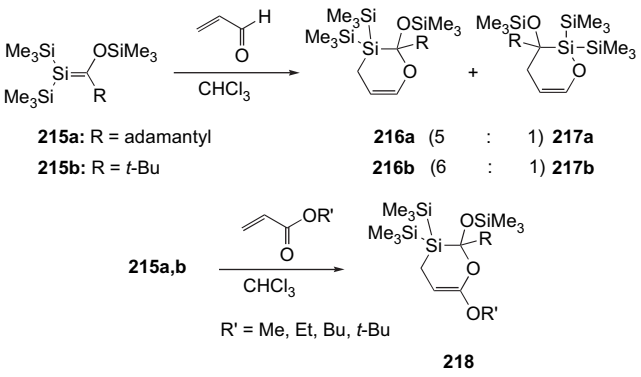
**4.1.2. Preparation by formation of a carbon–silicon bond.** Few results have been reported concerning the possibility of obtaining oxa- or thiasilinanes by intramolecular hydrosilylation. In a study reported[28] 10 years ago, Voronkov et al. claimed that thiasilanes could not be obtained by intramolecular hydrosilylation. The preparation of oxasilinanes using such a method has been reported in the case of vinyl enol ethers, but oxasilonanes were the major products of these reactions (Scheme 16).[28]

**4.1.2.1. Preparation of oxasilinanes.** Brook and coworkers have studied the cycloaddition of stable silenes **215** with α,β-ethylenic carbonyl compounds. In the case of propenal, formation of the two regioisomers **216** and **217** was observed, but, the major product was the 3-oxa-1-sila-cyclohexene **216**. Similar results were observed in the reaction of methyl vinyl ketone (Scheme 56).[92] In these two examples, when substituents were present on the carbon–carbon double bond of the unsaturated carbonyl compound, 1,3-oxasilinenes were never obtained. Quantitative formation of 1,3-oxasilinenes **218** was observed during the reaction of acrylates with **215**, but these cycloadditions were not observed with crotonates.[93] The results were explained by an interaction of the LUMO of the carbonyl compounds



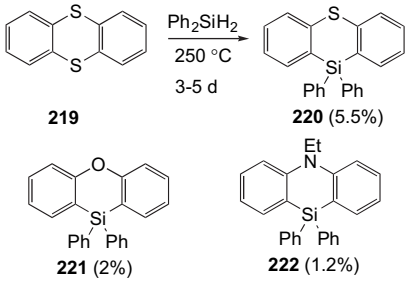

**Scheme 55**.

with the HOMO of the dienophile. The presence of β-substituents on the carbon–carbon double bond introduced steric interactions, which modified the regio- and chimioselectivity of the reaction.




**Scheme 56**.

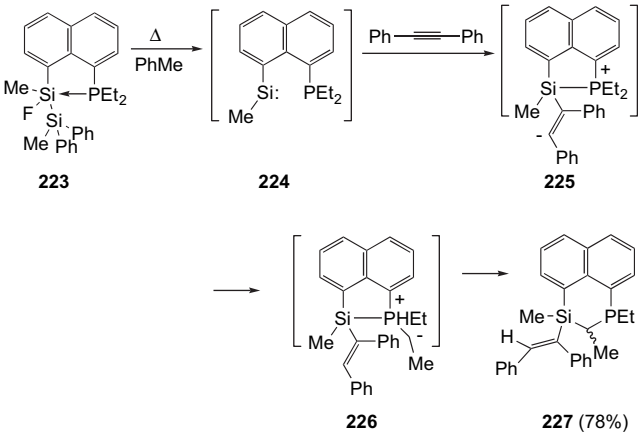
**4.1.2.2. Preparation of thiasilinanes.** Gilman and co-workers found that heating of thiaanthracene **219** with diphenylsilane for several days at 250–260 °C led to the formation of phenoxythiasiline **220** in 5.5% yield (Scheme 57).[94] Other sulfur heterocyclic compounds led also, under the same conditions, to sila-substituted products. By this method, compounds **221** and **222** have been obtained. The




**Scheme 57**.

yields were, however, always very low and this reaction has not been further developed to date.

**4.1.2.3. Preparation of phosphasilinanes.** Tamao and co-workers have reported an interesting preparation of silylene **224** by thermal decomposition of phosphosilane **223** (Scheme 58).[95] When the reaction was carried out in the presence of diphenylacetylene, phosphosilinane **227** was isolated in good yield as a mixture of two diastereomers (2:1). Addition of silylene to diphenylacetylene should give zwitterionic intermediate **225**, which rearranged into the six-membered compound **227** after a ring expansion of zwitterionic intermediate **226** formed by proton migration. The course of the reaction was different if two phenyl substituents were present on the phosphorus atom instead of the ethyl groups and formation of a seven-membered heterocycle was observed (see Scheme 121).




**Scheme 58**.

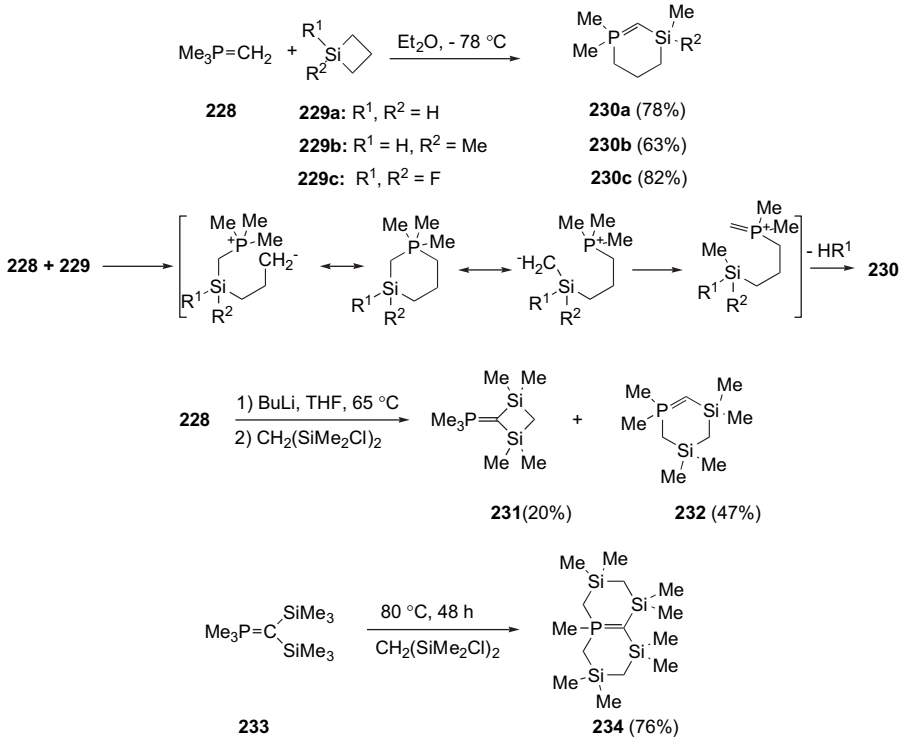
Schmidbauer et al., during their study of methylenephosphoranes, have examined[96,97] their reactivity with silyl compounds. Ylide **228** reacted with silacyclobutanes **229** to give compounds **230**. These reactions should occur through ring

opening (C–Si bond cleavage) and subsequent recyclization with elimination of dihydrogen or hydrogen fluoride (Scheme 59).[96] The formation of compounds **230** was not observed with triisopropylmethylenephosphorane. Reaction of methylenetrimethylphosphorane **228** with 2 equiv of butyllithium led, after addition of bis(chlorodimethylsilyl)-methane, to a mixture of compounds **231** and **232**. When the reaction was carried out, e.g., in THF at 65 °C, compound **232** was obtained in 47% yield.[97] Compound **232** was isolated after formation of the phosphonium salt by the addition of HCl. The same group described the formation of the bicyclic compound **234** by heating bis(chlorodimethylsilyl)methane with bis(trimethylsilyl)methylenetrimethylphosphorane **233**.

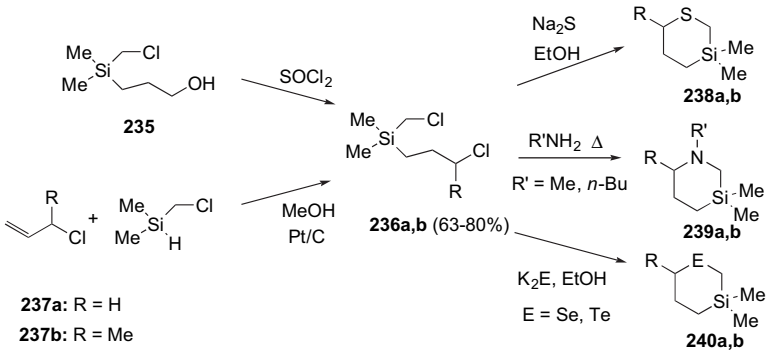
### 4.2. Preparation by formation of carbon–heteroatom bonds

**4.2.1. Preparation by reaction of functionalized silanes with heteroatom-containing reagents.** The simplest methodology implies the reaction of di(haloalkyl)silanes with heteroatomic reagents such as amines or sulfur derivatives. Fessenden and Coon first used this approach.[98] Reaction of alcohol **235** with $SOCl_2$ led to chloromethyl-(3-chloropropyl)silane **236a**, which reacted with sodium sulfide and primary amines to lead to the formation of the corresponding heterocyclic compounds **238a** and **239a**, respectively, in good yields (Scheme 60). Dedeyne and Anteunis have developed this work.[99] The preparation of dihalosilaalkanes **236a**,**b** was achieved by the hydrosilylation of allyl chloride derivatives **237a**,**b** with Pt/C as catalyst. Unstable 1,3-seleno and 1,3-tellurosilanes **240a**,**b** were also obtained using this approach.

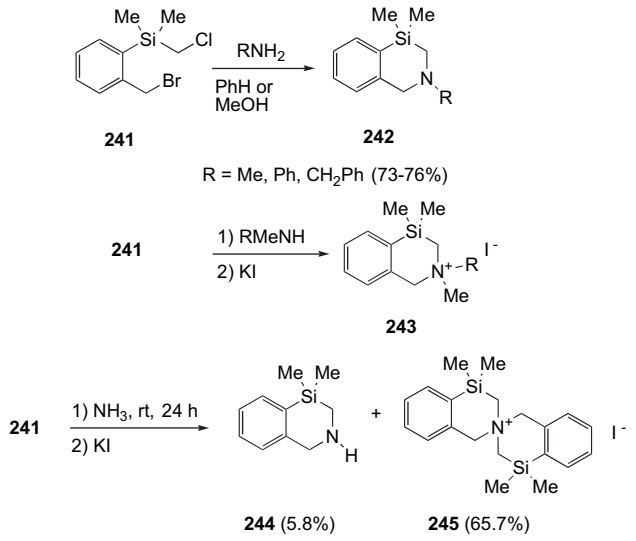
Sato and co-workers have applied the same methodology to the syntheses of compounds **242** and **243** by reaction of chloromethylsilane **241** bearing a bromomethylphenyl group with amines (Scheme 61). In the case of ammonia, a spiranic ammonium derivative **245** was mainly obtained, together with a small amount of secondary amine **244**.[100]




**Scheme 59**.

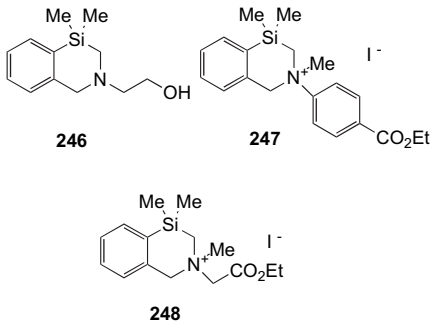



**Scheme 60**.



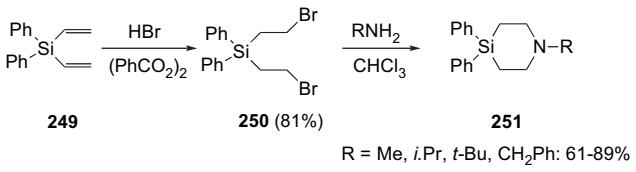

**Scheme 61**.

Lukevics and co-workers used this method for the preparation of compounds having biological properties (Scheme 62). Compound **246** showed antiblastic activity, closed to that of the parent carbon compound.[101] In the case of compounds **247** and **248**, psychotropic activity and acute toxicity were reported.[102] The psychotropic activity of compound **248** was not observed for the parent carbon compound, which possesses sedative activity.[103]




**Scheme 62**.

This strategy was also found to be efficient for the preparation of 1,4-azasilinanes. The first report was due to Jutzi's group. The bis(bromoethyl)silane **250** was obtained by radical addition of HBr to divinylsilane **249**, and was treated with various primary amines (Scheme 63).[104] Another approach to these azasilinanes **251**, much less efficient (0–5%), implied the direct addition of lithium amides to divinylsilanes.[104] Compounds **251** showed an interesting binding




**Scheme 63**.

ability on the neurotransmitter receptor in the homogenate of rat brains and to different receptors. It was reported that UV irradiation was more efficient for the 1,2-addition of HBr to vinylsilanes than chemical initiators.[105]

Subsequently, Tacke's group undertook significant work in this field. Numerous silapiperidines with antipsychotic activity have been obtained.[106] In particular, a silapiperidine **254** non-substituted on the nitrogen atom has recently been prepared from **252**, via **253**. This compound could be viewed as a synthon allowing the preparation of more complex compounds (Scheme 64).[107] Cleavage of an aryl–silicon bond in **255**, using a strong acid, allowed access to new silaperidols such as compound **257** (via **256**).[108]

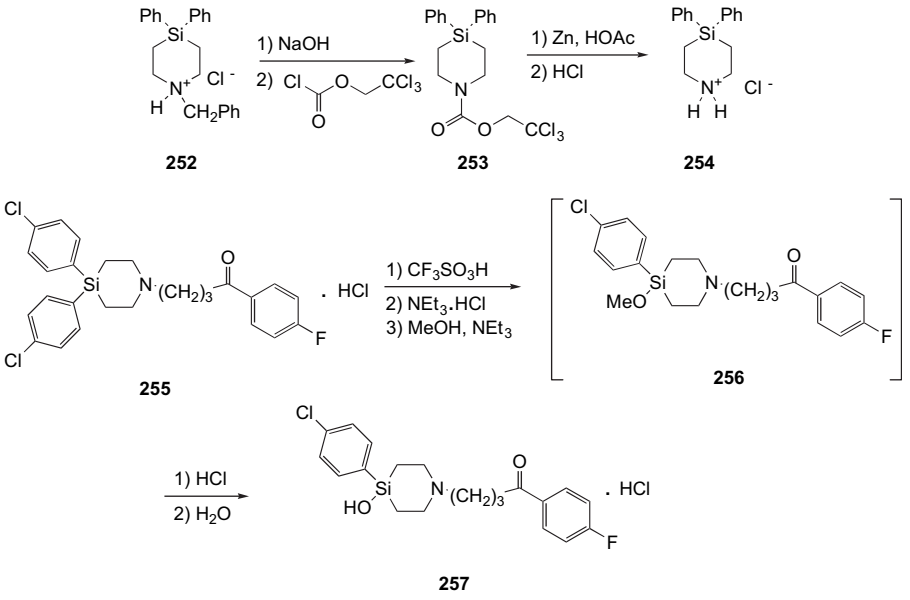
Kim and Cho have reported another interesting approach to 4-silapiperidines from divinylsilanes. Instead of the formation of dibromides, they prepared diol **258** by hydroboration of divinylsilane **249** using 9-BBN and subsequent oxidation (Scheme 65).[109] Diol **258** was transformed into ditosylate **259**, which reacted easily with various primary amines to give the desired 1,4-azasilinanes **260**. The high yields observed for the formation of compounds such as **260** led the authors to propose this procedure as a new method for the protection of primary amines. Regeneration of the free amines was carried out by reaction of the 4-silapiperidines with a combination of tetrabutylammonium fluoride and cesium fluoride (1:1) in DMF or THF.

The preparation of a 1,3-diphospha-5-silacyclohexane **263** has been reported by the reaction of 1,3-diiodosilapropane **261** with tetraethyl methylenediphosphonate **262**. The trans stereochemistry of compound **263** was confirmed by X-ray structure analysis (Scheme 66).[110]

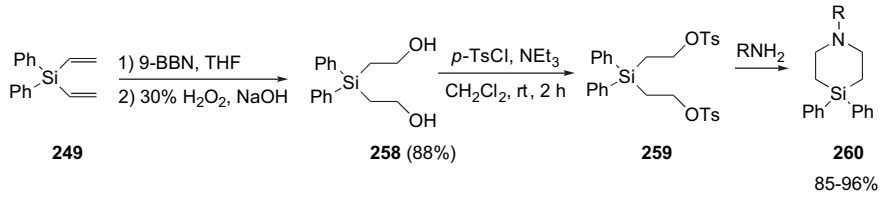
The methodology, which implies the electrophilic reaction of heteroatom-containing reagents with polymetallated silanes, was also examined. Nakayama's group used this method for the preparation of phosphasilatriptycene **265**. Its synthesis was realized as reported in Scheme 67, starting from tris(thienyl)silane **264**. Reaction of this latter silane with 3 equiv of butyllithium followed by the addition of triphenyl phosphite led to the triptycene **265** in low yield.[111] The reactions of this latter compound with *m*-chloroperbenzoic acid or 1,2-epithiocyclohexane gave easily the corresponding phosphine oxide and phosphine sulfide (79–97%).

More recently, Sawamura and co-workers also used this approach for the preparation of phosphasilinane **269**. Phenyltrivinylsilane **266** was converted into triol **267** through hydroboration followed by $H_2O_2$/NaOH oxidation. This triol was converted into the tri-iodide **268**. The reaction of the dilithium derivative with the complex $PhPH_2$–$BH_3$ led to phosphasilinane **269**. The transformation of this phosphine into bicyclic silaphosphine **271** was then accomplished via phosphonium salt **270**. Compound **271**, the structure of which was established by X-ray diffraction appeared to be stable to air at room temperature (Scheme 68).[112]

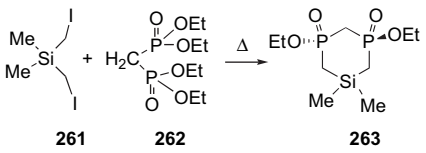
The strain of propellanes, by modification of the carbon atom hybridization, allows the formation of lithiated derivatives by reaction with butyllithium in the presence of TMEDA. This property was applied in the case of



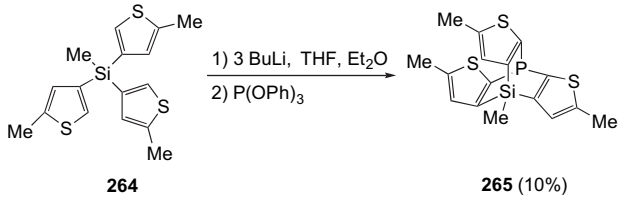
**Scheme 64**.



**Scheme 65**.



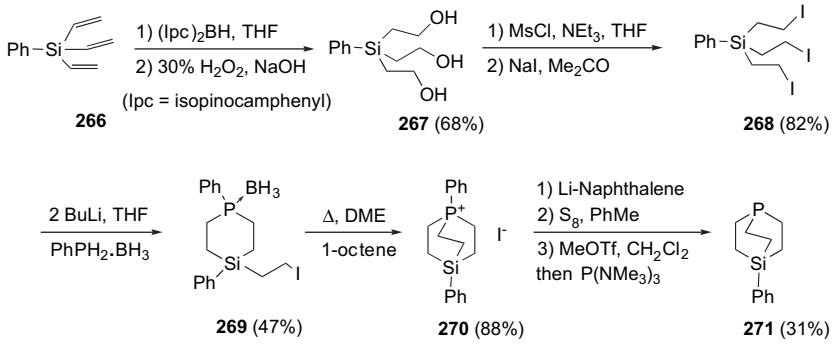
**Scheme 66**.



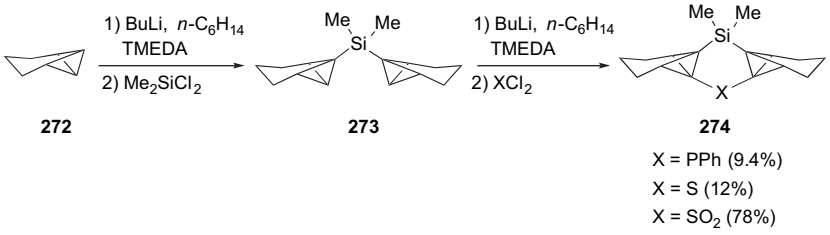
**Scheme 67**.

bis(tricyclo[4.1.0.0$^{2,7}$]heptanyl)silane **273**[113] to obtain the dilithiated derivative, which reacted with dichlorophosphorus or dichlorosulfur electrophiles to lead to the heterocyclic compounds **274** (Scheme 69).[114] Except in the case of $SO_2Cl_2$, the yields were low. Silane **273** was obtained by metallation of tricyclohexane **272** followed by the addition of dichlorodimethylsilane.

**4.2.2. Preparation by intramolecular cyclization of functionalized silanes.** Fessenden and Coon appear to be the first to have developed this method for the preparation of heterocyclic compounds with a silicon atom and another heteroatom. Hydrosilylation of allyl trimethylsilyl ethers **275a–c** with (chloromethyl)dimethylsilane using platinum over carbon as catalyst allowed the preparation of alcohols **276a–c** after hydrolysis of the trimethylsilyl ethers.[98] These



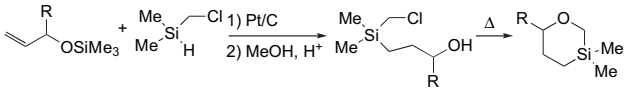
**Scheme 68**.




**272** **273** **274**

**Scheme 69**.

compounds led to the formation of oxacyclic compounds **277a–c** by simple heating (Scheme 70). Dedeyne and Anteunis have completed this work.[99] The cyclization of alcohols **276a**,**d** to **277a**,**d** was also found to be possible by reaction with $Na_2CO_3$.

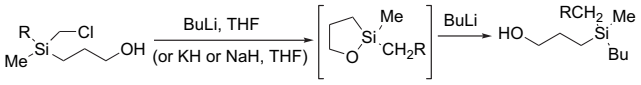



**275a:** R = Me
**275b:** R = Et
**275c:** R = Pr
**275d:** R = H

**276a-d** (80%) **277a-d** (46-57%)

**Scheme 70**.

Hudrlik and co-workers confirmed these results for the preparation of compound **277d** (R=H) (Scheme 70). They also showed that, when the alcohols **276d** and **278** were treated with BuLi or alkaline hydrides instead of sodium carbonate, a completely different reaction pathway occurred, leading mainly to alcohols **279** by transfer of a silicon atom substituent to the carbon atom bearing the halogen (Scheme 71).[115]




**276d:** R = Me
**278:** R = Ph, allyl, 2-furyl

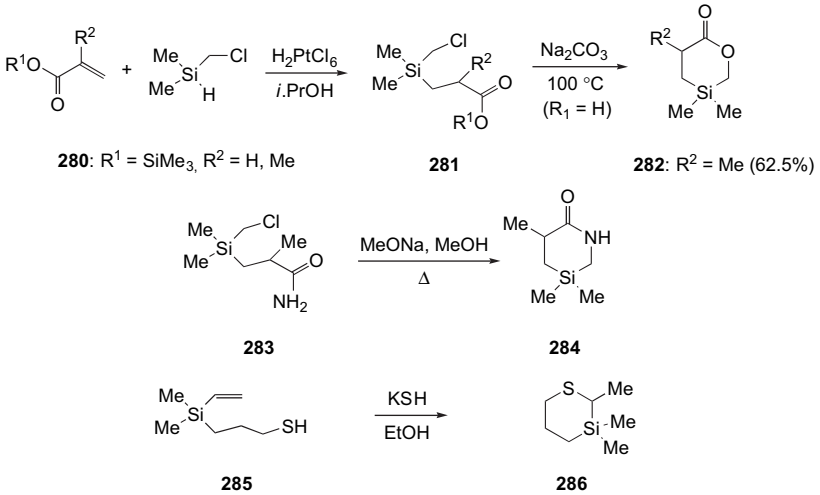
**279**

**Scheme 71**.

Subsequently, Mironov and co-workers applied this methodology to the preparation of 6-, 9-, and 14-membered silalactones. Substrates **281** necessary for the cyclization steps were prepared by hydrosilylation of α,β-ethylenic esters **280** by (chloromethyl)dimethylsilane using $H_2PtCl_6$ as catalyst (Scheme 72). Lactones **282** were obtained in good yields by reaction with anhydrous sodium carbonate. When the hydrosilylation was carried out with the unsubstituted acrylate **280** ($R^2$=H), the lactone **282** was obtained without isolation of the intermediate ester.[116] This lactone appeared unstable and gave a dimer upon standing at room temperature. It was reported, later, that these lactones could be obtained using a one-pot procedure if 20% aqueous sodium carbonate was added to the crude reaction mixture resulting from the hydrosilylation step.[117] Cross-linked silalactone polymers were prepared and tested for permeability to gases. One application could be the reduction of the $CO_2$ content of $CO_2$–$O_2$ mixtures.[118] Lactam **284** was obtained by reaction of amide **283** with sodium methylate.[116,119] The same group also reported the formation of thiasilinane **286** in medium yield by reaction of thiol **285** with KSH (Scheme 72).[40a] Formation of the seven-membered ring compounds was not observed using this method.

Recently, the preparation of lactam **289** was reported by reduction of azide **288**, obtained from **287**, with triphenylphosphine in the presence of water or by catalytic hydrogenation. The intermediate amine, which makes the intramolecular substitution, was not detected (Scheme 73).[120]

Kirpichenko and co-workers have reported an efficient preparation of 1,3-thiasilinane **238a** after saponification of




**280**: $R^1$ = $SiMe_3$, $R^2$ = H, Me

**281**

**282**: $R^2$ = Me (62.5%)

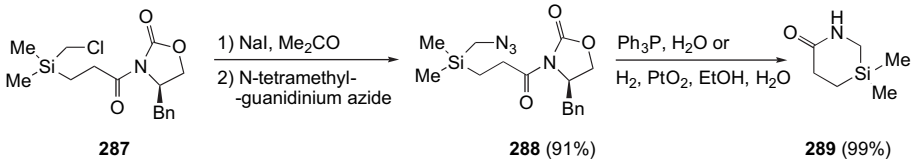
**283**

**284**

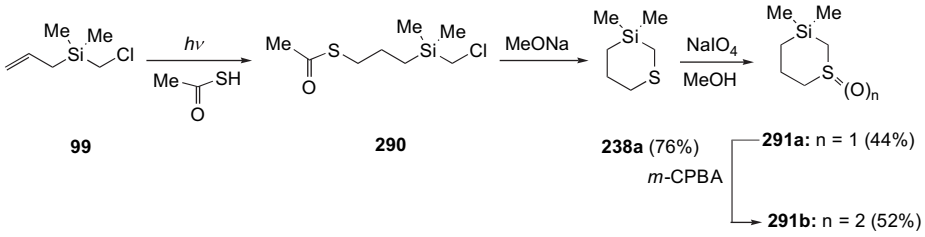
**285**

**286**

**Scheme 72**.



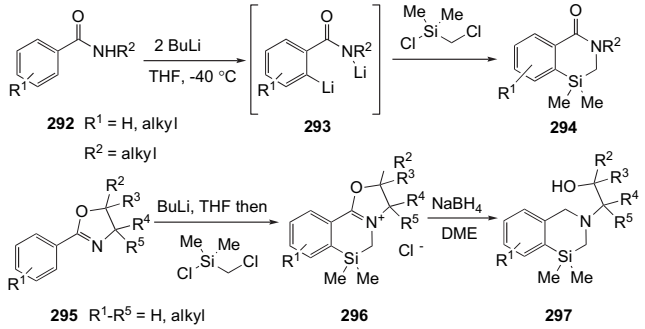

**Scheme 73**.




**Scheme 74**.

thioacetate **290**, obtained by radical 1,2-addition of thioacetic acid to allylsilane **99** (Scheme 74).[121] Selective oxidations of the sulfur atom allowed for the first time the preparation of sulfone **291a** and sulfoxide **291b**.

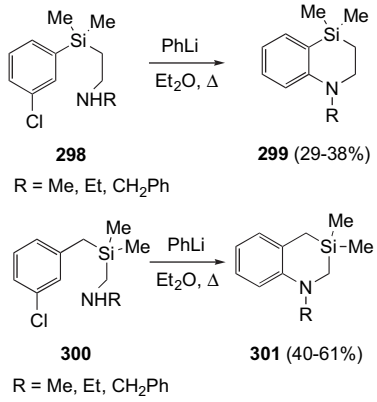
Barcza has reported interesting preparations of 1,3-benzoazasilinane derivatives using 1,4-dilithiated species. Reaction of *N*-alkylbenzamides **292** with 2 equiv of butyllithium led to the dilithiated intermediates **293**, which reacted with chloro(chloromethyl)dimethylsilane to give benzoazasilinanes **294** via chloromethylphenylsilane intermediates.[122] Using a similar methodology, tricyclic oxazolidinium compounds **296** were obtained after monolithiations of oxazolines **295** and their reduction led to 1,3-benzoazasilinanes **297** (Scheme 75).[123] These compounds possess sleep-inducing activities. Derivatives having neurotransmitter antagonist properties have subsequently been reported.[124]




**Scheme 75**.

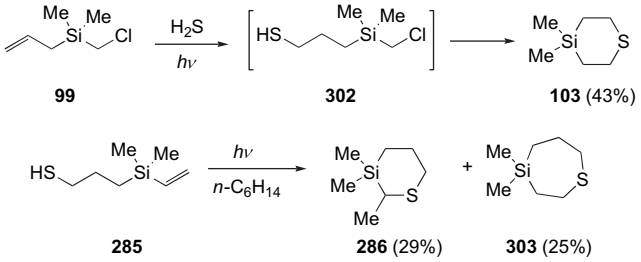
Sato and co-workers prepared 1,4- and 1,3-benzoazasilines **299** and **301** from **298** and **300** using the intramolecular reaction of benzyne moiety with lithium amide (Scheme 76).[125] This method was also studied for the preparation of azasilolines (Scheme 32).

Voronkov and co-workers have shown that 4-thiasilinane **103** could be obtained by a radical addition of $H_2S$ to allylsilane **99** via **302** (Scheme 77; see also Scheme 27).[40,41] Six-membered ring compounds could not be obtained during the




**Scheme 76**.

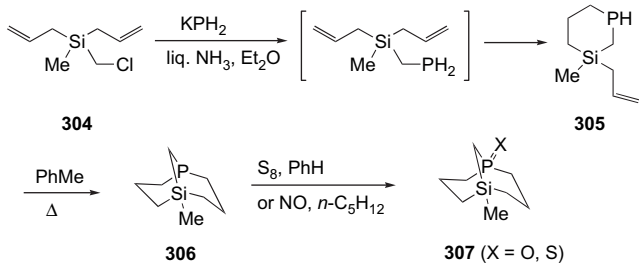
irradiation of 2-[allyl(dimethyl)silyl]ethanethiol. The *endo* cyclization leading to the seven-membered compound was observed (see Scheme 112). Starting from the 3-sila regioisomer **285**, the two heterocyclic compounds **286** and **302** were formed by, respectively, 6-*exo* and 7-*endo* cyclizations.[126]




**Scheme 77**.

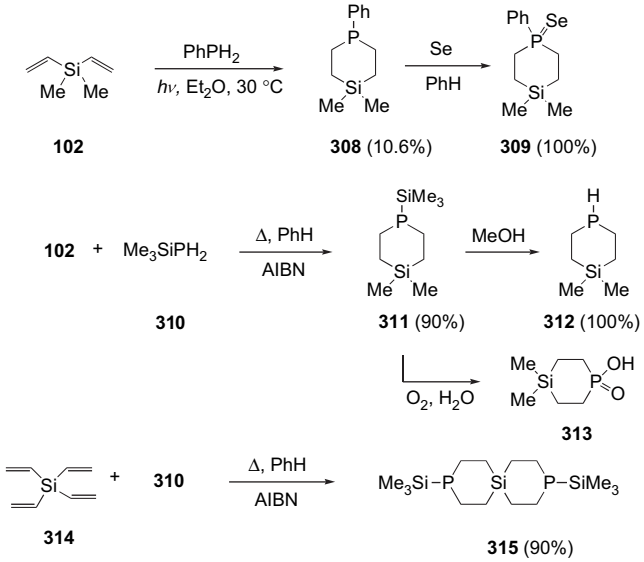
Radical additions of compounds containing P–H bonds are well-known reactions.[127] The first application of this reaction to unsaturated silanes, with the target to prepare cyclic compounds, was reported 20 years ago by Kuehne and coworkers, who examined the reaction of potassium dihydrogen phosphide with diallyl(chloromethyl)silane **304**.[128a] At

low temperature in liquid ammonia, only the monocyclic compound **305** was obtained. Heating of this latter compound in toluene at reflux gave rise to the formation of the bicyclic compound **306**. This compound reacted easily with sulfur, NO (Scheme 78), chlorodiethylphosphine, and methyl iodide to give $P^{(V)}$ derivatives **307**.[128]




**Scheme 78**.

Intermolecular addition of phenylphosphine to divinylsilane **102** led in low yield (11%) to phosphasilinane **308**. This compound was stabilized as selenophosphine **309**.[129] Norman's group obtained much better yields using trimethylsilylphosphine **310**.[130] In all these reactions, only small amounts (<10%) of the five-membered heterocycles were isolated. Release of the trimethylsilyl group from compound **311** was achieved in methanol to give the parent phosphasilinane **312**. Oxidation with oxygen of compound **311** led to the phosphinic acid derivative **313**. Spiro compound **315** was obtained in the same way starting from tetravinylsilane **314** (Scheme 79). Attempts to obtain higher-ring-size heterocycles using this method were not successful.[130]




**Scheme 79**.

Electrophilic cyclizations have been explored for the preparation of azasilinanes and silaborinanes. The first study using this method was reported by Barluenga and co-workers for the preparation of silapiperidines.[131] During this study, concerning the aminomercuration of unsaturated compounds, the reactivity of allylsilanes was examined. The reaction of arylamines with allyltrimethylsilane **316** led to the formation of the 2-aminoalkylsilanes **317** after reductive demercuration (Scheme 80). In the case of diallylsilane **318**, monomercuration products were formed, which, after reduction, allowed the preparation of the unsaturated amines **319**. A second aminomercuration followed by a reduction led to azasilinanes **320** in modest yields. Kirpichenko and co-workers confirmed this difficult formation of six-membered heterocyclic compounds, compared to the five-membered products (Scheme 29).[43] Vinylsilane **321** gave mainly, as expected, 1,3-azasilepane **323** and 1,3-azasilinane **322** in lower yield (Scheme 80). A very low yield (3%) for the ring closure of dimethyl(2-phenylaminoethyl)vinylsilane to 4-silapiperidine was reported. Allylsilane **324** gave 1,4-azasilinane **325** in moderate yield. [43]

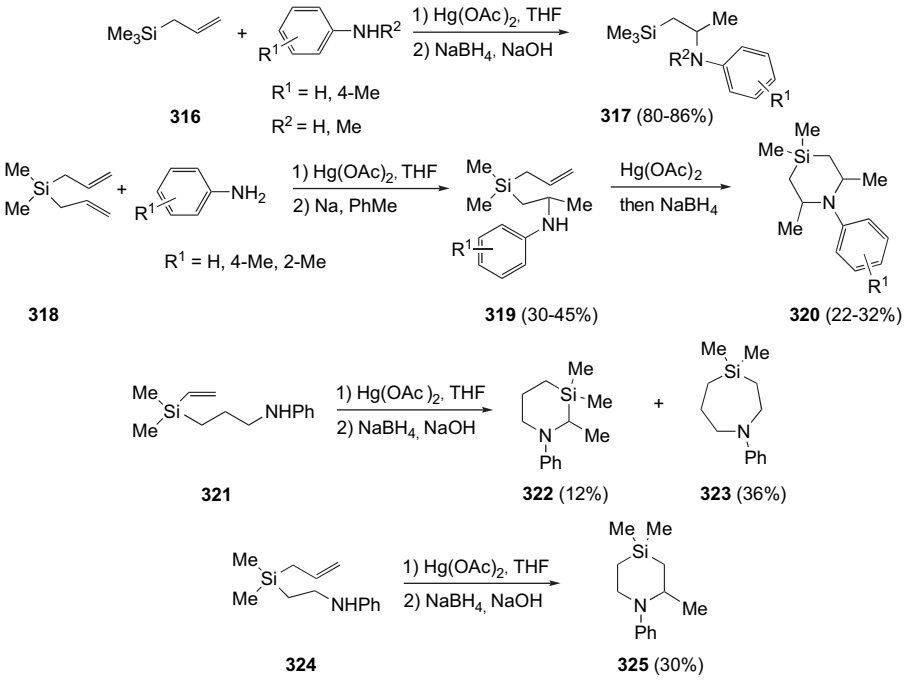
Hawthorne has studied the reaction of *tert*-butylborane with 1,3- and 1,4-dienes. The preparation of 1,4-silaborinanes by the reaction of divinylsilane **102** with boranes has been reported. Boronheterocyclic compound **326** was obtained in good yield using an amine–borane complex (Scheme 81).[132] Soderquist and co-workers showed that the formation of 1,4-silaborinanes such as compound **327** was very efficient if the reaction was carried out in two steps. The first reaction implied the addition of 9-borabicyclo[3.3.1]nonane (9-BBN) to divinylsilane **102**, and the second step an exchange using the borane–dimethyl sulfide complex. These steps could be carried out in a one-pot reaction. Transformation of silaborinane **327** into silacyclohexanone **328** was also reported, and this constitutes a convenient preparation of this compound.[133]

Bioreduction of silyl ketone **329** using the yeast *Trigonopsis variabilis* led to the formation of a 1:1 mixture of the diastereomers **330** in high enantiomeric excesses. After separation, each diastereomer **335** was transformed into the acetonide **331** by hydrogenolysis of the benzyl group followed by reaction with acetone dimethyl acetal (Scheme 82).[134] This enantioselective bioreduction of chiral silaketones constitutes a good method to prepare optically active compounds with a silicon stereogenic center.

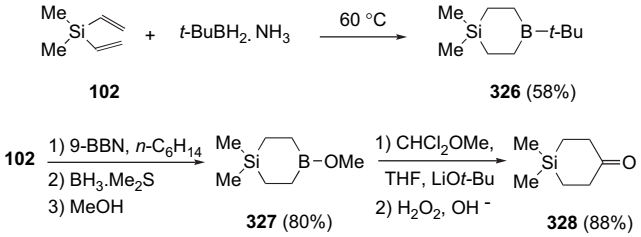
Sieburth and Kim reported the formation of 1,3-azasilinane **333** during the oxidation of alcohol **332** with a benzyloxycarbonylaminomethylsilyl group. When the nitrogen atom was protected as phthalimide, such a cyclization was prevented (Scheme 83).[135]

Linderman and Chen have studied the intermolecular allylation reaction of mixed 1-(allylsilyl)alkyl acetals, e.g., allylsilanes **334** reacted in the presence of Lewis acids to lead, after basic treatment, to silanols **335.** If two methyl groups were fixed on the terminal carbon of the double bond (compound **336**), this reaction was not observed and the oxasilinone **337** resulting from a diastereoselective cyclization was isolated in good yield (Scheme 84).[136]

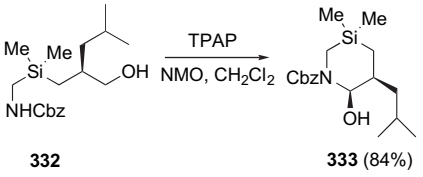
It has been mentioned earlier in this report that the pyrolysis of phenyl tris(trimethylsilyl)methyl borinates led to the formation of silaborolanes (Scheme 19). Flash vacuum pyrolysis of an analogous benzyl borinate **338** led to the formation of 1,3-silaborinane **340**, via the methylene borane intermediate **339** (Scheme 85).[31]




**Scheme 80**.




**Scheme 81**.

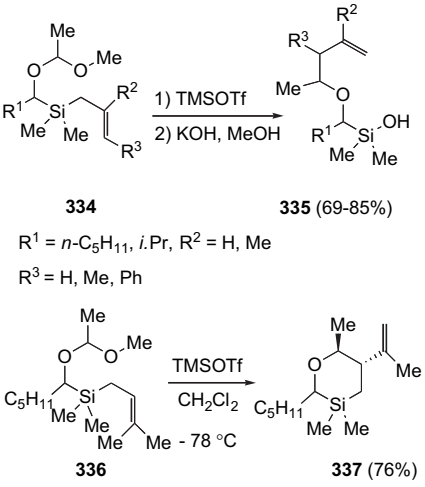



**Scheme 83**.

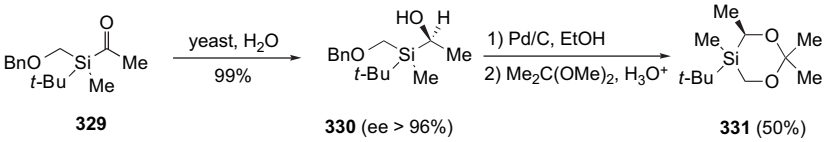
Intramolecular trapping of 2-(dimethylaminomethyl)-phenylsilene **342** formed by flash vacuum pyrolysis of (1-trimethylsilylalkyl)methoxysilane **341** was reported to give 1,3-azasilinane **343** (Scheme 86).[137] Thermolysis in a sealed tube at 350 °C led to the formation of the desilylated product **344**.

## 4.3. Preparation by formation of carbon–carbon bonds

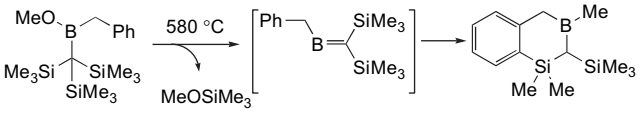
Coelho and Blanco have studied the intramolecular Diels–Alder reaction of various chiral silatrienic compounds. Heating at 110–140 °C of amides **345** gave the bicyclic compounds **347** as a mixture of diastereoisomers (Scheme 87).[138,139] The oxabicyclo[2.2.2]octenone intermediate **346** (R=Cy) could be isolated if the Diels–Alder reaction was carried out at 80 °C.[139] This cycloaddition was not observed starting from the corresponding ester. Diels–Alder cycloadditions also occurred when the diene was fixed on the




**Scheme 84**.

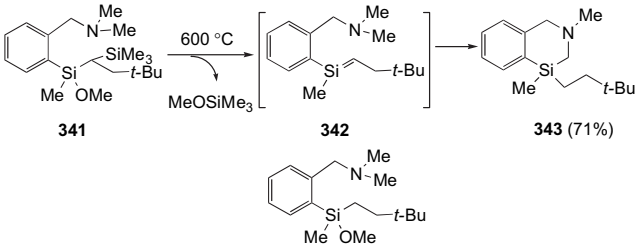



**Scheme 82**.




**338** **339** **340** (92%)

**Scheme 85**.




**341** **342** **343** (71%) **344**

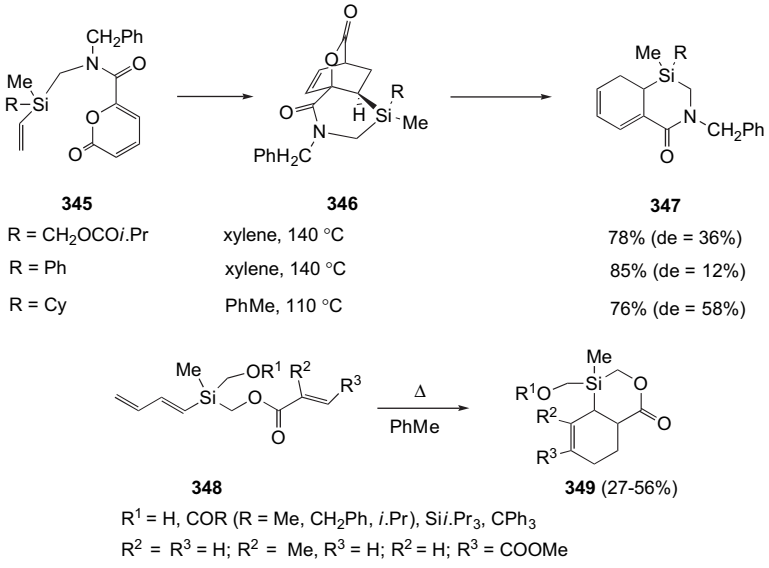
**Scheme 86**.

silicon atom. Heating of dienes **348** at 140–220 °C led to the desired products **349** in low to medium yields (Scheme 87).[140] In the case of acyloxymethylsilanes **348**, ($R_1$=acyl), these cycloadditions could be carried out in the presence of $EtAlCl_2$ in dichloromethane at room temperature. Mixtures of four diastereomers were generally obtained. When the two substituents fixed on silicon were methyl and 2-methoxyphenyl groups, a high diastereoselectivity was obtained in the acid-catalyzed reaction (90% of one diastereomer).[141] A comparable strategy was applied to the formation of seven-membered heterocycles (Scheme 116).

1,3-Oxasilinane **351** has been prepared from compound **350** by an intramolecular Diels–Alder reaction of benzyne with furan (Scheme 88).[142] This compound **351** was then transformed into the C-glycoside **352**, to test its antibiotic activity. This methodology was applied with the same efficiency for obtaining a 1,4-oxasilepane derivative (Scheme 117).

Taddei's group have reported a preparation of carbacephams in which one carbon atom of the six-membered ring was replaced by silicon.[143] [2+2] Cycloaddition of allylsilane **99** with an isocyanate led to the β-lactam **353**, which was *N*-alkylated to compound **354**. Cyclization of the corresponding iodide via an ester enolate led to the desired silacepham **355** (Scheme 89). The corresponding acid did not show any particular biological activity.

Fuchs and van Dort have studied a new method for the desulfonylation of alkyl sulfones **356**, bearing a bromomethylsilylphenyl group, induced by radical reactions to form **357** and **358** (Scheme 90).[144] When a vinyl substituent was present on the silicon atom of the sulfone (compound **359**), the radical




**345** **346** **347**

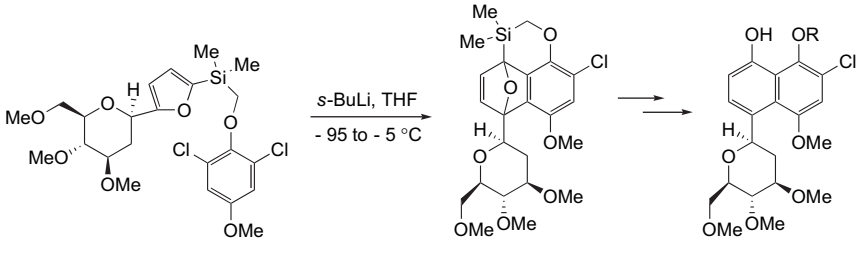
| | | |
|---|---|---|
| R = $CH_2OCOi$.Pr | xylene, 140 °C | 78% (de = 36%) |
| R = Ph | xylene, 140 °C | 85% (de = 12%) |
| R = Cy | PhMe, 110 °C | 76% (de = 58%) |

**348** **349** (27-56%)

$R^1$ = H, COR (R = Me, $CH_2Ph$, *i*.Pr), Si*i*.$Pr_3$, $CPh_3$

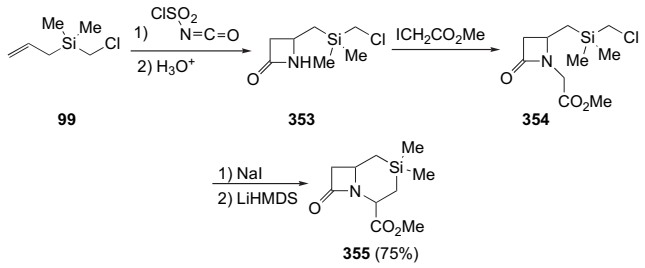
$R^2$ = $R^3$ = H; $R^2$ = Me, $R^3$ = H; $R^2$ = H; $R^3$ = COOMe

**Scheme 87**.



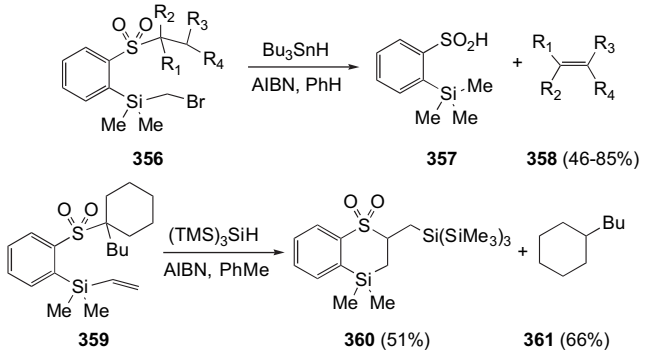

**350** **351** (68%) **352**

**Scheme 88**.

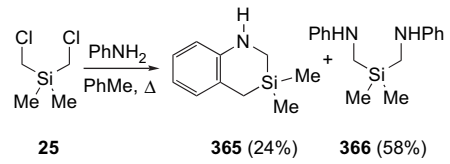


**Scheme 89**.

formed attacked the sulfur atom and induced the formation of benzothiasilinane **360** and butylcyclohexane **361**. It has recently been reported that this family of compounds and the corresponding benzooxasilinanes could be ligands of retinoid receptors and thus useful in numerous therapies.[145]



**Scheme 90**.



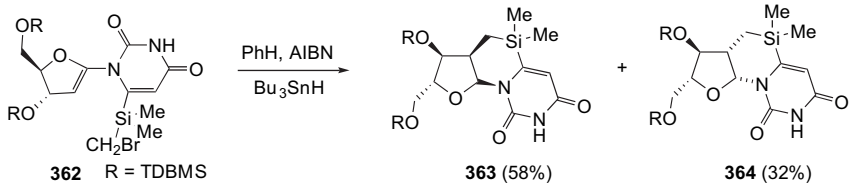
**Scheme 92**.

Tanaka and co-workers have studied the radical cyclization of nucleoside 2-sila-5-hexenyl radicals. They observed the formation of 1,3-azasilinanes **363** and **364**, formed by 6-*endo* cyclizations, by reaction of nucleoside **362** with tributyltin hydride in the presence of AIBN (Scheme 91; see also Scheme 37).[57]

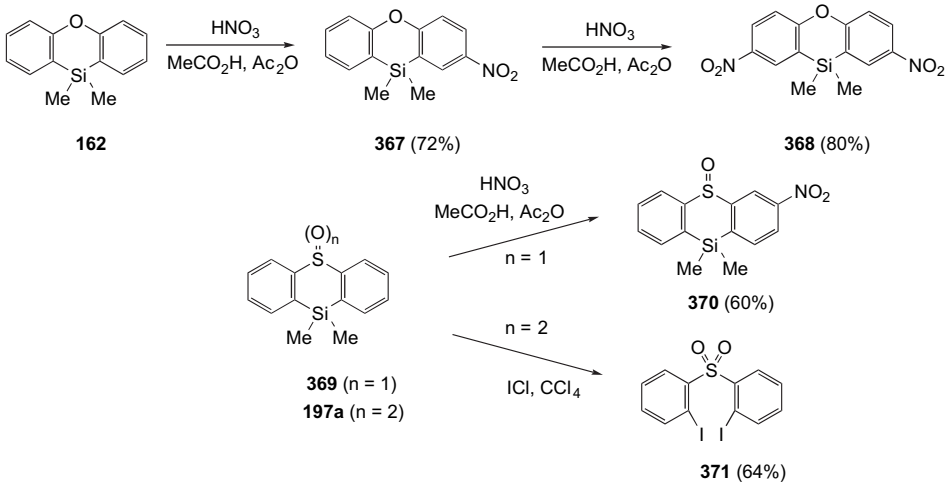
Hwu and King have obtained a mixture of 1,3-azasilinane **365** and 1,1-dimethyl-*N*,*N*′-diphenylsilanediamine **366** after the heating of (dichloromethyl)dimethylsilane **25** with an excess of aniline (Scheme 92).[146]

### 4.4. Reactivity and applications

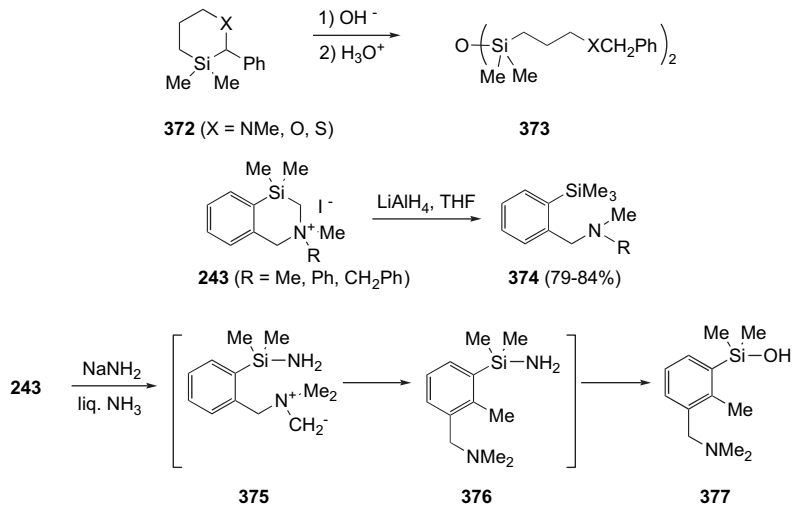
Six-membered silaheterocyclic compounds appear to be stable in numerous reaction conditions; e.g., dibenzooxasilinanes were reported to be stable in concentrated $HNO_3$ and hot acetic anhydride.[59] This stability allowed the mono- (**367**) and dinitration (**368**) of the aromatic rings of phenoxasilinine **162**. This nitration is also possible with thiasilinane **369** to **370** (Scheme 93).[147] Cleavage of the central thiasilinane core of **197a** by ICl has, however, been reported



**Scheme 91**.



**Scheme 93**.

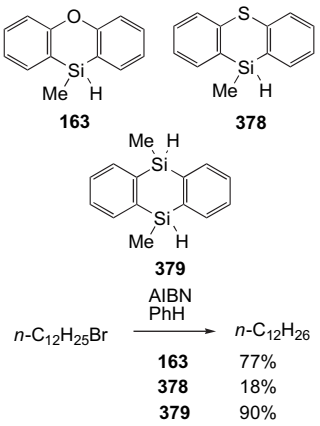



**Scheme 94**.

to occur with the formation of 1-(2-iodophenylsulfonyl)-2-iodobenzene **371**.[83] Cleavage was also observed in the reaction of 10,10-diphenyl-10*H*-phenoxasilin **160a** with lithium in dioxane, which gave, after hydrolysis, 2-hydroxyphenyltriphenylsilane.[82]

Alkaline hydrolytic cleavage of 1,3-heterosilinanes **372** to give **373** has been reported. These particular results seem to be due to stabilization by the phenyl group of the intermediate α-cabanion, formed after the Si–C bond cleavage (Scheme 94).[91] Reaction of azasilinium iodides **243** with $LiAlH_4$ led to benzylamines **374**, corresponding to cleavage of the $SiCH_2$–$N^+$ bonds.[100] In the presence of sodium amide in liquid ammonia, silanol **377** was obtained. This compound was obtained after a Sommelet–Hauser rearrangement of intermediate ylide **375**→**376**, formed by cleavage of the Si–$CH_2N^+$ bond.[148]

10-Methylphenoxasiline **163** and 10-methylphenothiasiline **378** were examined as reducing agents in the dehalogenation of organic halides (Scheme 95). These compounds appeared less efficient than 5,10-dimethylsilaanthrene **379**.[66]

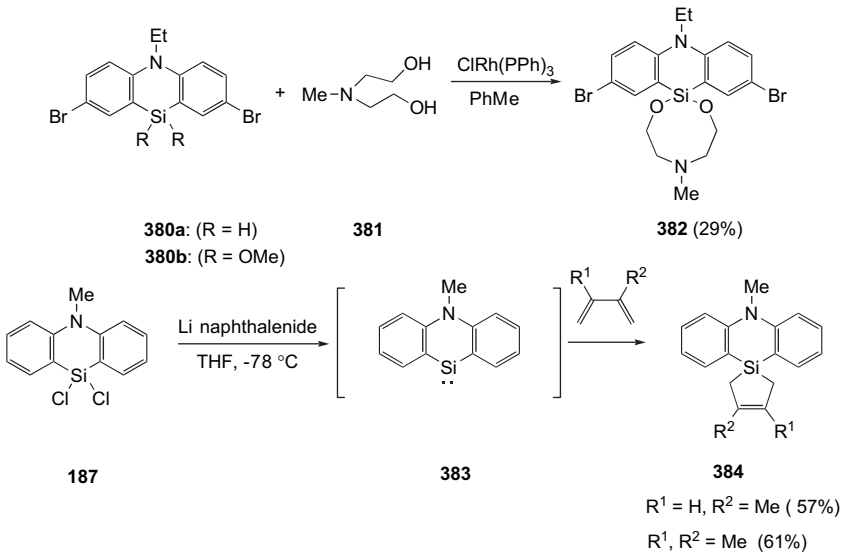



**Scheme 95**.

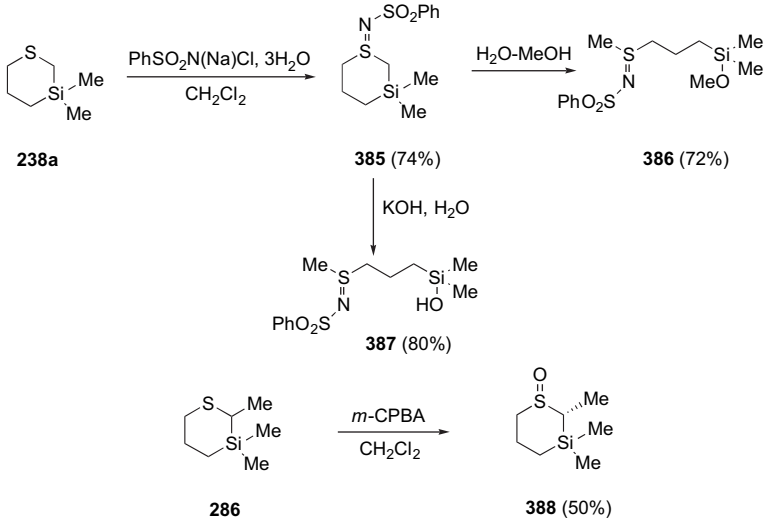
Spiro compound **382** was obtained by the reaction of dihydrophenazasiline **380a** with diol **381** in the presence of a Wilkinson catalyst (Scheme 96).[149] This compound was also prepared starting from the 10,10-dimethoxysilane **380b** (64%). Silylene **383** has been generated by the reaction of dichlorophenazasiline **187** with lithium naphthalenide at −78 °C. This unstable species was trapped by 1,3-butadiene derivatives and gave spiranic compounds **384** (Scheme 96).[78]

Shainyan and Kirpichenko have studied the reactivity of 1,3-thiasilinanes. Oxidation of 3,3-dimethyl-1,3-thiasilinane **238a** with *m*-chloroperbenzoic acid led to the formation of the sulfoxide or sulfone, depending upon the amount of reagent used (Scheme 74).[121] Similar results were obtained using $NaIO_4$ as oxidant.[58] Reaction with chloramine T under phase-transfer conditions gave the corresponding sulfimide **385**.[58,150] Ring opening by Si–C bond cleavage of this compound was observed in aqueous methanol to form **386** or in the presence of potassium hydroxide to give **387** (Scheme 97).[58] Addition of methyl iodide to compound **238a** led to a sulfonium salt, which was also opened in the presence of water.[58] When a substituent was located on the carbon atom between silicon and sulfur (compound **286**), oxidation using *m*-chloroperbenzoic acid led to a diastereoselective reaction to form **388** (Scheme 97).[151]

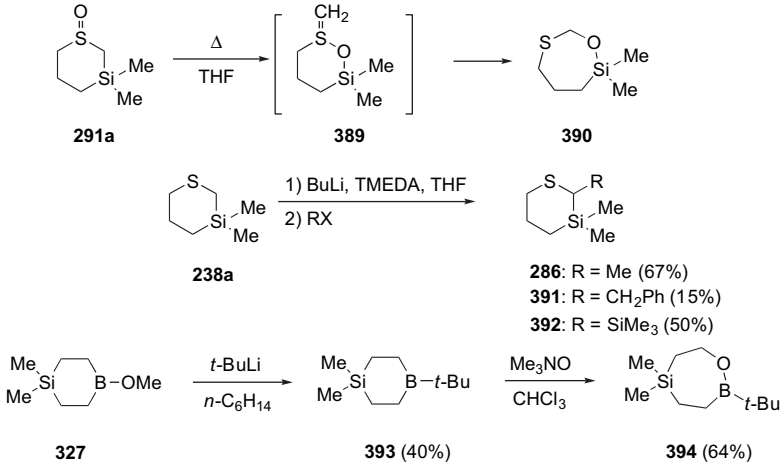
By heating in THF, sulfoxide **291a** undergoes a sila-Pummerer rearrangement, leading to the formation of the seven-membered compound **390** (Scheme 98).[152] This transformation was explained by the formation of intermediate **389**, which underwent a rearrangement with ring enlargement. This hypothesis was confirmed by a computational study.[153] Regioselective monoalkylations were observed by treatment of the carbanions of thiasilinane **238a** with alkyl and silyl halides to form compounds **286**, **391**, and **392** (Scheme 98).[154] 1,4-Silaborinane **393**, obtained by reaction of 1,4-silaborinane **327** with *tert*-butyllithium, reacted with 1 equiv of trimethylamine *N*-oxide at 0 °C to give the enlarged oxidation product **394** (Scheme 98).[155]




**Scheme 96**.



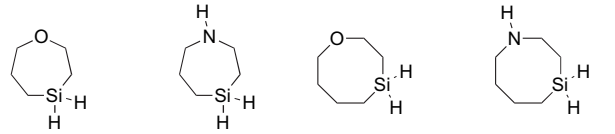

**Scheme 97**.




**Scheme 98**.

## 5. Preparation of seven-membered and higher heterocyclic compounds

Methods for the formation by ring closure of heterocyclic compounds with higher than six-membered rings are, in general, limited, compared to the methods known for the formation of five- and six-membered ring compounds.[156,157] This difference seems less obvious in the case of silaheterocyclic compounds. Methods used for the formation of normal cycles have often been used with success to form higher ring-sized compounds. This result seems to be due to the presence of a dialkylsilyl group instead of a methylene, which favors the cyclization process, probably by an influence of the *gem*-dialkyl effect. In Scheme 99, representative IUPAC names and structures for these ring-size compounds have been summarized.



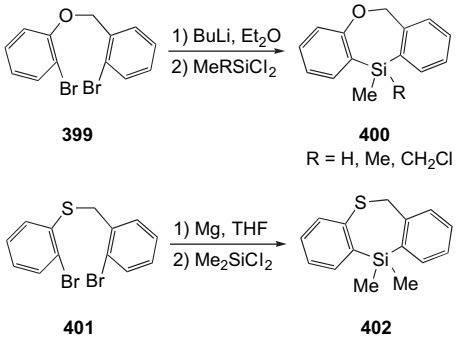
**1,4-oxasilepane** **1,4-azasilepane** **1,4-oxasilocane** **1,4-azasilocane**

**Scheme 99**.

### 5.1. Preparation by formation of carbon–silicon bonds

**5.1.1. Formation by reaction of dihalosilanes with dianionic species.** Different groups have reported the preparation of silaporphyrin analogues. Kauffmann and Kniese showed that the reaction of dithienylsilane **395** in THF at 0 °C with 2 equiv of butyllithium followed by the addition of dichlorodimethylsilane led to the formation of the cyclic compounds **396** and **397** in low yields (Scheme 100).[158] Utilization of LDA at −20 °C led to the same products, with, however, a noticeable increase in the yield of the larger compound **397**.[159] Similar results were reported starting from thiophene **398** (X=S) using a mixture butyllithium–potassium *tert*-butoxide–TMEDA at low temperature.[160] This last method was also shown to be efficient in the case of furan and *N*-methyl-pyrrole (Scheme 100).[160] Electrochemical reaction of 2,5-dibromo-1-methyl pyrrole in the presence of dichlorodimethylsilane gave rise to the formation of compound **396** (X=NMe) in a slightly better yield (22%).[161]

The Gilman–Hithcock method (Scheme 43) was investigated for the preparation of oxasilepines starting from the dibromo ether **399**. The chemoselectivity of the condensation reactions appeared to be low and the heterocyclic compounds **400** could not be fully characterized (Scheme 101).[61,162] The formation of thiasilepin **402** was successful from the dibromo precursor **401**, by reaction with magnesium and quenching of the organodimetallic intermediate with dichlorodimethylsilane. No product could be obtained when the reaction was carried out using butyllithium, but the thiasilepin was obtained in low yield from the dilithiated intermediate when chlorodimethylsilane was used as electrophile.[82] Surprisingly, the preparation of azasilepanes was reported to be unsuccessful using analogous dilithio or dimagnesio intermediates.[162]

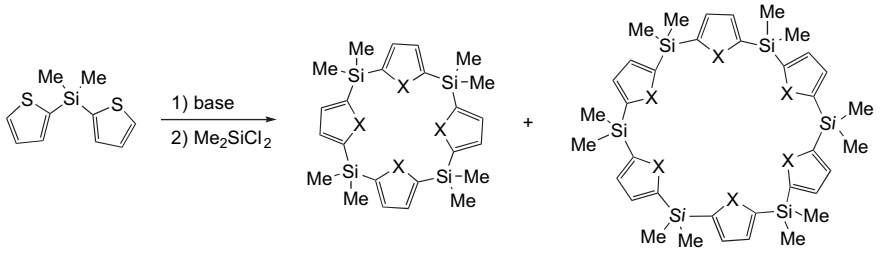



**399** **400**

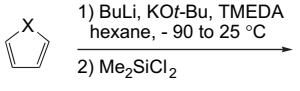
**401** **402**

**Scheme 101**.

This method was also found to be convenient for the preparation of azasilocanes. Azasilocane **404a** was obtained in low yield by the reaction of the dibromo compound **403**



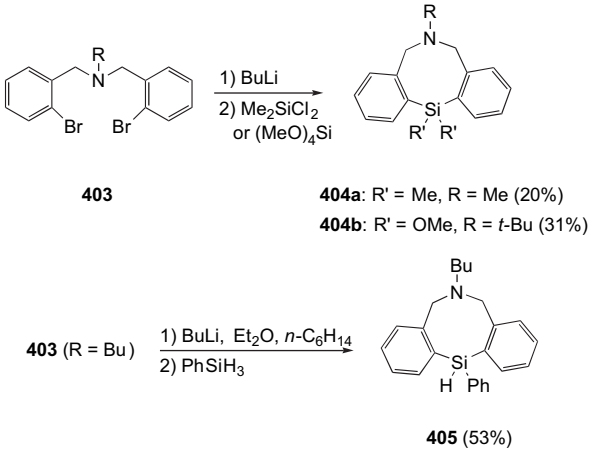

| **395** | | **396** (X = S) | **397** (X = S) |
|---|---|---|---|
| | BuLi | 16% | 2% |
| | LDA | 17% | 15% |




| **398** | | **396** | | **397** |
|---|---|---|---|---|
| X = S, O, NMe | X = S | 18% | | 17% |
| | X = O | 16% | | 10% |
| | X = NMe | 12% | | - |

**Scheme 100**.

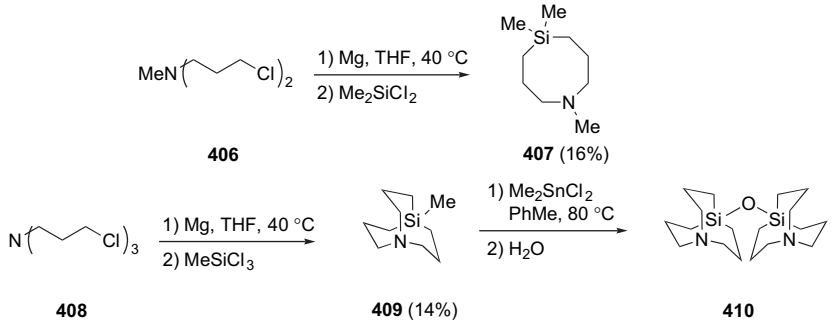
(R=Me) with butyllithium followed by the addition of dichlorodimethylsilane (Scheme 102).[163] The same approach was used for the preparation of compound **404b** using tetramethoxysilane as quenching agent of the dilithio intermediate.[164] More recently, the preparation of hydrosilane **405**, obtaining a mixture of two diastereomers, was reported using phenylsilane as quenching agent. The two isomers differed in that the Si–H bonds were apical or equatorial. The X-ray structure of the major apical isomer was published.[165]



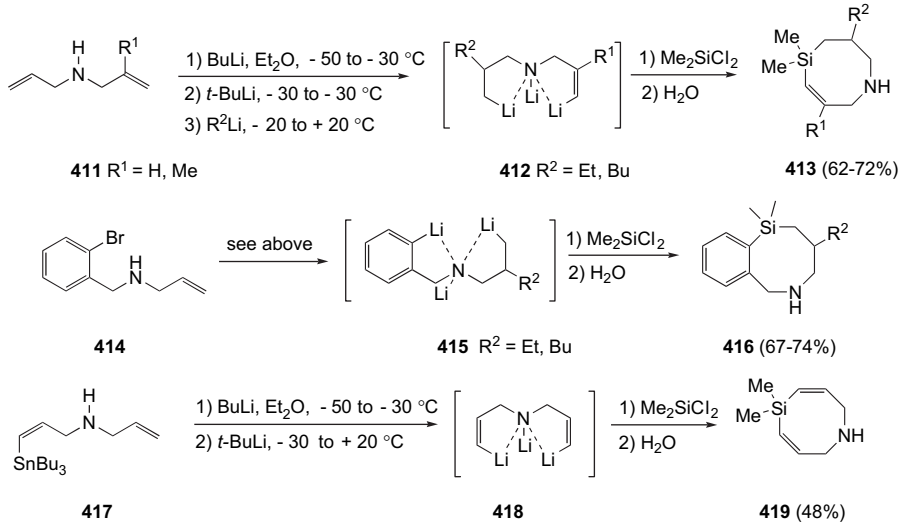

**Scheme 102**.

Tzschach and co-workers, with a view to examining the possible formation of a pentacoordinated silicon atom, have prepared 1,5-azasilocanes. Reaction of the bi- and trifunctionalized Grignard reagents, synthesized from the corresponding chlorides **406** and **408**, with, respectively, di- and trichlorosilanes led to 1,4-azasilocanes **407** and **409** in low yields. No shortening of the Si···N distance was observed according to the X-ray structure of compound **409** (Scheme 103).[166] Interestingly, treatment of the bicycloalkyl compound **409** with $Me_2SnCl_2$ allowed the selective cleavage of the Si–$CH_3$ bond to form **410**. Further studies undertaken by another group show that the pentacoordination of the silicon atom is possible when fluorine atoms are fixed on it.[164]

Barluenga and co-workers have studied the lithiation of allylamines and the formation of 1,4,7-trianionic intermediates was postulated. Reaction of these latter intermediates with dichlorosilane led to the formation of various azasilocanes, e.g., trilithiated intermediates **412** were obtained by the reaction of diallylamines **411** with butyllithium to substitute the proton of the amine, addition of *tert*-butyllithium to exchange one of the olefinic hydrogens and addition of alkyllithium to the second carbon–carbon double bond (Scheme 104).[167] When the trilithiated intermediates **412** were quenched by the addition of dichlorodimethylsilane, diazasilocanes **413** were obtained in good yields. This



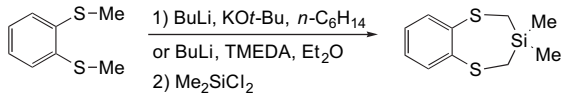

**Scheme 103**.




**Scheme 104**.

sequence was also carried in the case of amine **414** to give, via **415**, the benzoazasilocanes **416**. The preparation of the azasilocadiene **419** was reported starting from tin-substituted amine **417** via the trilithiated intermediate **418** (Scheme 104).[167]

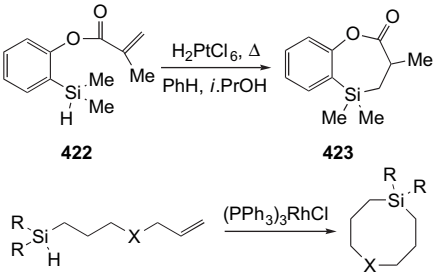
Cabiddu et al. during their study concerning the metallation of sulfur derivatives[22,23,90] examined the behavior of the bis(methylthio)benzene ether **420**. Benzodithiasilepin **421** was obtained in moderate yield after the addition of dichlorodimethylsilane to the corresponding dianion (Scheme 105).[168]




**420** **421** (53%)

**Scheme 105**.

**5.1.2. Preparation by formation of a carbon–silicon atom bond.** In the preceding sections, the formation of four- and five-membered ring compounds by intramolecular hydrosilylation was reported to occur in satisfactory yields, while the formation of six-membered ring compounds seems difficult. The first report concerning the preparation of seven-membered ring compounds using this method was by Mironov and co-workers. With the α,β-ethylenic ester **422**, intramolecular addition of the Si–H bond catalyzed by $H_2PtCl_6$ gave the benzoxasilepane derivative **423**.[169] Voronkov's group used the Wilkinson catalyst to obtain eight-membered ring compounds **425** when sulfur,[16b] oxygen,[170] and nitrogen[171] atoms were present in the silaoctene chain **424** to cyclize (Scheme 106).




**422** **423**

**424a**: R = Et, X = S **425a** (46%)

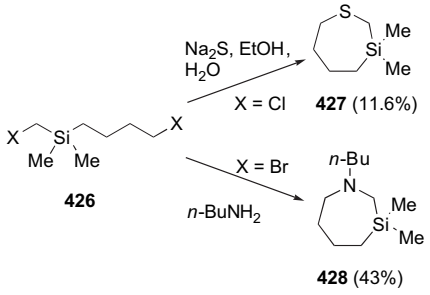
**424b**: R = Me, X = O **425b** (84%)

**424c**: R = Me, X = NMe **425c** (11%)

**Scheme 106**.

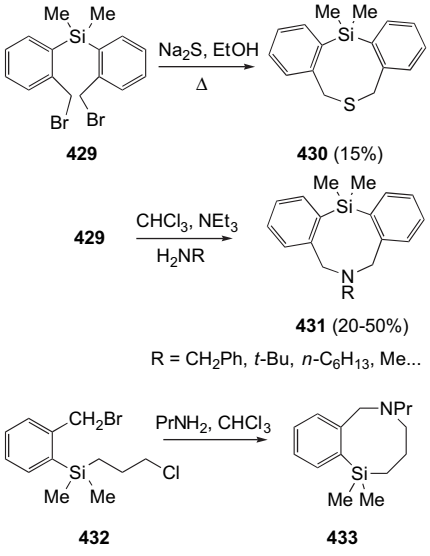
## 5.2. Preparation by formation of carbon–heteroatom bonds

**5.2.1. Preparation by reaction of functionalized silanes with heteroatom-containing reagents.** Fessenden, after his report concerning the preparation of 3-sila-1-heterocyclohexanes from 1,5-dihalosilapentane derivatives, applied this method to the synthesis of 3-sila-1-heterocycloheptanes.[172] Reactions of 4-halobutyl(halomethyl)-dimethylsilanes **426** with $Na_2S$ and butylamine led to the seven-membered heterocyclic compounds **427** and **428**, respectively (Scheme 107).



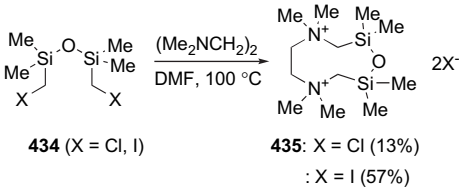

**Scheme 107**.

Heterosilocanes could also be prepared starting from mono or bis(*o*-bromomethylphenyl)silanes, e.g., dibenzothiasilocane **430** was obtained in low yield by reaction of the dibrominated silane **429** with sodium sulfide (Scheme 108).[84] Reaction of this silane **429** with primary amines led similarly to azasilocanes **431**.[162,173] This method was used by the Lukevic group to access benzocyclooctane **433** starting from 3-chloropropylsilane **432** bearing a 2-(bromomethyl)-phenyl substituent.[174]




**Scheme 108**.

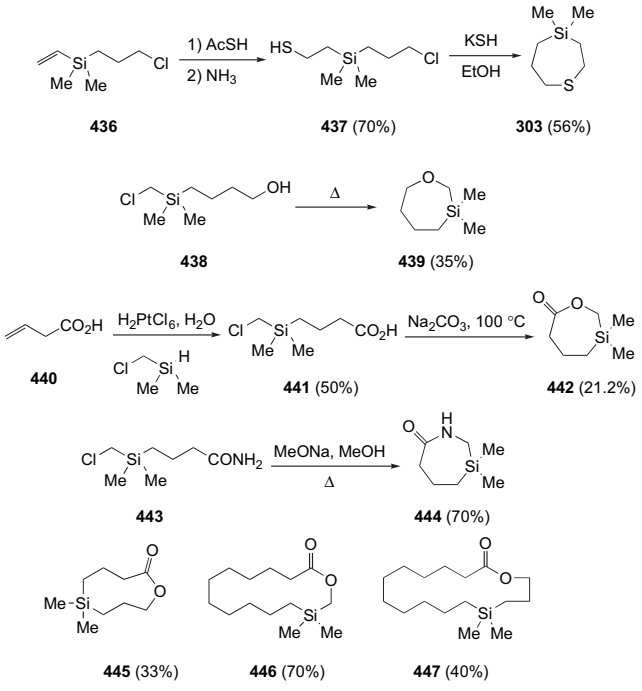
Formation of oxadiazadisilonanes **435** was reported by the reactions of a diamine with bis(halomethylsilyl) ethers **434**. The yield of this cyclization is remarkable for such a ring size, starting from the diiodinated substrate (Scheme 109).[175]




**434** (X = Cl, I) **435**: X = Cl (13%)
: X = I (57%)

**Scheme 109**.

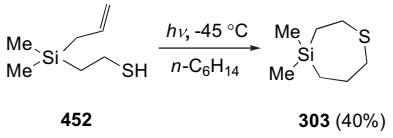
**5.2.2. Preparation by intramolecular cyclization of functionalized silanes.** The formation of 5- and 6-ring-sized 1,3-thiasilacycloalkanic compounds has been reported using intramolecular cyclizations of ω-halosilathiols.[40a] Voronkov and co-workers have subsequently reported that the procedure developed by Dedeyne[99] could be applied to the formation of seven-membered ring compounds (Scheme 110).[176] E.g., chlorothiol **437**, obtained by radical addition of thioacetic acid to vinylsilane **436** and subsequent treatment with ammonia, underwent an intramolecular cyclization to **303** when treated with KSH. These conditions could not, however, be applied to the formation of eight-membered ring compounds.[40a] 1-Oxa-3-silacycloheptane **439** was obtained, as in the case of six-membered compounds, by simple heating of alcohol **438**.[172] Mironov's group applied the Fessenden method to the preparation of different lactones and lactams (see Scheme 72). Similarly, the reaction of acid **441** and amide **443** with, respectively, sodium carbonate and sodium methylate led to the desired seven-membered compounds **442** and **444** (Scheme 110).[116,119] The medium-ring lactone **445** and large-ring lactones **446**, **447** were also obtained in satisfactory yields using this method.[177] The acids necessary for these cyclizations, such as acid **441**, were obtained by hydrosilylation of the carbon–carbon double bond of unsaturated acid **440** using (chloromethyl)dimethylsilane in the presence of chloroplatinic acid as catalyst. A one-pot procedure leads to improved results.[117]




**Scheme 110**.

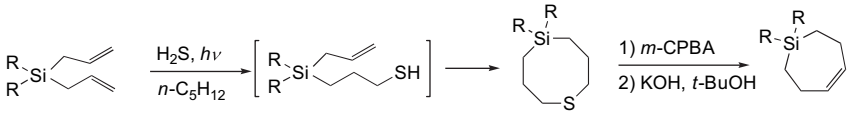
Weber et al. were the first to report that photochemically induced cyclization of unsaturated silathiols led to the formation of 1,5-thiasilocanes.[178] This reaction was subsequently developed mainly for the formation of five-membered ring silaheterocyclic compounds.[40,41,126] Irradiation of a mixture of diallylsilanes **448a**,**b** and $H_2S$ in pentane at low temperature led to the formation of thiasilocanes **450a**,**b**, without any formation of the six- or seven-membered ring compounds. Similar results were reported with silanes **448c**,**d**, to form **450c**,**d**[179] or when the irradiation was carried out in the presence of the photocatalyst $YCl_3$.[180] The intermediate formation of the unsaturated thiols **449a–d** was confirmed by the fact that irradiation of compound **449a** led to thiasilocane **450a** with the same yield. Compounds **450a**,**b** were transformed into silacycloheptenes **451a**,**b** by a Ramberg–Backland reaction with the corresponding sulfones (Scheme 111).[178]

Kirpichenko et al., with the aim of studying the regioselectivity of these photocyclizations, compared the behavior of 4,4-dimethyl-4-silahex-5-ene-1-thiol **285** with that of 3,3-dimethyl-3-silahex-5-ene-1-thiol **452**. With vinylsilane **285**, a mixture of products, corresponding to the competition between the *endo* and *exo*-mode cyclizations, was observed (Scheme 77)[126] while, with the allylsilane **452**, only the seven-membered heterocyclic compound **303** was obtained (Scheme 112).[126,176]




**Scheme 112**.

The aminomercuration of 3-chloropropylsilanes bearing a vinyl or an allyl group in the presence of aniline was reported to lead mainly to the uncyclized 2-aminoalkylsilanes. From allylsilane **453**, an azasilepane **455** was isolated in very low yield together with **454** (Scheme 113).[42b] This work was resumed and the intramolecular aminomercuration of *N*-(4,4-dimethyl-4-silahex-5-en-yl)aniline **321** was reported




**448a**: R = Me
**448b**: R = Ph
**448c**: R = OMe
**448d**: R = F

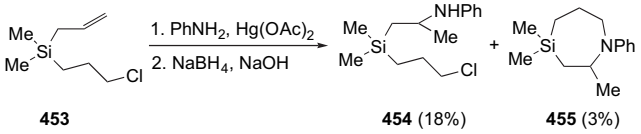
**449a-d**

**450a** (25%)[179], (35%)[40a]
**450b** (10%)[179]
**450c** (30%)[180]
**450d** (19%)[180]

**451a** (48%)
**451b** (40%)

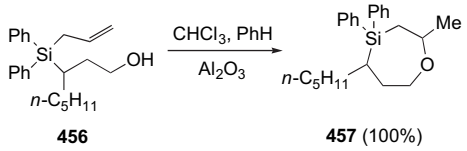
**Scheme 111**.

to lead mainly to the seven-membered ring compound **323** (Scheme 80).[43]




**Scheme 113**.

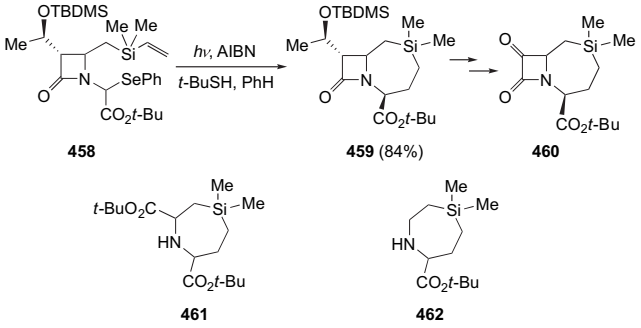
A quantitative formation of oxasilepane **457** was observed when alcohol **456** was mixed with acidic alumina (Scheme 114).[181] This interesting reaction was not further examined.




**Scheme 114**.

### 5.3. Preparation by formation of carbon–carbon bonds

Taddei and co-workers obtained the bicyclic β-lactam **459** (Scheme 115) by intramolecular addition of a radical on the CC double bond of a vinylsilane **458**.[182] In this case, only one regioisomer and stereomer was obtained. Sila β-lactam **459** did not show any particular antibiotic activity. This result is not very surprising since the replacement of a methylene group by a $SiMe_2$ group induces steric constraints, which could prevent the entry of the molecule into the enzymatic sites. β-Lactam **459** was transformed into β-diketone **460** by oxidation of the corresponding ethylidene β-lactam. This latter ketolactam was unstable in the reaction conditions and gave, among various products, compounds **461** and **462**.



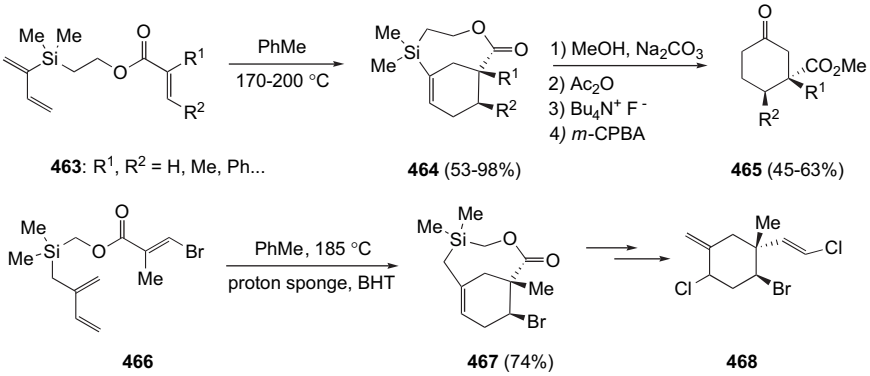

**Scheme 115**.

Shea et al. during their studies on intramolecular Diels–Alder reactions[183] examined the thermal behavior of butadienylsilanes **463**. At 170 °C, intramolecular cycloadditions occurred and bicyclic silalactones **464** were obtained in excellent yields (Scheme 116).[184] Only one diastereomer was obtained. Oxidative cleavage of the silicon part allowed the preparation of substituted cyclohexanones **465**. In a subsequent study, these authors showed that the position of the silicon in the carbon chain could be modified. Such an intramolecular Diels–Alder reaction was applied to the synthesis from **466** via **467** of the trihalogenated compound **468**, which is a metabolite of the red marine algae *Plocamium* sp.[185]

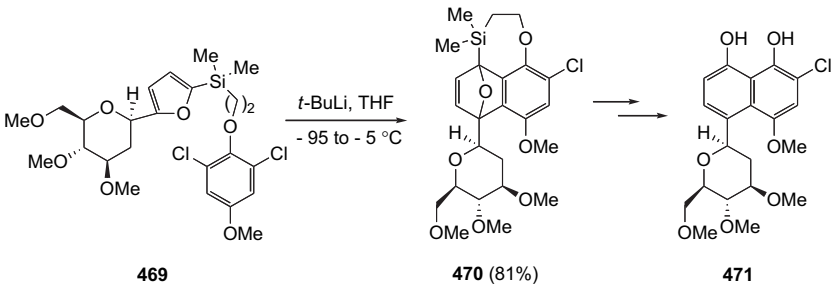
1,4-Oxasilepane **470** has been prepared from the sugar derivative **469** (Scheme 117) by an intramolecular Diels–Alder reaction of benzyne with the furan moiety.[142] The preparation of compound **470** was reported to be more efficient than the formation of the analogous six-membered heterocyclic compound **351** (see Scheme 88), and compound **470** was subsequently transformed into the C-glucoside **471**.

### 5.4. Formation by ring expansion

Corey and co-workers have intensively studied the ring expansion of phenoazasilinines and phenoxasilinines. Contrary to dibenzosiline **472**, for which the ring expansion to **473** was shown to be possible using Lewis acids such as $AlCl_3$,[186] utilization of these conditions was not adapted to the heterocyclic analogues with oxygen or nitrogen atoms. It was found that the ring enlargement occurred efficiently using fluoride ions. Treatment of compounds **474a**,**b** with KF in MeCN at reflux (1–2 days) led to the seven-membered ring products **475a**,**b**.[187] The reactions were accelerated in the presence of 18-crown-6. In the case of sulfone **476**, the ring expansion took place, but the product **477** appeared unstable in the reaction conditions and the ring-cleavage product **478** was isolated in good yield when 2 equiv of KF were used. Different fluorine sources were tested, without great

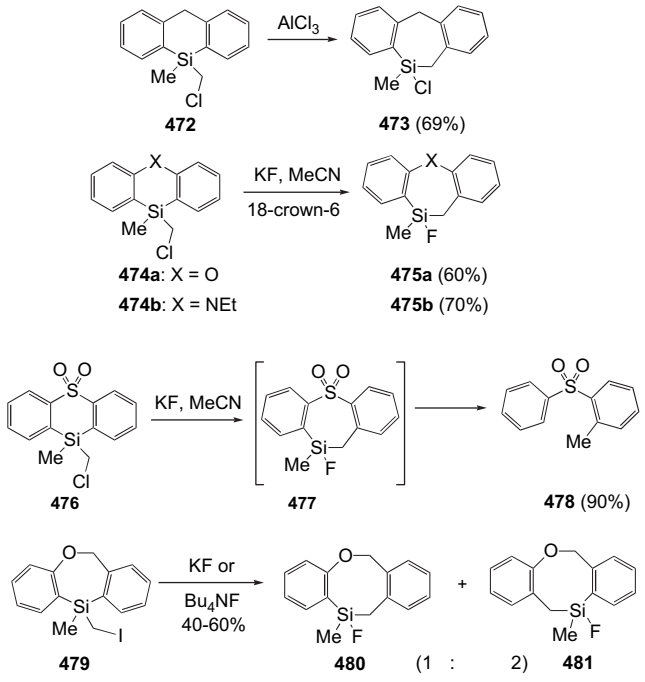



**Scheme 116**.




**Scheme 117**.

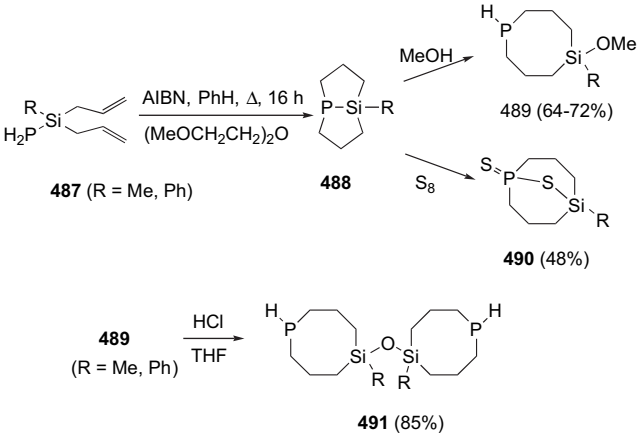
success, to improve these reactions.[188] This transformation occurred only if a halomethyl group was fixed on the silicon atom. With α-chloroethyl and β-chloroethyl as substituents, no rearrangement was observed. Transformation of oxasilepine **479** into a mixture of regioisomer oxasilocines **480** and **481** was also reported. In this case, the iodomethyl derivative led to a better result than the chloromethyl derivative (Scheme 118).[189]



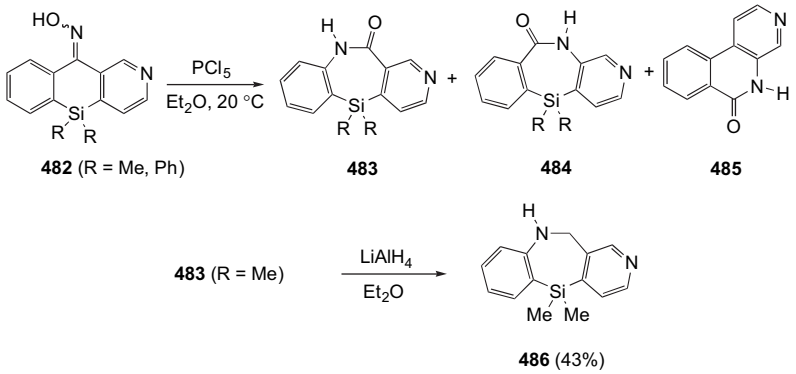

**Scheme 118**.

The Beckmann rearrangement was also used to obtain azasilepines. Reaction of oximes **482** with $PCl_5$ in ether led to a mixture of amides **483** and **484** (14–31%) and of the product of subsequent desilylation **485**. Compound **485** could be obtained in almost quantitative yield by heating amide **486** (R=Me) at 230 °C. $LiAlH_4$ reduction of amides **483** (R=Me) and **484** (R=Me) led to the corresponding amines, e.g., **486** (Scheme 119).[190]

Kuehne et al., during their work concerning the reactivity of P–H bonds,[128] examined the intramolecular cyclization of compounds **487**. In benzene in the presence AIBN, the stable bicyclic compounds **488** were obtained. Addition of methanol induced cleavage of the P–Si bond and phosphasilocanes **489** were isolated in good yields.[191] The bicyclo[3.3.1]nonanic compounds **490** were obtained by insertion of sulfur into the P–Si bond of compounds **488** (Scheme 120).



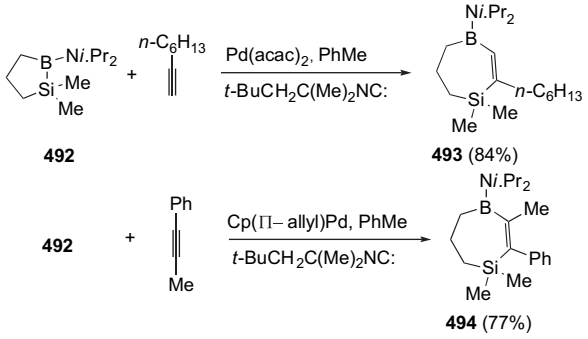

**Scheme 120**.




**Scheme 119**.

Phosphasilocanes **489** were stable in acidic conditions and gave disiloxanes **491** as expected.

Recently Suginome and co-workers have reported a study on the reactivity of silaborane **492** with alkynes. In the presence of palladium catalysts, cleavage of the Si–B bond allowed the regioselective insertion of an alkyne unit giving the 1,4-silaborepenes **493** and **494** in good yields (Scheme 121).[192]



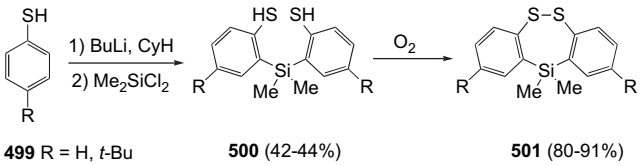

**Scheme 121**.

Tamao and co-workers have reported the formation of phosphasilinene (six-membered ring compound) by thermal decomposition of the silylated phosphine **223** in the presence of diphenylacetylene, via silylene **224** (Scheme 58).[95] When two phenyl substituents were present on phosphorus atom (**495**), the seven-membered heterocyclic compound **498** was obtained (Scheme 122). The intermediate phosphasilete **497** should be formed by the reaction of silylene **496** with the acetylenic reagent and a P→Si phenyl migration could induce a ring opening of the four-membered ring.

## 5.5. Other methods

Reaction of thiophenols **499** with 2 equiv of butyllithium in the presence of TMEDA was also reported to lead to dilithiated intermediates. Subsequent reaction with dichlorodimethylsilane led to the silylated compounds **500**, which, by heating or in the presence of oxygen, gave dithiasilepins **501** in good yields (Scheme 123).[193]

Le Floch and co-workers have reported the preparation of compound **504** by heating phosphinine **502** bearing two phosphazinylsilyl groups with diethynylsilane **503**. Compound **504** was stable and was purified by liquid chromatography (Scheme 124).[194] The same substrate **502** led, by reaction with the heterocyclic compound **505**, to the




**Scheme 123**.

formation of the air-sensitive polycyclic compound **506**. Such cycloadditions were also possible using thiophene and furan derivatives **507** with diacetylenic reagents **508**, to give rise to the mixed polyaromatic compounds **509**. Silaheterocyclic compounds **504**, **506**, and **509** possess holes of different radii and can probably be used to encapsulate metal ions with coordination spheres of different sizes.

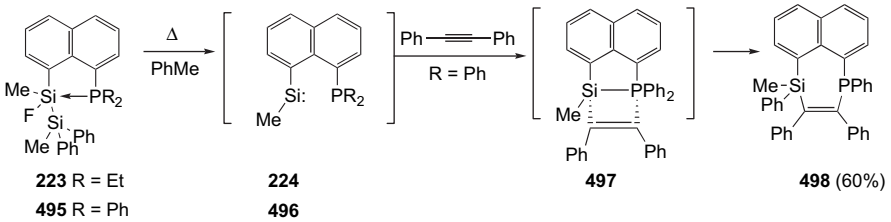
Reactions of siloles **510** with dimethyl acetylenedicarboxylate in toluene were found to give mainly the seven-membered ring heterocycles **512** (Scheme 125), and minor amounts of the bicyclic silalactones **513**. Cleavage of the bicyclo[2.2.1]silaheptane intermediate **511** was postulated to occur by a radical pathway, and the postulated diradical should give the bicyclic products **512** by reaction with a second molecule of dimethyl acetylenedicarboxylate.[195]

## 5.6. Reactivity and applications

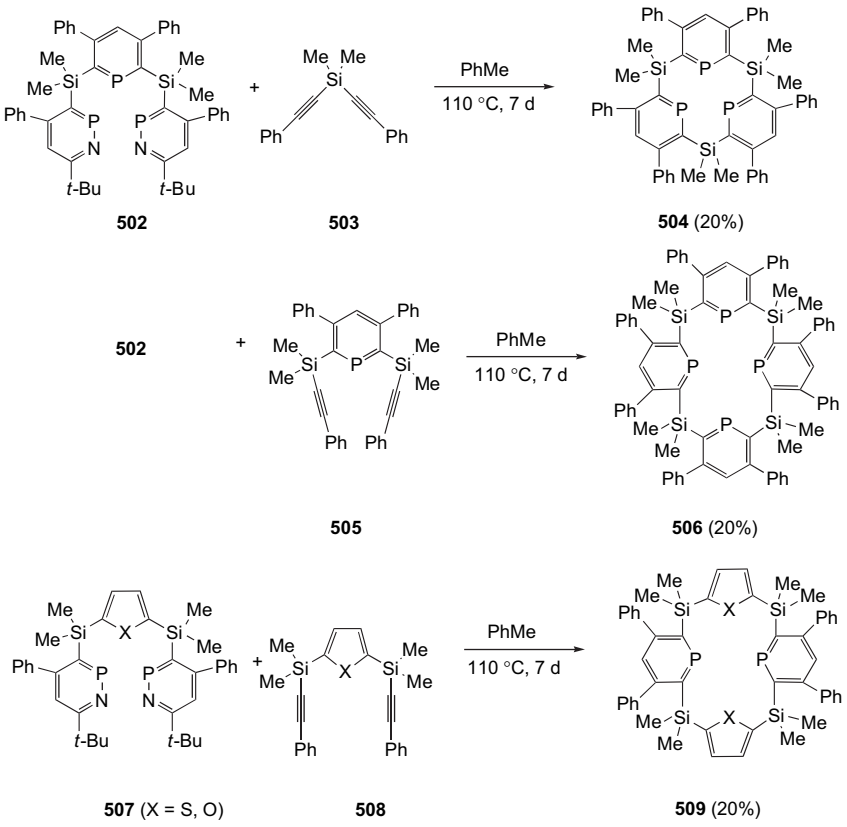
It has been found that 7- and 8- membered heterocyclic compounds may be used in various reactions without transformation of their heterocyclic cores. Oxasilepine **475a** was reduced using $LiAlH_4$ to provide hydrosilane **514**, which could add to allylamine to give the carbo-functionalized silane **515**. Reaction of compound **514** with methylmagnesium bromide afforded dimethylsilane **516**. This latter compound reacted with NBS to lead to the dibromo derivative **517** (Scheme 126).[64]

Reaction of silaheterocyclic compound **404b** with $BF_3 \cdot Et_2O$ led to difluorosilane **518**, while reaction with $LiAlH_4$ gave dihydrosilane **519** (Scheme 127).[164] Treatment of compound **518** with Li metal, in the presence of 2,3-dimethylbuta-1,3-diene, gave rise to the formation of the silacyclopentenyl compound **520**, via a silylene intermediate. Monosubstitution of dihydrosilane **519** was also reported to lead to useful unsymmetrical difunctionalized silanes **521** (60–90% yields).[163]

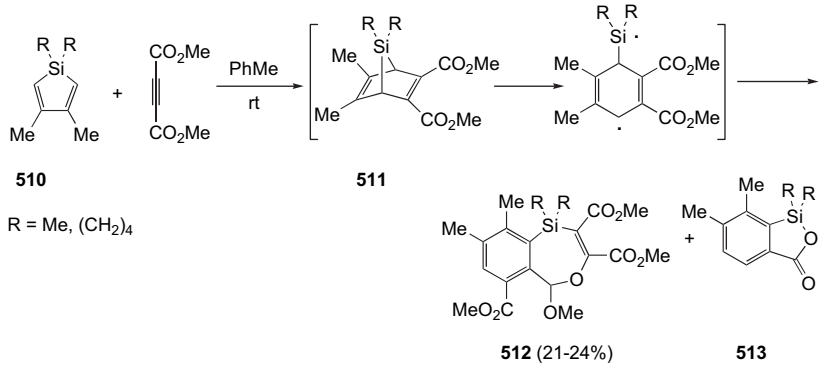
Regioselective metallation of thiasilepin **402** occurred using phenyllithium, and subsequent addition of a chloroalkylamine allowed the formation of the alkylated compound **522** (Scheme 128).[84]



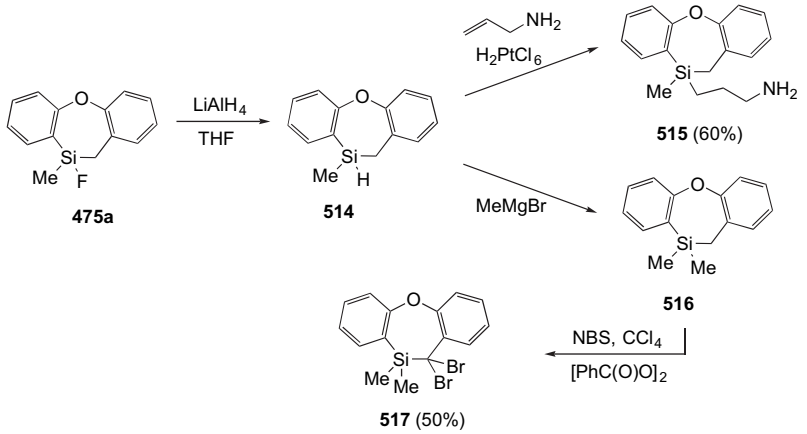

**Scheme 122**.



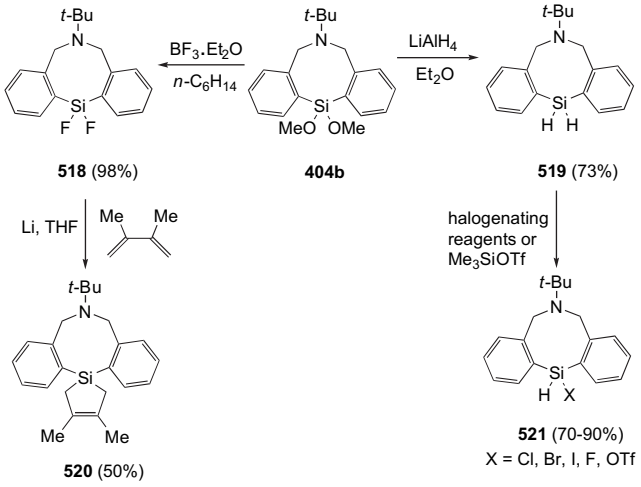

**Scheme 124**.



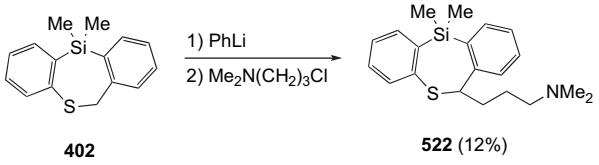

**Scheme 125**.




**Scheme 126**.

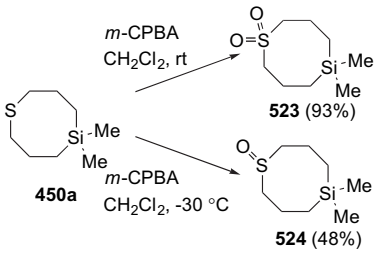



**Scheme 127**.




**Scheme 128**.

The oxidation of thiasilocane **450a** has been studied in detail. At −30 °C, sulfoxide **524** could be obtained, while, at room temperature, sulfone **523** was formed, without any cleavage products (Scheme 129).[196] Similar results were obtained using thiasilepane **303**.




**Scheme 129**.

## 6. Conclusions

We have seen in this review that numerous methods have been reported concerning the preparation of sila–heterocyclic compounds in which the silicon atom and the heteroatom are separated by at least one carbon atom. These results show that the preparation of new compounds in which a silicon atom replaces one carbon atom becomes possible and these compounds can be planned in strategies to obtain various heterocyclic compounds. Interesting properties can be anticipated for these compounds, as already reported for some products possessing biological activities or others as new materials.[1,2]

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**Biographical sketch**

**Dr. Gérard Rousseau** was born in 1946 in Versailles, France. He obtained his PhD at the Université Paris-Sud, Orsay, France, under the supervision of Professor J. M. Conia in 1976 on the reaction of singlet oxygen with cyclopropanic derivatives. Then he carried out a post-doctoral research with Professor R. B. Woodward on the total synthesis of erythromycin A. After his return to France, he worked principally on the chemistry of ketene acetals, the utilization of enzymes in organic chemistry, the chemistry of medium-ring compounds and more recently on electrophilic cyclizations. His present interest concerns the preparation of silaheterocycles. He is director of research at the CNRS.

**Luis Blanco** was born in 1948 in Paris, France. After a previous study of Conia-ene reactions, he completed his PhD in 1982 under the supervision of Professor Jean-Marie Conia at the Université Paris-Sud, Orsay, France, where he worked on the synthesis and the transformations of halosilyloxycylopropanes. He entered the Centre National de Recherche Scientifique in 1973. In 1985, he joined for one year Professor K. P. C. Vollhardt's group at University of Berkeley, California, as a post-doctoral fellow to work on the synthesis of multiphenylenes. His research interests concentrated on silyl enol ethers and on cyclopropanic compounds as synthetic tools, using ionic, radical, and oxidative methods to open the cyclopropanic rings, and on the use of enzymes in organic synthesis. More recently, he was involved in the enantio- and diastereoselective synthesis of sila-substituted organic compounds and he works to obtain sila drugs.

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# Solid silica sulfuric acid (SSA) as a novel and efficient catalyst for acetylation of aldehydes and sugars

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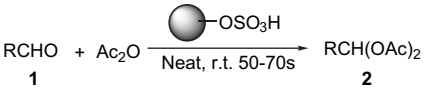
**Abstract**—Acetylation of aldehydes and sugars catalyzed by solid silica sulfuric acid (SSA) is described. In these reactions SSA shows a highly catalytic nature: easy to handle procedure, short reaction time, recycle exploitation, insensitivity to air and moisture, excellent isolated yields. The catalyst could be recycled at least five times.


## 1. Introduction

Protection of aldehydes is a frequently desired exercise in organic synthesis as it is often necessary to carry out a reaction on a multifunctional substrate without affecting a carbonyl group.[1] Previously, aldehydes are often protected by acetalization through reaction between aldehydes and alcohols[2] or trimethyl orthoformate[3] in the presence of acid catalyst or others such as copper(II) tetrafluoroborate,[4] DDQ–EtOH,[5] CAN–$Na_2CO_3$,[6] etc. However, these methods have some drawbacks such as long reaction time, high temperature, use of costly catalysts, use of additional reagents, requirement of special effort for catalyst preparation, need to use special apparatus, moderate yields, and side reactions. The most serious drawback is that these methods have no global utility and most of the products are liquid, which may contain impurities and are difficult to be purified compared to the powder and crystal.

Thus, 1,1-diacetates are developed as new protecting groups for aldehydes due to their stabilities, easy purification, and easy conversion into parent aldehydes.[7–11] Usually, they are obtained from aldehydes and acetic aldehyde using strong proton acids such as sulfuric acid,[12] phosphoric acid,[12] methanesulfonic acid[12] or Lewis acid as Nafion-H,[13] $ZnCl_2$,[14] ferric chloride,[11] phosphorus trichloride[15] or LiBr,[16] $H_2NSO_3H$.[17] These methods have not been entirely satisfactory owing to such drawbacks as low yields (4% in the case of 4-nitrobenzaldehyde[15]), long reaction time (up to 120 h in the case of 2-furaldehyde[15]), problems of corrosion, effluent pollution and non-recoverable catalysts and use of toxic organic solvents. In order to overcome these drawbacks, mild, quick, and environmentally friendly conditions have been developed. There are so many solid catalysts, such as β-zeolite,[18] sulfated zirconia,[19] montmorillonite clays,[20] expensive graphite,[21] trimethylchlorosilane/sodium iodide,[22] scandium triflate,[23] $TiO_2/SO_4^{2-}$ solid superacid,[24] iodine,[25] $Bi(OTf)_3xH_2O$,[26] $AlPW_{12}O_{40}$,[27] and LiOTf.[28]

We herein disclose a new mild and efficient protocol (Scheme 1) for diacetylation of aldehydes using $Ac_2O$ (3–20 equiv) catalyzed by 0.06 mol % of SSA in short time.




**Scheme 1**.

Carbohydrates, which are central to a wide array of biological processes,[29] have received much attention. Based on the concept of protected and unprotected glycosylation reagents, further extension to so-called 'programmable' syntheses[30] need efficient synthesis of fast and convenient protected sugar building blocks for the synthesis of biologically potent oligosaccharides, glycoconjugates, as well as natural products.[31] Per-O-acetylation is a frequently used reaction for protection of sugars and is often carried out using acetic anhydride as reagent and a catalyst such as pyridine,[32] pyridine derivatives,[33] sodium acetates.[34] However, dealing with large volumes of pyridine and other homogeneous catalysts is troublesome and recovery of catalysts is also difficult. A variety of other catalysts, iodine,[35] strong inorganic

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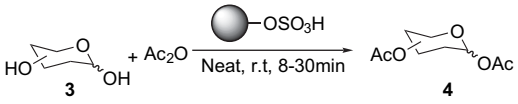
acid,[36] Lewis acid,[37] anionic surfactants,[38] montmorillonite K10,[39] Nafion-H,[40] H-β zeolite,[41] zirconyl sulfophenyl phosphonate,[42] lipases,[43] $Cu(OTf)_2$,[44] and $Sc(OTf)_3$[45] have been investigated.

SSA is an excellent acidic catalyst, which was frequently used to promote some important reaction.[46–48] But it is never used to catalyze acetylation reactions. Herein, we report a new mild and efficient protocol (Scheme 2) for acetylating sugar with $Ac_2O$ catalyzed by SSA at room temperature.




**Scheme 2**.

## 2. Results and discussion

As shown in Table 1, a series of geminal diacetates **2** were synthesized with the catalyst SSA at room temperature. We found that both aromatic and aliphatic aldehydes gave high yields (≥80%) and the reaction time was shorter than that of previous methods. The results indicated that the nature of substituents on the aromatic ring had no effect on the reaction, except 2-methoxybenzaldehyde, which gave lower yield due to the steric hindrance effect. Ketones, for example, acetophenone and cyclohexanone could not be converted into the corresponding geminal diacetates even when the reaction complexes were stirred for 24 h.

The results in Table 2 indicate that in contrast to the conventional **4**, wherein an excessive amount of $Ac_2O$ was needed and neutralization followed by tedious workup and purification, our method employing stoichiometric amount of $Ac_2O$ offers a chance to carry out the **4** under solvent-free conditions. Disaccharides (entries **3f–3g**) required longer reaction time than pentoses and hexoses (entries **3a–3e**) and the amount of SSA for disaccharides was 0.06 mol %, while it was 0.03 mol % for monosaccharides. The reaction terminal could easily be monitored when the reaction system cooled to room temperature automatically due to its heat liberation. It could also be judged by TLC. The outstanding feature of this method was that the catalyst could be easy recycled five times without significant deactivation. A comparison of this method with previous ones, in Table 3, clearly shows the advantages of this method. The data in Table 3 also show that some protocols took much longer time, some used no-recovery catalyst, or some used dangerous materials with reduced isolated yields. This protocol is so efficient in acetylation of 3-nitrobenzaldehyde in less than 0.8 min, while the same transformation requires 0.5–12 h if $FeCl_3$,[11] β-zeolite,[18] and LiOTf[28] are used. The use of LiOTf is equally effective for benzaldehyde, but reaction time is much longer (14 h). Compared with K-10, which has shown no effect for 4-hydroxybenzaldehyde, the catalytic activity of SSA is observed in 99% yield and in a very short time (70 s).

**Table 1**. SSA-catalyzed solvent-free acetylation of aldehydes with acetic anhydride

| Entry | Aldehyde | $Ac_2O$ (equiv) | Time (s) | Yield[a,b] (%) | Mp (°C) found | Reported |
|---|---|---|---|---|---|---|
| 1a | Butyraldehyde | 3 | 60 | 91 | | |
| 1b | Pentanal | 3 | 60 | 85 | | |
| 1c | Benzaldehyde | 3 | 60 | 82 | 44–45 | 44–45[25] |
| 1d | *p*-Nitrobenzaldehyde | 20 | 50 | 99 | 124–125 | 125–126[20] |
| 1e | *m*-Nitrobenzaldehyde | 20 | 50 | 93 | 64–65 | 64–65[20] |
| 1f | 4-Chlorobenzaldehyde | 15 | 50 | 99 | 81–82 | 81–82[25] |
| 1g | 2,4-Dichlorobenzaldehyde | 20 | 50 | 85 | 102–104 | 101–102[17] |
| 1h | 4-Hydroxybenzaldehyde | 15 | 70 | 99 | 92–93 | |
| 1i | *p*-Tolualdehyde | 3 | 50 | 99 | 80–81 | 81–82[17] |
| 1j | 4-Cyanobenzaldehyde | 15 | 50 | 98 | 101–102 | 98–102[9] |
| 1k | 4-Methoxybenzaldehyde | 3 | 50 | 95 | 67–68 | 67–68[25] |
| 1l | 2-Bromobenzaldehyde | 3 | 60 | 98 | 89–90 | |
| 1m | 4-Bromobenzaldehyde | 15 | 60 | 96 | 90–91 | |
| 1n | Salicylaldehyde | 3 | 60 | 96 | 101–103 | 103–104[17] |
| 1o | 2-Methoxybenzaldehyde | 3 | 50 | 80 | 66–68 | |

[a] Yield of pure isolated products.
[b] Products characterized by $^1H$ NMR spectroscopy and compared with authentic samples.

**Table 2**. SSA-catalyzed solvent-free per-O-acetylation of sugar with acetic anhydride[a]

| Entry | Sugar | Product | $Ac_2O$ (equiv) | Time (min) | α:β | Yield (%) |
|---|---|---|---|---|---|---|
| 3a | D-Glucose | D-Glucopyranose pentaacetate | 5.1 | 20 | 1.7 | 94[b] |
| 3b | D-Xylose | D-Xylopyranose tetraacetate | 4.1 | 10 | 20 | 96[b] |
| 3c | D-Galactose | D-Galactopyranose pentaacetate | 5.1 | 10 | 2.1 | 98[b] |
| 3d | D-Mannose | D-Mannopyranose pentaacetate | 5.1 | 20 | 4.2 | 89[b] |
| 3e | L-Rhamnose | L-Rhamnopyranose tetraacetate | 4.1 | 8 | 14 | 90[b] |
| 3f | D-Lactose | D-Lactose octaacetate | 9.0 | 25 | 1.9 | 91[c] |
| 3g | D-Maltose | D-Maltose octaacetate | 9.0 | 25 | 1.1 | 88[c] |
| 3h | Sucrose | Sucrose octaacetate | 9.0 | 30 | 20 | 91[c] |

[a] Yield of pure isolated products.
[b] SSA 0.03 mol %.
[c] SSA 0.06 mol %.

**Table 3**. Comparison of protocols for acylation of aldehydes and sugars

| Entry | Substrate | Catalyst | $T$ (°C) | Time (min) | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| 3a | D-Galactose | SSA | 25 | 10 | 98 | [a] |
| | | $I_2$[c] | 25 | 120 | 98 | 35b |
| | | K-10[b] | 25 | 600 | 92 | 39 |
| | | $Cu(OTf)_2$[b] | 0→15 | 1500 | 90 | 44 |
| | | $Sc(OTf)_3$[b] | 25 | 510 | 88 | 45 |
| 1b | 3-Nitrobenzaldehyde | SSA | 25 | 0.8 | | [a] |
| | | $FeCl_3$ | 0 | 30 | 93 | 9 |
| | | β-Zeolite[e] | 60 | 120 | 91 | 18 |
| | | LiOTf[b] | 25 | 720 | 93 | 28 |
| 1c | 4-Methoxybenzaldehyde | SSA | 25 | 0.8 | 95 | [a] |
| | | LiOTf[b] | 25 | 1740 | 91 | 28 |
| 1d | 4-Hydroxybenzaldehyde | SSA | 25 | 1.2 | 99 | [a] |
| | | K-10[d] | 25 | | | 20 |

[a] Present work.
[b] Long reaction time.
[c] No recovery of catalyst.
[d] No reaction.
[e] Heat is needed.

In conclusion, SSA is a cheap, green, easily recycled, and efficient catalyst for acetylation of aldehydes and sugar at excellent yield. We believe that this method should be given a wide application in protection of the hydroxyl and carboxy.

## 3. Experimental

### 3.1. General

Melting points were measured with a Fisher–Johns melting point apparatus without correction. The nuclear magnetic resonance spectra were measured on a Bruker AM-400 spectrometer with $Me_4Si$ (TMS) as the internal reference and $CDCl_3$ as solvent.

### 3.2. General procedure for acetylation of aldehydes

Aldehyde (1 mmol), acetic anhydride (3–20 mmol), and SSA (0.06 mol %) were added in a flask and then stirred for about 1 min. The reaction was monitored by TLC. On completion $NaHCO_{3(aq)}$ and $CH_2Cl_2$ were added to the reaction system yielding three layers: water on the top, silica sulfuric acid in the middle, and $CH_2Cl_2$ at the bottom. The bottom layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to crude product and subjected to flash column chromatography.

### 3.3. General procedure for per-O-acetylation of sugar

To a mixture of sugar (2 mmol) and acetic anhydride (4.1–9 mmol), SSA (0.03–0.06 mmol %) was added at room temperature, and the reaction system was stirred until the starting material disappeared completely (as monitored by TLC).

The workup procedure was as described above.

### 3.4. Preparation and recycle of SSA

The preparation of SSA was according to Mohammad Ali Zolfigol.[49] The middle layer in the first stage of the above work up procedure was separated. The residue was washed with 95% EtOH and dried at 110 °C for 12 h to give pure SSA for further use.

#### 3.4.1. Spectral data of new products.

**3.4.1.1. 4-Hydroxybenzaldehyde.** Colorless crystal; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67 (s, 1H), 7.54 (d, $J$=8.4 Hz, 2H), 7.13 (d, $J$=8.4 Hz, 2H), 2.31 (s, 3H), 2.12 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 168.95, 168.42, 151.29, 132.79, 127.80, 121.54, 88.85, 20.83, 20.57. Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.59; H, 5.41%.

**3.4.1.2. 4-Bromobenzaldehyde.** Colorless crystal; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.62 (s, 1H), 7.54 (d, $J$=8.4 Hz, 2H), 7.39 (d, $J$=8.0 Hz, 2H), 2.13 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 168.38, 134.23, 131.54, 128.14, 123.69, 88.85, 20.53. Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.02; H, 3.86. Found: C, 46.15; H, 3.96%.

**3.4.1.3. 2-Bromobenzaldehyde.** Colorless crystal; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.93 (s, 1H), 7.62 (dd, $J$=8.4 Hz, $J$=1.2 Hz, 1H), 7.57 (dd, $J$=8.4 Hz, $J$=1.6 Hz, 1H), 7.30 (m, 2H), 2.13 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 168.08, 134.58, 132.94, 130.78, 127.58, 127.32, 122.24, 88.77, 20.41. Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.02; H, 3.86. Found: C, 46.11; H, 3.85%.

**3.4.1.4. 2-Methoxybenzaldehyde.** Colorless crystal; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (s, 1H), 7.49 (d, $J$=8.4 Hz, 2H), 7.36 (t, $J$=7.6 Hz, 1H), 7.00 (t, $J$=7.6 Hz, 1H), 6.91 (d, $J$=8.4 Hz, 1H), 3.83 (s, 3H), 2.11 (s, 6H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 168.31, 156.71, 130.65, 128.68, 123.54, 120.19, 110.69, 85.38, 55.36, 20.60. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.54; H, 5.96%.

**3.4.1.5. Sucrose.** Yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.62 (d, $J$=4 Hz, 1H), 5.35 (m, 3H), 5.01 (t, $J$=9.6 Hz, 1H), 4.82 (d, $J$=8 Hz, 1H), 2.11–1.95 (m, 26H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.30, 170.11, 169.73, 169.69, 169.65, 169.52, 169.26, 169.14, 103.60, 89.52, 78.71, 77.22, 76.58, 75.30, 74.60, 69.84, 69.20, 68.07, 67.78, 63.23, 62.44, 61.37, 20.26, 20.23, 20.18, 20.15, 20.12, 20.10. Anal. Calcd for $C_{29}H_{40}O_{19}$: C, 50.29; H, 5.82. Found: C, 50.36; H, 5.91%.

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# Synthesis of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives via $ZnCl_2$ catalyzed cyclocondensation reaction

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**Abstract**—A short and facile synthesis of a series of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives was accomplished in moderate to good yields via the novel cyclocondensation of substituted *o*-aminobenzonitrile with aldehydes or ketones catalyzed by $ZnCl_2$.


## 1. Introduction

A literature survey of important and valuable physiological properties for 1,2-dihydro-4*H*-3,1-benzoxazine derivatives includes nonsteroidal progesterone receptor agonists,[1,2] plant growth regulating, and herbicide activities.[3] In addition, these compounds can be transformed into their 4*H*-3,1-benzoxazine analogues,[4] which also include important pharmacologically active compounds.[5,6]

The main synthetic approach to 1,2-dihydro-4*H*-3,1-benzoxazines is the condensation of *o*-aminobenzyl alcohols with carbonyl compounds.[7,8] However, limitations related to difficulty in obtaining these benzyl alcohols have prevented the use of these reactions for the synthesis of 1,2-dihydro-4*H*-3,1-benzoxazines. Here, we wish to describe a new method for the preparation of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives using substituted *o*-aminobenzonitrile as the starting material in DMF catalyzed by $ZnCl_2$.[9]

## 2. Results and discussion

### 2.1. Choice of catalyst

The choice of the catalyst played a crucial role and the use of $ZnCl_2$ was at the center of our study. In the course of our work on applications of $ZnCl_2$ in organic reactions, we have found that it is an effective catalyst for the preparation of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives. The use of anhydrous $AlCl_3$, CuCl, $CuCl_2$, $TiCl_4$, and *p*-toluenesulfonic was much less effective. When a mixture of 2-amino-5-nitrobenzonitrile **1a** and cyclohexanone **2** in DMF was stirred under reflux in the presence of $ZnCl_2$, the reaction was completed within 1 h. After work up, the product **3a** was obtained in 75% yield (Table 1). In contrast to the above result, we carried out the reaction of **1a** with **2** in the presence of anhydrous $AlCl_3$. However, the product **3a** was not obtained. After screening several Lewis acids, we found that $ZnCl_2$ was the best catalyst for the reaction of 2-amino-5-nitrobenzonitrile **1a** and cyclohexanone **2** (Table 1).

### 2.2. Synthesis of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives

Then, we studied the reaction of differently substituted *o*-aminobenzonitrile with cyclohexanone. Thus, treatment of a solution of 2-amino-4-chlorobenzonitrile with cyclohexanone in the presence of $ZnCl_2$ in DMF at reflux for 2 h afforded 1,2-dihydro-4*H*-3,1-benzoxazines **3b** in 70% yield (Table 2). The same treatment of *o*-aminobenzonitrile with cyclohexanone gave the cyclocondensation product **3c** in 64% yield. Similarly, when cyclopentanone was used instead of cyclohexanone, 1,2-dihydro-4*H*-3,1-benzoxazines were also obtained. The optimized results are summarized in Table 2.

Encouraged by this study, we investigated the reaction of differently substituted *o*-aminobenzonitrile **1** with a range of aliphatic ketones, aldehydes, or aromatic aldehydes **4** bearing either electron-donating or electron-withdrawing substitutes, affording moderate to good yields of products 1,2-dihydro-4*H*-3,1-benzoxazine derivatives **5**. The optimized results are summarized in Table 3.

*Keywords*: $ZnCl_2$; Cyclocondensation; 1,2-Dihydro-4*H*-3,1-benzoxazine derivatives; Aldehydes; Ketones.
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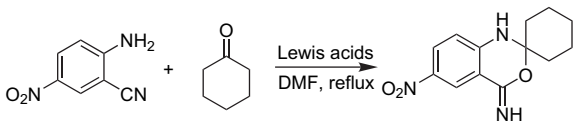
**Table 1**. Screening of Lewis acids[a,b]

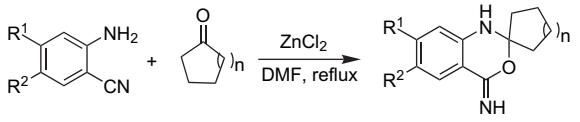



**1a** **2** **3a**

| Entry | LA | Time (h) | Yield (%)[c] |
|---|---|---|---|
| 1 | $AlCl_3$ | 1 | 0 |
| 2 | CuCl | 1 | 38 |
| 3 | $CuCl_2$ | 1 | 32 |
| 4 | $TiCl_4$ | 1 | 0 |
| 5 | $ZnCl_2$ | 1 | 75 |
| 6 | $p$-$CH_3C_6H_4SO_3H$ | 1 | 13 |

[a] Yields of **3a** using different LAs in the reaction of 2-amino-5-nitrobenzonitrile and cyclohexanone.
[b] All reactions were carried out using **1a** (6 mmol), **2** (4 mL), LAs (6 mmol), and DMF (8 mL).
[c] Isolated yield.

**Table 2**. The cyclocondensation of substituted *o*-aminobenzonitrile and cyclic ketones[a]




**1** **2** **3**

| Entry | $R^1$ | $R^2$ | $n$ | Time (h) | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | H | $NO_2$ | 2 | 1 | **3a** | 75 |
| 2 | Cl | H | 2 | 1.5 | **3b** | 70 |
| 3 | H | H | 2 | 2.5 | **3c** | 64 |
| 4 | H | $NO_2$ | 1 | 1 | **3d** | 70 |
| 5 | Cl | H | 1 | 2 | **3e** | 67 |
| 6 | H | H | 1 | 2.5 | **3f** | 62 |

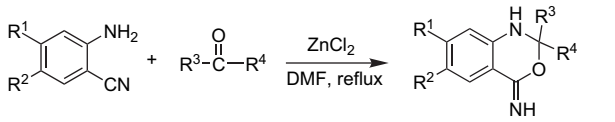
[a] All reactions were carried out using **1** (6 mmol), **2** (4 mL), $ZnCl_2$ (6 mmol), and DMF (8 mL).
[b] Isolated yield.

As shown in Table 3, various ketones or aldehydes reacted with substituted *o*-aminobenzonitrile in the presence of $ZnCl_2$ affording the desired 1,2-dihydro-4*H*-3,1-benzoxazine derivatives in moderate to good yields. When 2-amino-4-chlorobenzonitrile was used instead of 2-amino-5-nitrobenzonitrile for the reaction, the yields of **5d–f** and **5p–u** were lower than that of **5a–c** and **5j–o**. Moreover, when *o*-aminobenzonitrile reacted with various ketones or aldehydes, the yields of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives were lower. So, the yields seemed to depend on the substituted groups in *o*-aminobenzonitrile. The reaction proceeded more readily and gave better yields if the *o*-aminobenzonitrile derivatives possessed stronger electron-withdrawing substituent.

## 2.3. Mechanism

The formation of products 1,2-dihydro-4*H*-3,1-benzoxazine derivatives can be explained by Scheme 1. The attack of the amino group of **1** onto the carbonyl carbon atom of **4** gave intermediate **6** and the product **5** was obtained through subsequent cyclization by attack of the oxygen atom onto the nitrile group of **1**.

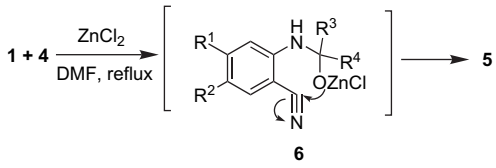
**Table 3**. The synthesis of 1,2-dihydro-4*H*-3,1-benzoxazines catalyzed by $ZnCl_2$




**1** **4** **5**

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Time (h) | Product | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | H | $NO_2$ | $CH_3$ | $CH_3$ | 1 | **5a** | 82 |
| 2 | H | $NO_2$ | $CH_3CH_2$ | $CH_3$ | 1 | **5b** | 80 |
| 3 | H | $NO_2$ | $C_6H_5$ | $CH_3$ | 2 | **5c** | 78 |
| 4 | Cl | H | $CH_3$ | $CH_3$ | 1.5 | **5d** | 71 |
| 5 | Cl | H | $CH_3CH_2$ | $CH_3$ | 1.5 | **5e** | 74 |
| 6 | Cl | H | $C_6H_5$ | $CH_3$ | 2.5 | **5f** | 70 |
| 7 | H | H | $CH_3$ | $CH_3$ | 2.5 | **5g** | 65 |
| 8 | H | H | $CH_3CH_2$ | $CH_3$ | 2.5 | **5h** | 67 |
| 9 | H | H | $C_6H_5$ | $CH_3$ | 3 | **5i** | 62 |
| 10 | H | $NO_2$ | $CH_3CH_2CH_2$ | H | 1 | **5j** | 75 |
| 11 | H | $NO_2$ | $C_6H_5$ | H | 1 | **5k** | 80 |
| 12 | H | $NO_2$ | $m$-$O_2NC_6H_4$ | H | 1 | **5l** | 80 |
| 13 | H | $NO_2$ | $p$-$O_2NC_6H_4$ | H | 1 | **5m** | 71 |
| 14 | H | $NO_2$ | $p$-$CH_3OC_6H_4$ | H | 1 | **5n** | 82 |
| 15 | H | $NO_2$ | $p$-$ClC_6H_4$ | H | 1 | **5o** | 80 |
| 16 | Cl | H | $CH_3CH_2CH_2$ | H | 2 | **5p** | 72 |
| 17 | Cl | H | $C_6H_5$ | H | 2 | **5q** | 75 |
| 18 | Cl | H | $m$-$O_2NC_6H_4$ | H | 2 | **5r** | 78 |
| 19 | Cl | H | $p$-$O_2NC_6H_4$ | H | 2 | **5s** | 70 |
| 20 | Cl | H | $p$-$CH_3OC_6H_4$ | H | 2 | **5t** | 76 |
| 21 | Cl | H | $p$-$ClC_6H_4$ | H | 2 | **5u** | 75 |
| 22 | H | H | $CH_3CH_2CH_2$ | H | 2.5 | **5v** | 60 |
| 23 | H | H | $C_6H_5$ | H | 2.5 | **5w** | 71 |
| 24 | H | H | $m$-$O_2NC_6H_4$ | H | 2.5 | **5x** | 73 |
| 25 | H | H | $p$-$O_2NC_6H_4$ | H | 2.5 | **5y** | 67 |
| 26 | H | H | $p$-$CH_3OC_6H_4$ | H | 2.5 | **5z** | 73 |
| 27 | H | H | $p$-$ClC_6H_4$ | H | 2.5 | **5aa** | 70 |

[a] Isolated yield.




**6**

**Scheme 1**. Proposed mechanism.

## 2.4. Crystallographic structure of compound 3d

The structure of the products was further confirmed by X-ray crystallographic analysis of **3d**. Crystals of **3d** was obtained by recrystallization from ethanol. Molecular structure and the crystal packing of **3d** are shown in Figure 1. The structure showed cyclopentane rings with an envelope conformation. The C1–N2 bond (1.238 Å) possessing double bond character was significantly shorter than the C8–N1 bond (1.463 Å). The tight crystal packing with significant N1–H···O3 (2.996 Å) and N2–H···O1 (2.896 Å) hydrogen bonds in the structure was in agreement with the observed high melting point.

## 3. Conclusion

In conclusion, we have described a novel method for the efficient and convenient synthesis of 1,2-dihydro-4*H*-3,1-

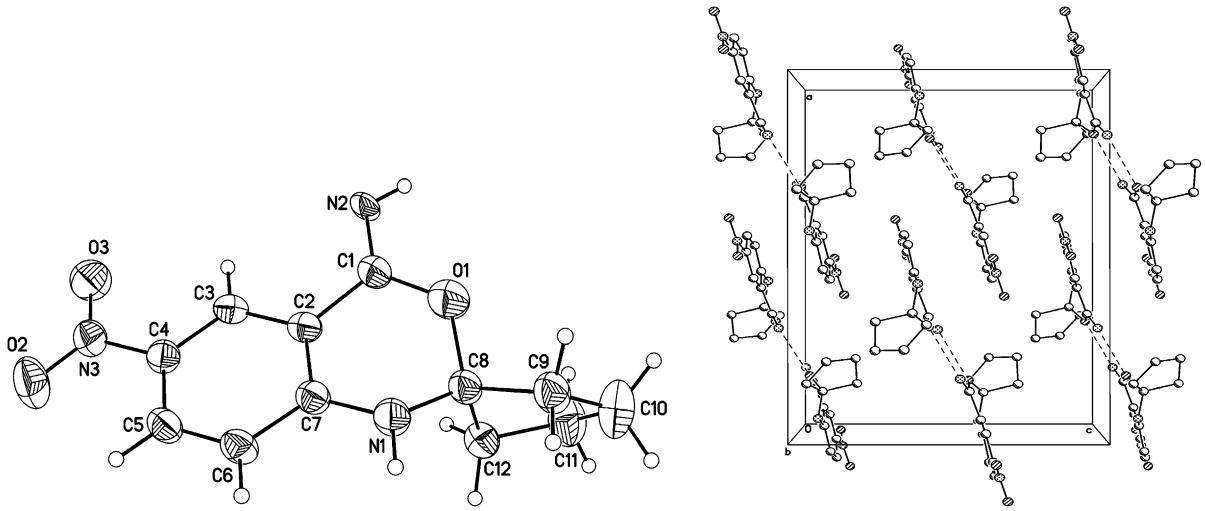



**Figure 1**. Crystal structure and packing diagram of compound **3d**.

benzoxazine derivatives via cyclocondensation of substituted *o*-aminobenzonitrile and aldehydes or ketones using the easily available $ZnCl_2$ as catalyst in DMF. The advantages of our method are the easily accessible starting materials, facile experimental work up procedure, and moderate to good yields.

## 4. Experimental

### 4.1. General

Melting points were determined using XT4 microscope melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer and were run as KBr pellets. $^1H$ and $^{13}C$ NMR spectra were recorded at 400 MHz on a Bruker 400 spectrometer. Chemical shifts were reported in $\delta$ (ppm) relative to internal tetramethylsilane. Mass spectra were recorded on a ZAB-HS mass spectrometer using ESI ionization. Elemental analyses were within ±0.4% of theoretical values and were performed on an Elementar Vario EL.

**4.1.1. Typical procedure for the preparation of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives (3a–f, 5a–i).** To a solution of DMF (8 mL) and $ZnCl_2$ (6 mmol) were added substituted *o*-aminobenzonitrile **1** (6 mmol) and ketones (4 mL). The mixture was heated at reflux for the specified time (see Tables 2 and 3). After completion of the reaction as indicated by TLC (eluent: ethyl acetate), the cooled reaction mixture was quenched with water (10 mL) and the precipitate was separated by filtration. The filtration residue was dispersed into water and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the product was isolated by column chromatography (200–300 mesh silica gel, ethyl acetate–petroleum=1:2).

**4.1.1.1. 6-Nitro-1,2-dihydro-2,2-(1′,5′-pentylene)-4-imino-4*H*-3,1-benzoxazine (3a).** Yellow solid. Mp 297–299 °C. IR (KBr): 3359, 3188, 2935, 1672, 1618, 1529, 1313 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.05–1.80 (10H, m, $C_5H_{10}$), 6.94 (1H, d, $J$=7.7 Hz, ArH), 8.08 (1H, s, NH), 8.10 (1H, dd, $J$=2.8, 7.7 Hz, ArH), 8.39 (1H, d, $J$=2.8 Hz, ArH), 8.44 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 21.13 (2C), 24.74, 38.36 (2C), 69.19, 112.88, 114.99, 124.57, 129.26, 137.27, 151.85, 161.66; MS (ESI): $m/z$ (%)=262.2 (100) $[M+H]^+$; $C_{13}H_{15}N_3O_3$: calcd C 59.76, H 5.78, N 16.08; found C 59.73, H 5.79, N 16.09.

**4.1.1.2. 7-Chloro-1,2-dihydro-2,2-(1′,5′-pentylene)-4-imino-4*H*-3,1-benzoxazine (3b).** Pale yellow solid. Mp 220–221 °C. IR (KBr): 3320, 3176, 2920, 1641, 1607, 1476 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.25–1.78 (10H, m, $C_5H_{10}$), 6.63 (1H, dd, $J$=8.0, 2.0 Hz, ArH), 6.87 (1H, d, $J$=2.0 Hz, ArH), 6.91 (1H, s, NH), 7.55 (1H, d, $J$=8.0 Hz, ArH), 8.06 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 20.83 (2C), 24.48, 37.22 (2C), 68.14, 113.17, 113.60, 116.40, 129.07, 137.60, 147.71, 162.29; MS (ESI): $m/z$ (%)=251.1 (100) $[M+H]^+$; $C_{13}H_{15}N_2OCl$: calcd C 62.27, H 6.03, N 11.17; found C 62.14, H 6.16, N 10.96.

**4.1.1.3. 1,2-Dihydro-2,2-(1′,5′-pentylene)-4-imino-4*H*-3,1-benzoxazine (3c).** White solid. Mp 231–233 °C. IR (KBr): 3365, 3170, 2923, 1648, 1610, 1504, 1484, 1382 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.23–1.74 (10H, m, $C_5H_{10}$), 6.60 (1H, d, $J$=8.0 Hz, ArH), 6.63 (1H, s, NH), 6.79 (1H, d, $J$=8.0 Hz, ArH), 7.20 (1H, t, $J$=8.0 Hz, ArH), 7.56 (1H, t, $J$=8.0 Hz, ArH), 7.89 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 20.84 (2C), 24.61, 37.12 (2C), 67.76, 114.42, 114.53, 116.43, 127.05, 133.07, 146.72, 163.14; MS (ESI): $m/z$ (%)=217.1 (100) $[M+H]^+$; $C_{13}H_{16}N_2O$: calcd C 72.19, H 7.46, N 12.95; found C 71.88, H 7.44, N 12.82.

**4.1.1.4. 6-Nitro-1,2-dihydro-2,2-(1′,4′-butylene)-4-imino-4*H*-3,1-benzoxazine (3d).** Yellow solid. Mp 281–283 °C. IR (KBr): 3319, 3180, 2912, 1672, 1619, 1534, 1310 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.67–1.88 (8H, m, $C_4H_8$), 6.82 (1H, d, $J$=8.0 Hz, ArH), 8.10 (1H, dd, $J$=2.4, 8.0 Hz, ArH), 8.30 (1H, s, NH), 8.42 (1H, d, $J$=2.4 Hz, ArH), 8.56 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 21.90 (2C), 40.15 (2C), 77.32, 112.31, 114.14, 124.11, 128.62, 136.68, 151.63, 161.21; MS (ESI): $m/z$ (%)=248.2 (100) $[M+H]^+$; $C_{12}H_{13}N_3O_3$: calcd C 58.29, H 5.30, N 17.00; found C 58.33, H 5.31, N 17.08.

**4.1.1.5. 7-Chloro-1,2-dihydro-2,2-(1′,4′-butylene)-4-imino-4*H*-3,1-benzoxazine (3e).** Pale yellow solid. Mp 250–251 °C. IR (KBr): 3310, 3181, 2942, 1648, 1608, 1481 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.66–1.80 (8H, m, $C_4H_8$), 6.64 (1H, dd, $J$=8.0, 2.0 Hz, ArH), 6.73 (1H, d, $J$=2.0 Hz, ArH), 7.04 (1H, s, NH), 7.56 (1H, d, $J$=8.0 Hz, ArH), 8.21 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 20.91 (2C), 38.96 (2C), 72.10, 113.02, 113.21, 116.12, 129.01, 136.92, 147.15, 162.01; MS (ESI): $m/z$ (%)=237.1 (100) $[M+H]^+$; $C_{12}H_{13}N_2OCl$: calcd C 60.89, H 5.53, N 11.83; found C 60.51, H 5.46, N 11.48.

**4.1.1.6. 1,2-Dihydro-2,2-(1′,4′-butylene)-4-imino-4*H*-3,1-benzoxazine (3f).** White solid. Mp 268–270 °C. IR (KBr): 3289, 3166, 2934, 1638, 1613, 1429 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.75–2.08 (8H, m, $C_4H_8$), 6.07 (1H, s, NH), 6.73 (2H, dd, $J$=7.8, 8.0 Hz, ArH), 7.19 (1H, s, =NH), 7.24–7.26 (1H, m, $J$=7.2 Hz, ArH), 7.73 (1H, d, $J$=8.0 Hz, ArH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 21.97 (2C), 38.88 (2C), 77.05, 114.32, 114.57, 116.53, 127.23, 132.99, 147.49, 163.42; MS (ESI): $m/z$ (%)=203.1 (100) $[M+H]^+$; $C_{12}H_{14}N_2O$: calcd C 71.26, H 6.98, N 13.85; found C 71.38, H 6.71, N 13.49.

**4.1.1.7. 6-Nitro-1,2-dihydro-2,2-dimethyl-4-imino-4*H*-3,1-benzoxazine (5a).** Yellow solid. Mp 291–293 °C. IR (KBr): 3322, 3177, 1671, 1618, 1534, 1306, 1149 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.45 (6H, s, $CH_3$), 6.74 (1H, d, $J$=8.8 Hz, ArH), 8.09 (1H, dd, $J$=2.7, 8.8 Hz, ArH), 8.24 (1H, s, NH), 8.41 (1H, d, $J$=2.7 Hz, ArH), 8.56 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 29.68 (2C), 67.57, 111.70, 114.09, 124.15, 128.85, 136.68, 151.33, 160.87; MS (ESI): $m/z$ (%)=222.1 (100) $[M+H]^+$; $C_{10}H_{11}N_3O_3$: calcd C 54.29, H 5.01, N 18.99; found C 54.41, H 5.12, N 18.78.

**4.1.1.8. 6-Nitro-1,2-dihydro-2-methyl-2-ethyl-4-imino-4*H*-3,1-benzoxazine (5b).** Yellow solid. Mp 283–285 °C. IR (KBr): 3322, 3177, 2919, 1671, 1618, 1534, 1306, 1149 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 0.88 (3H, t, $J$=7.2 Hz, $CH_3$), 1.43 (3H, s, $CH_3$), 1.64–1.73 (2H, m, $J$=7.2 Hz, $CH_2$), 6.75 (1H, d, $J$=8.8 Hz, ArH), 8.08 (1H, dd, $J$=2.7, 8.8 Hz, ArH), 8.17 (1H, s, NH), 8.36 (1H, s, =NH), 8.40 (1H, d, $J$=2.7 Hz, ArH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 7.93, 28.57, 34.99, 70.29, 111.42, 113.75, 124.12, 128.90, 136.39, 151.78, 161.01; MS (ESI): $m/z$ (%)=236.1 (100) $[M+H]^+$; $C_{11}H_{13}N_3O_3$: calcd C 56.16, H 5.57, N 17.86; found C 55.98, H 5.67, N 17.48.

**4.1.1.9. 6-Nitro-1,2-dihydro-2-methyl-2-phenyl-4-imino-4*H*-3,1-benzoxazine (5c).** Yellow solid. Mp 329–331 °C. IR (KBr): 3352, 3188, 1674, 1617, 1535, 1310, 1150 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.74 (3H, s, $CH_3$), 6.89 (1H, d, $J$=8.8 Hz, ArH), 7.24 (1H, t, $J$=7.2 Hz, ArH), 7.34 (2H, t, $J$=7.2, 8.0 Hz, ArH), 7.47 (2H, d, $J$=8.0 Hz, ArH), 8.10 (1H, dd, $J$=2.7, 8.8 Hz, ArH), 8.33 (1H, d, $J$=2.7 Hz, ArH), 9.02 (1H, s, NH), 9.22 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 30.14, 70.50, 113.00, 114.44, 124.05, 124.79 (2C), 127.61, 128.33 (2C), 128.93, 137.22, 146.64, 151.55, 161.82; MS (ESI): $m/z$ (%)=284.1 (100) $[M+H]^+$; $C_{15}H_{13}N_3O_3$: calcd C 63.59, H 4.62, N 14.83; found C 63.42, H 4.75, N 14.96.

**4.1.1.10. 7-Chloro-1,2-dihydro-2,2-dimethyl-4-imino-4*H*-3,1-benzoxazine (5d).** Pale yellow powder. Mp 227–229 °C. IR (KBr): 3311, 2978, 1627, 1602 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.52 (6H, s, $CH_3$), 6.57 (1H, s, NH), 6.71 (1H, dd, $J$=2.0, 8.0 Hz, ArH), 6.80 (1H, d, $J$=2.0 Hz, ArH), 7.70 (1H, d, $J$=8.0 Hz, ArH), 8.16 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 29.45 (2C), 69.68, 111.32, 112.83, 116.15, 129.12, 137.83, 148.32, 162.34; MS (ESI): $m/z$ (%)=211.1 (100) $[M+H]^+$; $C_{10}H_{11}N_2OCl$: calcd C 57.01, H 5.26, N 13.30; found C 57.37, H 5.33, N 13.18.

**4.1.1.11. 7-Chloro-1,2-dihydro-2-methyl-2-ethyl-4-imino-4*H*-3,1-benzoxazine (5e).** Pale yellow solid. Mp 174–176 °C. IR (KBr): 3297, 3188, 2971, 1640, 1606 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 0.86 (3H, t, $J$=7.2 Hz, $CH_3$), 1.36 (3H, s, $CH_3$), 1.57–1.67 (2H, m, $J$=7.2 Hz, $CH_2$), 6.60 (1H, dd, $J$=2.0, 8.0 Hz, ArH), 6.67 (1H, d, $J$=2.0 Hz, ArH), 6.89 (1H, s, NH), 7.54 (1H, d, $J$=8.0 Hz, ArH), 8.00 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 8.12, 27.59, 34.09, 69.63, 111.28, 112.91, 115.96, 129.06, 137.64, 148.18, 162.24; MS (ESI): $m/z$ (%)=225.1 (100) $[M+H]^+$; $C_{11}H_{13}N_2OCl$: calcd C 58.80, H 5.83, N 12.47; found C 59.12, H 5.99, N 12.28.

**4.1.1.12. 7-Chloro-1,2-dihydro-2-methyl-2-phenyl-4-imino-4*H*-3,1-benzoxazine (5f).** Pale yellow solid. Mp 106–107 °C. IR (KBr): 3318, 3181, 1668, 1606 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.65 (3H, s, $CH_3$), 6.60 (1H, dd, $J$=1.8, 8.0 Hz, ArH), 6.80 (1H, d, $J$=1.8 Hz, ArH), 7.20 (1H, t, $J$=7.2 Hz, ArH), 7.31 (2H, t, $J$=7.2, 8.0 Hz, ArH), 7.47 (3H, d, $J$=8.0 Hz, ArH), 7.92 (1H, s, NH), 8.90 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 30.51, 70.34, 113.31, 113.75, 116.85, 124.99 (2C), 127.19, 128.08 (2C), 129.21, 137.70, 147.19, 148.09, 162.91; MS (ESI): $m/z$ (%)=273.2 (100) $[M+H]^+$; $C_{15}H_{13}N_2OCl$: calcd C 66.05, H 4.80, N 10.27; found C 65.78, H 5.12, N 10.01.

**4.1.1.13. 1,2-Dihydro-2,2-dimethyl-4-imino-4*H*-3,1-benzoxazine (5g).** White solid. Mp 190–191 °C. IR (KBr): 3325, 3166, 1629, 1606, 1511 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.38 (6H, s, $CH_3$), 6.59 (1H, d, $J$=7.6 Hz, ArH), 6.62 (1H, s, NH), 6.64 (1H, d, $J$=1.6 Hz, ArH), 7.20–7.23 (1H, m, $J$=1.6, 1.2, 7.6 Hz, ArH), 7.57 (1H, dd, $J$=1.2, 7.6 Hz, ArH), 7.87 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 28.90 (2C), 66.73, 113.78, 114.13, 116.31, 127.06, 133.05, 146.96, 162.92; MS (ESI): $m/z$ (%)=177.1 (100) $[M+H]^+$; $C_{10}H_{12}N_2O$: calcd C 68.16, H 6.86, N 15.90; found C 68.50, H 6.98, N 15.74.

**4.1.1.14. 1,2-Dihydro-2-methyl-2-ethyl-4-imino-4*H*-3,1-benzoxazine (5h).** White solid. Mp 153–155 °C. IR (KBr): 3340, 2913, 1631, 1609, 1540 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 0.72 (3H, t, $J$=6.8 Hz, $CH_3$), 1.15 (3H, s, $CH_3$), 1.70–1.76 (2H, m, $CH_2$), 6.16 (1H, s, NH), 6.55–6.59 (1H, m, $J$=8.0 Hz, ArH), 6.63 (1H, d, $J$=8.0 Hz, ArH), 7.18–7.22 (1H, m, $J$=1.2, 8.0 Hz, ArH), 7.61 (1H, dd, $J$=1.2, 8.0 Hz, ArH), 8.11 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 8.35, 27.37, 34.88, 71.59, 112.35, 115.51, 118.16, 128.72, 136.16, 148.57, 167.68; MS (ESI): $m/z$ (%)=191.1 (100) $[M+H]^+$; $C_{11}H_{14}N_2O$: calcd C 69.45, H 7.42, N 14.73; found C 69.23, H 7.71, N 14.58.

**4.1.1.15. 1,2-Dihydro-2-methyl-2-phenyl-4-imino-4*H*-3,1-benzoxazine (5i).** White solid. Mp 232–234 °C. IR (KBr): 3389, 3181, 1663, 1613 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 1.79 (3H, s, $CH_3$), 6.63–6.67 (1H, m, $J$=0.8, 8.0 Hz, ArH), 6.83 (1H, t, $J$=0.8, 8.0 Hz, ArH), 6.89 (1H, s, NH), 7.21–7.23 (2H, m, ArH), 7.28–7.32 (2H, m, ArH), 7.61–7.68 (3H, m, ArH), 7.93 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 31.14, 71.54, 115.36, 116.67, 118.26, 126.09 (2C), 128.00, 128.45, 128.87 (2C), 134.05, 147.95, 148.23, 164.90; MS (ESI): $m/z$ (%)=239.1 (100) $[M+H]^+$; $C_{15}H_{14}N_2O$: calcd C 75.61, H 5.92, N 11.76; found C 75.28, H 6.11, N 11.43.

**4.1.2. Typical procedure for the preparation of 1,2-dihydro-4*H*-3,1-benzoxazine derivatives (5j–aa).** To a solution of DMF (10 mL) and $ZnCl_2$ (6 mmol) were added substituted *o*-aminobenzonitrile **1** (6 mmol) and aldehydes (8.4 mmol). The mixture was heated at reflux for the specified time (see Table 3). After completion of the reaction as indicated by TLC (eluent: ethyl acetate), the cooled reaction mixture was quenched with water (10 mL) and the precipitate was separated by filtration. The filtration residue was dispersed into water and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the product was isolated by column chromatography (200–300 mesh silica gel, ethyl acetate–petroleum=1:2).

**4.1.2.1. 6-Nitro-1,2-dihydro-2-propyl-4-imino-4*H*-3,1-benzoxazine (5j).** Yellow powder. Mp 235–237 °C. IR (KBr): 3362, 3190, 2927, 1689, 1623, 1515, 1450, 1324, 1302 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 0.90 (3H, t, $J$=7.2 Hz, $CH_3$), 1.38–1.42 (2H, m, $CH_2$), 1.61–1.67 (2H, m, $CH_2$), 4.94 (1H, t, $J$=5.0 Hz, CH), 6.80 (1H, d, $J$=8.8 Hz, ArH), 8.08 (1H, dd, $J$=2.7, 8.8 Hz, ArH), 8.13 (1H, s, NH), 8.36 (1H, s, =NH), 8.39 (1H, d, $J$=2.7 Hz, ArH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 13.66, 16.21, 38.18, 63.94, 112.64, 114.12, 124.19, 128.76, 136.76, 152.76, 161.57; MS (ESI): $m/z$ (%)=236.1 (100) $[M+H]^+$; $C_{11}H_{13}N_3O_3$: calcd C 56.16, H 5.57, N 17.86; found C 56.19, H 5.48, N 17.46.

**4.1.2.2. 6-Nitro-1,2-dihydro-2-phenyl-4-imino-4*H*-3,1-benzoxazine (5k).** Yellow powder. Mp 264–265 °C. IR (KBr): 3385, 3166, 1690, 1618, 1530, 1329, 1140 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 6.02 (1H, t, $J$=1.7 Hz, CH), 6.83 (1H, d, $J$=8.8 Hz, ArH), 7.39 (1H, t, $J$=7.2 Hz, ArH), 7.42 (2H, t, $J$=7.2, 8.0 Hz, ArH), 7.49 (2H, d, $J$=8.0 Hz, ArH), 8.11 (1H, dd, $J$=2.8, 8.8 Hz, ArH), 8.44 (1H, d, $J$=2.8 Hz, ArH), 8.57 (1H, s, NH), 8.75 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 66.30, 112.64, 114.24, 124.18, 126.54 (2C), 128.65 (2C), 128.88, 128.97, 137.12, 141.09, 152.13, 161.28; MS (ESI): $m/z$ (%)=270.1 (100) $[M+H]^+$; $C_{14}H_{11}N_3O_3$: calcd C 62.45, H 4.12, N 15.61; found C 62.28, H 3.80, N 15.25.

**4.1.2.3. 6-Nitro-1,2-dihydro-2-*m*-nitrophenyl-4-imino-4*H*-3,1-benzoxazine (5l).** Yellow powder. Mp 294–296 °C. IR (KBr): 3321, 3191, 1685, 1618, 1532, 1324 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 6.25 (1H, s, CH), 6.89 (1H, d, $J$=8.8 Hz, ArH), 7.75 (1H, t, $J$=8.0 Hz, ArH), 7.94 (1H, d, $J$=8.0 Hz, ArH), 8.14 (1H, dd, $J$=2.8, 8.8 Hz, ArH), 8.26–8.27 (1H, m, $J$=1.6 Hz, ArH), 8.35 (1H, t, $J$=1.6 Hz, ArH), 8.44 (1H, d, $J$=2.8 Hz, ArH), 8.73 (1H, s, NH), 8.96 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.03, 112.69, 114.55, 121.38, 123.69, 124.16, 129.11, 130.45, 133.02, 137.50, 143.45, 147.80, 151.78, 161.19; MS (ESI): $m/z$ (%)=315.4 (100) $[M+H]^+$; $C_{14}H_{10}N_4O_5$: calcd C 53.51, H 3.21, N 17.82; found C 53.22, H 3.27, N 17.72.

**4.1.2.4. 6-Nitro-1,2-dihydro-2-*p*-nitrophenyl-4-imino-4*H*-3,1-benzoxazine (5m).** Yellow powder. Mp 263–265 °C. IR (KBr): 3350, 3084, 1690, 1621, 1522, 1330 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 6.21 (1H, s, CH), 6.87 (1H, d, $J$=8.8 Hz, ArH), 7.73 (2H, d, $J$=8.4 Hz, ArH), 8.13 (1H, dd, $J$=2.8, 8.8 Hz, ArH), 8.29 (2H, d, $J$=8.4 Hz, ArH), 8.43 (1H, d, $J$=2.8 Hz, ArH), 8.72 (1H, s, NH), 8.96 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.14, 112.63, 114.49, 123.92 (2C), 124.16, 127.80 (2C), 129.11, 137.44, 147.66, 148.29, 151.73, 161.09; MS (ESI): $m/z$ (%)=315.4 (100) $[M+H]^+$; $C_{14}H_{10}N_4O_5$: calcd C 53.51, H 3.21, N 17.82; found C 53.33, H 3.31, N 17.46.

**4.1.2.5. 6-Nitro-1,2-dihydro-2-*p*-methoxy-4-imino-4*H*-3,1-benzoxazine (5n).** Yellow powder. Mp 242–243 °C. IR (KBr): 3385, 3162, 1660, 1620, 1512, 1309 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 3.75 (3H, s, $CH_3$), 5.97 (1H, s, CH), 6.82 (1H, d, $J$=8.8 Hz, ArH), 6.98 (2H, d, $J$=8.4 Hz, ArH), 7.39 (2H, d, $J$=8.4 Hz, ArH), 8.11 (1H, dd, $J$=2.8, 8.8 Hz, ArH), 8.43 (1H, d, $J$=2.8 Hz, ArH), 8.50 (1H, s, NH), 8.68 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 55.19, 65.91, 112.62, 113.90 (2C), 114.20, 124.16, 127.94 (2C), 128.93, 132.94, 136.99, 152.19, 159.67, 161.36; MS (ESI): $m/z$ (%)=300.1 (100) $[M+H]^+$; $C_{15}H_{13}N_3O_4$: calcd C 60.19, H 4.38, N 14.04; found C 60.05, H 4.40, N 14.11.

**4.1.2.6. 6-Nitro-1,2-dihydro-2-*p*-chlorophenyl-4-imino-4*H*-3,1-benzoxazine (5o).** Yellow powder. Mp 263–265 °C. IR (KBr): 3366, 3180, 1692, 1615, 1492, 1328 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 6.06 (1H, s, CH), 6.84 (1H, d, $J$=8.8 Hz, ArH), 7.50 (4H, s, ArH), 8.13 (1H, dd, $J$=2.8, 8.8 Hz, ArH), 8.43 (1H, d, $J$=2.8 Hz, ArH), 8.59 (1H, s, NH), 8.80 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.49, 112.62, 114.32, 124.13, 128.45 (2C), 128.62 (2C), 128.99, 133.40, 137.23, 140.05, 151.96, 161.20; MS (ESI): $m/z$ (%)=304.4 (100) $[M+H]^+$; $C_{14}H_{10}N_3O_3Cl$: calcd C 55.37, H 3.32, N 13.83; found C 55.59, H 3.62, N 13.44.

**4.1.2.7. 7-Chloro-1,2-dihydro-2-propyl-4-imino-4*H*-3,1-benzoxazine (5p).** Pale yellow powder. Mp 222–223 °C. IR (KBr): 3285, 3180, 2920, 1674, 1602, 1447 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 0.93 (3H, t, $J$=7.2 Hz, $CH_3$), 1.71–1.77 (2H, m, $CH_2$), 2.56–2.59 (2H, m, $CH_2$), 5.38 (1H, t, $J$=5.0 Hz, CH), 7.48 (1H, dd, $J$=2.0, 8.4 Hz, ArH), 7.64 (1H, d, $J$=2.0 Hz, ArH), 8.06 (1H, d, $J$=8.4 Hz, ArH), 8.19 (1H, s, NH), 8.38 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 13.40, 20.08, 36.31, 65.21, 125.89, 126.14, 127.73, 138.83, 150.02, 159.00, 161.14; MS (ESI): $m/z$ (%)=225.1 (100) $[M+H]^+$; $C_{11}H_{13}N_2OCl$: calcd C 58.80, H 5.83, N 12.47; found C 59.20, H 5.48, N 12.21.

**4.1.2.8. 7-Chloro-1,2-dihydro-2-phenyl-4-imino-4*H*-3,1-benzoxazine (5q).** Pale yellow powder. Mp 245–247 °C. IR (KBr): 3392, 3079, 1669, 1603 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 5.81 (1H, t, $J$=1.7 Hz, CH), 6.69 (1H, dd, $J$=2.0, 8.4 Hz, ArH), 6.80 (1H, d, $J$=2.0 Hz, ArH), 7.15 (1H, t, $J$=7.2 Hz, ArH), 7.23 (2H, t, $J$=7.2, 8.0 Hz, ArH), 7.27 (2H, d, $J$=8.0 Hz, ArH), 7.31 (1H, s, NH), 7.60 (1H, d, $J$=8.4 Hz, ArH), 8.41 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.23, 113.51, 113.61, 117.23, 121.76 (2C), 123.85 (2C), 129.38, 133.17, 137.90, 148.74, 159.12, 162.21; MS (ESI): $m/z$ (%)=259.1 (100) $[M+H]^+$; $C_{14}H_{11}N_2OCl$: calcd C 64.99, H 4.29, N 10.83; found C 65.03, H 4.67, N 10.50.

**4.1.2.9. 7-Chloro-1,2-dihydro-2-*m*-nitrophenyl-4-imino-4*H*-3,1-benzoxazine (5r).** Yellow powder. Mp 258–260 °C. IR (KBr): 3301, 3166, 1665, 1609, 1523, 1345 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 6.02 (1H, s, CH), 6.72 (1H, dd, $J$=1.8, 8.0 Hz, ArH), 6.83 (1H, d, $J$=1.8 Hz, ArH), 7.61 (2H, t, $J$=4.0, 4.0 Hz, ArH), 7.72 (1H, t, $J$=7.8, 7.8 Hz, ArH), 7.93 (1H, d, $J$=8.0 Hz, ArH), 8.21–8.23 (1H, m, $J$=1.6, 1.6 Hz, ArH), 8.35 (1H, s, NH), 8.66 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.09, 113.58, 113.63, 117.47, 121.48, 123.40, 129.42, 130.17, 133.18, 138.05, 143.94, 147.75, 148.22, 162.46; MS (ESI): $m/z$ (%)=304.0 (100) $[M+H]^+$; $C_{14}H_{10}N_3O_3Cl$: calcd C 55.37, H 3.32, N 13.84; found C 55.76, H 3.35, N 13.75.

**4.1.2.10. 7-Chloro-1,2-dihydro-2-*p*-nitrophenyl-4-imino-4*H*-3,1-benzoxazine (5s).** Yellow powder. Mp 243–244 °C. IR (KBr): 3355, 3282, 1660, 1609, 1521, 1351 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 5.99 (1H, s, CH), 6.70 (1H, dd, $J$=2.0, 8.4 Hz, ArH), 6.82 (1H, d, $J$=2.0 Hz, ArH), 7.60 (2H, d, $J$=8.4 Hz, ArH), 7.73 (2H, d, $J$=8.4 Hz, ArH), 8.26 (1H, s, NH), 8.27 (1H, d, $J$=8.4 Hz, ArH), 8.66 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.22, 113.59, 113.63, 117.43, 123.72 (2C), 127.95 (2C), 129.43, 138.09, 147.52, 148.20, 148.97, 162.42; MS (ESI): $m/z$ (%)=304.0 (100) $[M+H]^+$; $C_{14}H_{10}N_3O_3Cl$: calcd C 55.37, H 3.32, N 13.84; found C 55.72, H 3.39, N 13.86.

**4.1.2.11. 7-Chloro-1,2-dihydro-2-*p*-methoxy-4-imino-4*H*-3,1-benzoxazine (5t).** Pale yellow powder. Mp 221–223 °C. IR (KBr): 3299, 3181, 1653, 1609, 1512 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 3.75 (3H, s, $CH_3$), 5.76 (1H, s, CH), 6.69 (1H, dd, $J$=2.0, 8.4 Hz, ArH), 6.78 (1H, d, $J$=2.0 Hz, ArH), 6.96 (2H, dd, $J$=1.6, 6.8 Hz, ArH), 7.29 (1H, s, NH), 7.41 (2H, dd, $J$=1.6, 6.8 Hz, ArH), 7.60 (1H, d, $J$=8.4 Hz, ArH), 8.32 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 55.21, 66.23, 113.45, 113.71, 113.76 (2C), 117.01, 128.17 (2C), 129.36, 133.17, 137.79, 148.94, 159.56, 162.84; MS (ESI): $m/z$ (%)=289.0 (100) $[M+H]^+$; $C_{15}H_{13}N_2O_2Cl$: calcd C 62.40, H 4.54, N 9.70; found C 62.00, H 4.55, N 9.94.

**4.1.2.12. 7-Chloro-1,2-dihydro-2-*p*-chlorophenyl-4-imino-4*H*-3,1-benzoxazine (5u).** Yellow powder. Mp 242–244 °C. IR (KBr): 3251, 3166, 1649, 1609, 1484 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 5.85 (1H, s, CH), 6.70 (1H, dd, $J$=2.0, 8.4 Hz, ArH), 6.80 (1H, d, $J$=2.0 Hz, ArH), 7.43 (1H, s, NH), 7.47–7.52 (4H, m, $J$=2.4 Hz, ArH), 7.61 (1H, d, $J$=8.4 Hz, ArH), 8.48 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.69, 113.51, 113.59, 117.20, 128.42 (2C), 128.65 (2C), 129.36, 133.15, 137.93, 140.34, 148.56, 162.61; MS (ESI): $m/z$ (%)=294.0 (100) $[M+H]^+$; $C_{14}H_{10}N_2OCl_2$: calcd C 57.36, H 3.44, N 9.56; found C 57.51, H 3.47, N 9.66.

**4.1.2.13. 1,2-Dihydro-2-propyl-4-imino-4*H*-3,1-benzoxazine (5v).** White powder. Mp 213–215 °C. IR (KBr): 3382, 3185, 2927, 1645, 1608, 1430 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 0.81 (3H, t, $J$=7.2 Hz, $CH_3$), 1.05–1.11 (2H, m, $CH_2$), 1.30–1.37 (2H, m, $CH_2$), 4.24 (1H, t, $J$=5.0 Hz, CH), 6.21 (1H, d, $J$=1.6 Hz, ArH), 6.42 (1H, s, NH), 6.51 (1H, d, $J$=1.6 Hz, ArH), 7.00–7.02 (1H, m, $J$=1.6, 1.2, 7.6 Hz, ArH), 7.37 (1H, dd, $J$=1.2, 7.6 Hz, ArH), 7.57 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 13.21, 18.21, 34.18, 66.45, 113.69, 114.19, 116.35, 127.16, 133.01, 146.89, 162.72; MS (ESI): $m/z$ (%)=191.1 (100) $[M+H]^+$; $C_{11}H_{14}N_2O$: calcd C 69.44, H 7.42, N 14.73; found C 69.30, H 7.25, N 14.92.

**4.1.2.14. 1,2-Dihydro-2-phenyl-4-imino-4*H*-3,1-benzoxazine (5w).** White powder. Mp 224–226 °C. IR (KBr): 3370, 3177, 1678, 1608, 1472 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 5.71 (1H, t, $J$=1.7 Hz, CH), 6.77–6.79 (4H, m, $J$=8.0 Hz, ArH), 7.11 (1H, s, NH), 7.25 (1H, d, $J$=8.0 Hz, ArH), 7.31 (1H, t, $J$=8.0 Hz, ArH), 7.78 (3H, t, $J$=8.0 Hz, ArH), 8.28 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.64, 113.82, 114.30, 124.81, 127.45 (2C), 128.80 (2C), 128.88, 129.33, 133.38, 140.56, 147.23, 163.28; MS (ESI): $m/z$ (%)=225.1 (100) $[M+H]^+$; $C_{14}H_{12}N_2O$: calcd C 74.98, H 5.39, N 12.49; found C 74.67, H 5.21, N 12.63.

**4.1.2.15. 1,2-Dihydro-2-*m*-nitrophenyl-4-imino-4*H*-3,1-benzoxazine (5x).** Yellow powder. Mp 210–212 °C. IR (KBr): 3296, 3188, 1653, 1610, 1532, 1353 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 5.95 (1H, s, CH), 6.70 (1H, t, $J$=7.6 Hz, ArH), 6.79 (1H, d, $J$=8.0 Hz, ArH), 7.29 (1H, t, $J$=8.0 Hz, ArH), 7.35 (1H, s, NH), 7.62 (1H, dd, $J$=7.6 Hz, ArH), 7.70 (1H, t, $J$=7.6 Hz, ArH), 7.94 (1H, d, $J$=7.6 Hz, ArH), 8.21–8.22 (1H, m, $J$=1.4, 1.4 Hz, ArH), 8.36 (1H, t, $J$=1.8, 1.8 Hz, ArH), 8.53 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.20, 114.61, 114.97, 117.55, 121.59, 123.29, 127.43, 130.06, 133.39, 133.59, 144.32, 147.32, 147.73, 163.36; MS (ESI): $m/z$ (%)=270.1 (100) $[M+H]^+$; $C_{14}H_{11}N_3O_3$: calcd C 62.45, H 4.12, N 15.61; found C 62.16, H 4.20, N 15.24.

**4.1.2.16. 1,2-Dihydro-2-*p*-nitrophenyl-4-imino-4*H*-3,1-benzoxazine (5y).** Yellow powder. Mp 198–200 °C. IR (KBr): 3389, 3282, 1647, 1615, 1520, 1349 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 5.91 (1H, s, CH), 6.68 (1H, t, $J$=7.6 Hz, ArH), 6.76 (1H, d, $J$=8.0 Hz, ArH), 7.26 (1H, t, $J$=7.6 Hz, ArH), 7.33 (1H, s, NH), 7.60 (1H, d, $J$=8.0 Hz, ArH), 7.73 (2H, d, $J$=8.4 Hz, ArH), 8.25 (2H, d, $J$=8.4 Hz, ArH), 8.51 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.76, 115.02, 115.38, 117.92, 124.02 (2C), 127.86, 128.48 (2C), 134.00, 147.68, 147.91, 149.81, 163.71; MS (ESI): $m/z$ (%)=270.1 (100) $[M+H]^+$; $C_{14}H_{11}N_3O_3$: calcd C 62.45, H 4.12, N 15.61; found C 62.21, H 4.51, N 15.36.

**4.1.2.17. 1,2-Dihydro-2-*p*-methoxy-4-imino-4*H*-3,1-benzoxazine (5z).** White powder. Mp 255–257 °C. IR (KBr): 3269, 3171, 1678, 1602 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 3.86 (3H, s, $CH_3$), 5.67 (1H, s, CH), 6.42 (2H, dd, $J$=2.0, 7.6 Hz, ArH), 6.89–6.90 (1H, m, $J$=8.0 Hz, ArH), 7.04 (1H, s, NH), 7.15 (1H, d, $J$=8.0 Hz, ArH), 7.20–7.21 (1H, m, $J$=8.0 Hz, ArH), 7.36 (1H, dd, $J$=8.0 Hz, ArH), 7.45 (2H, dd, $J$=2.0, 7.6 Hz, ArH), 8.21 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 55.43, 65.36, 114.45, 114.71, 117.12 (2C), 117.69, 128.31 (2C), 128.75, 132.76, 133.79, 140.59, 147.56, 163.20; MS (ESI): $m/z$ (%)=255.1 (100) $[M+H]^+$; $C_{15}H_{14}N_2O_2$: calcd C 70.85, H 5.55, N 11.02; found C 70.88, H 5.25, N 10.81.

**4.1.2.18. 1,2-Dihydro-2-*p*-chlorophenyl-4-imino-4*H*-3,1-benzoxazine (5aa).** White powder. Mp 227–228 °C. IR (KBr): 3325, 3188, 1658, 1609, 1483 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) $\delta_H$: 5.78 (1H, s, CH), 6.67 (1H, t, $J$=8.0 Hz, ArH), 6.75 (1H, d, $J$=8.0 Hz, ArH), 7.15 (1H, s, NH), 7.25–7.27 (1H, m, $J$=8.0 Hz, ArH), 7.46–7.47 (2H, m, $J$=2.0, 6.4 Hz, ArH), 7.52 (2H, dd, $J$=2.0, 6.4 Hz, ArH), 7.62 (1H, dd, $J$=8.0 Hz, ArH), 8.34 (1H, s, =NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz) $\delta_C$: 65.79, 114.48, 114.97, 117.30, 127.39, 128.33, 128.34, 128.78 (2C), 132.99, 133.42, 140.70, 147.67, 163.50; MS (ESI): $m/z$ (%)=259.1 (100) $[M+H]^+$; $C_{14}H_{11}N_2OCl$: calcd C 65.00, H 4.29, N 10.83; found C 65.38, H 4.36, N 10.88.

## 4.2. Crystallography

X-ray data for **3d** have been deposited at the Cambridge Crystallographic Data Centre, deposition number CCDC 295187. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk). Crystal data for **3d**: $C_{12}H_{13}N_3O_3$; $M$=247.25, colorless block crystals, 0.50×0.50×0.50 mm, monoclinic, space group $C2/c$, $a$=19.206(4), $b$=8.7663(18), $c$=13.720(3) Å, $\beta$=90.03(3)°, $V$=2310.0(8) $Å^3$, $Z$=8, $D_c$=1.422 g $cm^{-3}$, $F(000)$=1040, $\mu$ (Mo Kα)=0.105 $mm^{-1}$. Intensity data were collected on a Rigaku Raxis RApid IP diffractometer with graphite monochromated Mo Kα radiation ($\lambda$=0.71073 Å) by using a $\omega-2\theta$ scan mode in the range of $2.55°<\theta<25.00°$. Out of 1973 unique reflections measured 1502 reflections with $I>2\sigma(I)$ were used in the refinement. The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ using SHELXL-97.[10] Nonhydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located from a difference Fourier maps and refined without restraints. The final refinement was converged to $R$=0.0665 and $wR$=0.1947.

## Acknowledgements

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# Synthesis of plakevulin A and structure–activity relationships of its related compounds against DNA polymerases

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**Abstract**—Synthesis of plakevulin A and structure–activity relationships of its related compounds against DNA polymerases is described. We have achieved a total synthesis and revised the structure of plakevulin A. Several analogues including untenone A, manzamenone A, and optically active plakevulin A, were prepared and tested with an enzyme inhibition assay for mammalian DNA polymerases. The effect of the methyl ester moiety, and the substituents at the 1- and 4-positions of plakevulin A on DNA polymerase activities are discussed.


## 1. Introduction

The cytotoxic oxylipin, plakevulin A (**1**), was isolated from an Okinawan sponge *Plakortis* sp by Kobayashi et al.[1] Compound **1** exhibited cytotoxicity against murine leukemia L1210 and epidermoid carcinoma KB cells (Fig. 1). It was also reported that **1** inhibited the activities of DNA polymerases (pol) α and γ. Although the proposed structure was the levulinyl ester as depicted for **1a**, our synthetic studies and enzyme-inhibitory assays revealed that the structure of plakevulin A is actually as shown for **1**.[2] Recently a synthesis of optically active (+)-**1** has been reported by Honda et al.[3]

Untenone A (**2**), which inhibited the cell proliferation of L1210 cells, was isolated from the genus *Plakortis*.[4,5] The structurally related manzamenone A (**3**), a unique dimeric fatty acid derivative, was also isolated from the *Plakortis*.[6,7] Untenone A has been considered to be a plausible intermediate in the biosynthetic pathways of manzamenone A and plakevulin A.[1,7] Both **2** and **3** were found to inhibit mammalian pol α,β, and human terminal deoxynucleotidyl transferase (TdT).[8,9]

In this article, we fully describe our synthetic studies and biological evaluation of a series of plakevulin A analogues.

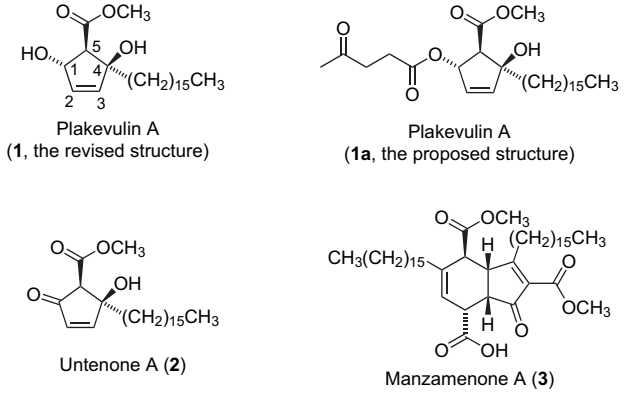


**Figure 1**. The revised structure of plakevulin A (**1**), the proposed structure of plakevulin A (**1a**), untenone A (**2**), and manzamenone (**3**).

## 2. Results and discussions

### 2.1. Synthesis and structural revision of plakevulin A

Our synthetic approach towards the proposed structure of plakevulin A (**1a**) was based on the assumed biosynthetic pathway.[1,2,7] The reduction of untenone A (**2**), followed by esterification of the resulting alcohol would provide **1a**. Our route to synthesize untenone A was based on the modified protocol reported by Yamada et al.[5b]

Protection of the alcohol (±)-**4** with TMSOTf and *i*-$Pr_2NEt$ gave a TMS ether (±)-**5** (Scheme 1). Methoxycarboxylation

*Keywords*: Plakevulin A; Untenone A; Manzamenone A; DNA polymerase.
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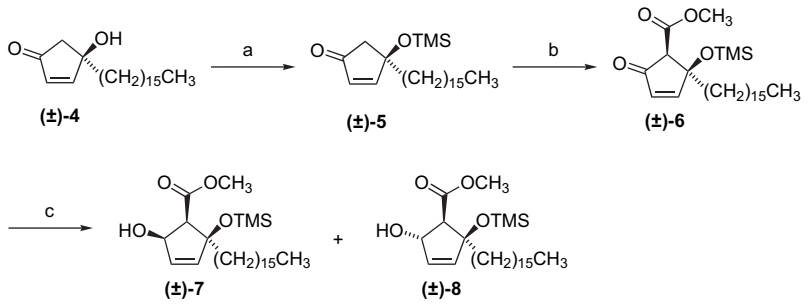



**Scheme 1**. Synthesis of the key intermediate (±)-**7**. (a) TMSOTf, *i*-$Pr_2NEt$, $CH_2Cl_2$, 0 °C, 90%; (b) LDA, THF/HMPA, then $NCCO_2CH_3$, −42 °C, 63% (dr=4.2:1) and (c) DIBAL, $CH_2Cl_2$, −78 °C, 41% for (±)-**7** and 6% for (±)-**8**.

of (±)-**5** with LDA and $NCCO_2CH_3$ afforded (±)-**6** as a 4.2:1 mixture of inseparable diastereomers in 63% yield.[5c] Reduction of (±)-**6** with DIBAL (2 equiv) in $CH_2Cl_2$ gave (±)-**7** and (±)-**8** in 41% and 6% yields, respectively, as the identified products. In this reaction, β-hydroxyaldehyde was obtained as the major byproduct, as a mixture that proved difficult to separate. When 1 equiv of DIBAL was used, no reaction occurred. Although the use of other reducing agents such as $NaBH_4$–$CeCl_3$, $LiBH_4$, $ZnBH_4$, and (*i*-PrO)$_3$Al/*i*-PrOH was examined, none or only a trace amount of (±)-**7** was obtained. The stereochemistry of the major isomer (±)-**7** was determined by its NOESY spectrum (Fig. 2a). The NOESY correlation between H-1 and H-5 in (±)-**7** indicated the *syn* relation for H-1/H-5. The *anti* relation for 4-OTMS and H-5 in (±)-**7** was determined by the NOESY correlations between H-5 and H-6, and between 4-OTMS and H-23.

The esterification of (±)-**7** was attempted with both inversion and retention of the stereochemistry at C-1 (Scheme 2). The Mitsunobu esterification of (±)-**7** with levulinic acid afforded (±)-**9** in 52% yield.[10] The observed NOEs between H-1 and 4-OTMS and between H-1 and H-23 of (±)-**9** indicated that the configuration of **9** was 1*S**,4*S**,5*R** (Fig. 2b). Deprotection of TMS ether (±)-**9** with TBAF provided the proposed structure of plakevulin A (**1a**). On the other hand, the esterification of (±)-**7** with levulinic acid by EDCI, followed by deprotection of the TMS ether afforded (±)-**11**, the 1-*epi*-isomer of **1a**.

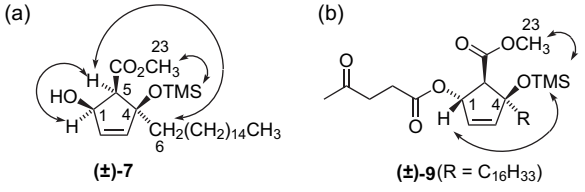


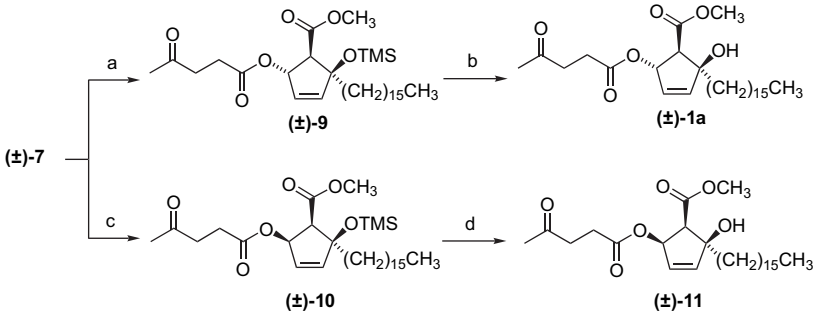

**Figure 2**. The NOESY correlations for (±)-**7** (left) and (±)-**9** (right).

Selected $^1H$ and $^{13}C$ NMR spectral data of (±)-**1a** and (±)-**11** are summarized in Table 1. As shown in Table 1, the $^1H$ and $^{13}C$ NMR spectral data of (±)-**1a** and (±)-**11** were different from those of the natural plakevulin A. In particular, both the proton and carbon signals at C-1 in (±)-**1a** appeared further downfield from those in the natural plakevulin A. These observations suggested that the natural plakevulin A is not the levulinyl ester, but the delevulinyl form.

Based on these considerations, the removal of the levulinyl moiety of (±)-**1a** was attempted (Scheme 3). Treatment of (±)-**1a** with hydrazine in pyridine and acetic acid gave the alcohol (±)-**1** in 92% yield.[11] The $^1H$ NMR and $^{13}C$ NMR spectral data of synthetic (±)-**1** were in good agreement with those of the natural plakevulin A except for the peaks derived from levulinic acid. Therefore the sample of the natural plakevulin A could be estimated to be an 1:1 mixture of (+)-**1** and levulinic acid. On the other hand, deprotection of TMS ether (±)-**7** with TBAF afforded (±)-**12** in 64% yield. The $^1H$ NMR and $^{13}C$ NMR spectral data of (±)-**12** were actually different from those of **1**.

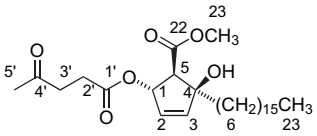
## 2.2. Synthesis of (+)- and (−)-plakevulin A, and (+)- and (−)-untenone A

Since natural plakevulin A is optically active ($[\alpha]_D^{25}$ +19 (*c* 2.0, $CHCl_3$)),[1] (+)-plakevulin A was synthesized from **13**.[5b] Compound **13** was prepared from (*S*)-(*tert*-butyldimethylsilyloxy)-2-cyclopentenone (99% ee by a chiral HPLC), which was derived from *cis*-3,5-diacetoxycyclopent-1-ene

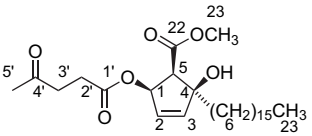



**Scheme 2**. Synthesis of the proposed structure of (±)-plakevulin A (**1a**) and (±)-**11**. (a) levulinic acid, DIAD, $PPh_3$, toluene, 52%; (b) TBAF, THF, 0 °C, 94%; (c) levulinic acid, EDCI, DMAP, 1,4-dioxane, 83% and (d) TBAF, THF, 0 °C, 49%.

**Table 1**. The selected $^{1}H$ and $^{13}C$ NMR spectral data of the natural plakevulin A, (±)-**1a**, and (±)-**11**

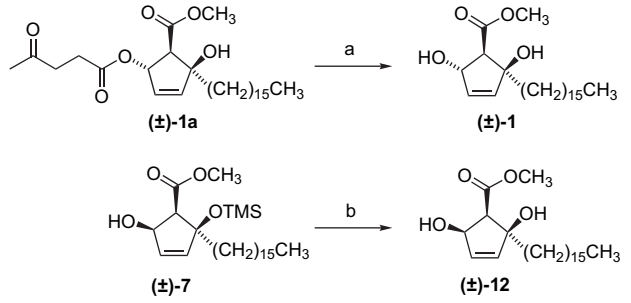


**(±)-1a (the proposed structure)**



**(±)-11**

| $^{1}H$ NMR | Natural plakevulin A | 1a | 11 |
|---|---|---|---|
| | δ (m, Hz) | δ (m, Hz) | δ (m, Hz) |
| 1 | 5.34 ddd, 5.2, 1.7, 1.5 | 6.04 ddd, 4.4, 1.5, 0.8 | 5.82 br d, 6.9 |
| 2 | 5.92 dd, 5.6, 1.8 | 5.91 dd, 5.4, 1.5 | 5.90 dd, 5.6, 2.1 |
| 3 | 5.85 dd, 5.6, 1.5 | 5.94 dd, 5.4, 0.8 | 6.08 d, 5.6 |
| 5 | 2.82 d, 5.2 | 2.96 d, 4.4 | 3.22 dd, 6.9, 1.0 |
| 6 | 1.81 m | 1.80 m | 1.65 m |
| 23 | 3.78 s | 3.76 s | 3.75 s |
| 2′ | 2.63 t, 6.4 | 2.56 m | 2.55 t, 6.5 |
| 3′ | 2.75 t, 6.4 | 2.75 m | 2.72 m |
| 5′ | 2.20 s | 2.18 s | 2.19 m |
| $^{13}C$ NMR | | | |
| 1 | 78.2 | 80.9 | 76.8 |
| 2 | 135.7 | 131.5 | 129.4 |
| 3 | 136.9 | 139.8 | 142.2 |
| 4 | 84.9 | 85.3 | 83.4 |
| 5 | 60.6 | 57.7 | 53.9 |
| 6 | 40.6 | 40.8 | 40.4 |
| 22 | 172.7 | 171.8 | 171.5 |
| 23 | 52.1 | 52.2 | 52.1 |
| 1′ | 177.6 | 172.4 | 172.0 |
| 2′ | 27.6 | 27.9 | 28.0 |
| 3′ | 37.7 | 37.8 | 37.7 |
| 4′ | 206.5 | 206.3 | 206.3 |
| 5′ | 29.7 | 29.8 | 29.8 |



**Scheme 3**. Synthesis of the alcohol (±)-**1** and (±)-**12**. (a) $NH_2NH_2 \cdot H_2O$, pyridine/AcOH, 92% and (b) TBAF, THF, 64%.

(Scheme 4).[12] Desilylation of **13** with TBAF afforded (−)-**14** in 82% yield. Oxidation of (−)-**14** with Jones reagent, followed by protection of the *tert*-alcohol as a TMS ether gave (−)-**5** in 90% yield (99% ee by a chiral HPLC). Treatment of (−)-**5** with LDA followed by $NCCO_2CH_3$ in THF/HMPA gave **6** in a 4.2:1 diastereomeric mixture.

Reduction of **6** with DIBAL afforded (−)-**7** and (+)-**8** in 36% and 5%, respectively (Scheme 5). Esterification of (−)-**7** with *p*-nitrobenzoic acid under Mitsunobu conditions gave (+)-**15** in 61% yield. Methanolysis of the *p*-nitrobenzoate **15** and spontaneous migration of TMS group provided 1-*O*-TMS ether **16**. Finally desilylation of (+)-**16** with TBAF afforded (+)-plakevulin A (**1**) in 73% yield. The optical rotation of our synthetic (+)-**1** ($[\alpha]_D^{21}$ +27.1 (*c* 0.55, $CHCl_3$)) was slightly higher than that of natural **1** ($[\alpha]_D^{25}$ +19 (*c* 2.0, $CHCl_3$)),[1] and almost the same value as that of the synthetic (+)-**1** reported by Honda et al. ($[\alpha]_D^{22}$ +24.1 (*c* 0.6, $CHCl_3$)).[3] Compound (+)-**1** was also obtained by desilylation of (+)-**8** with TBAF.

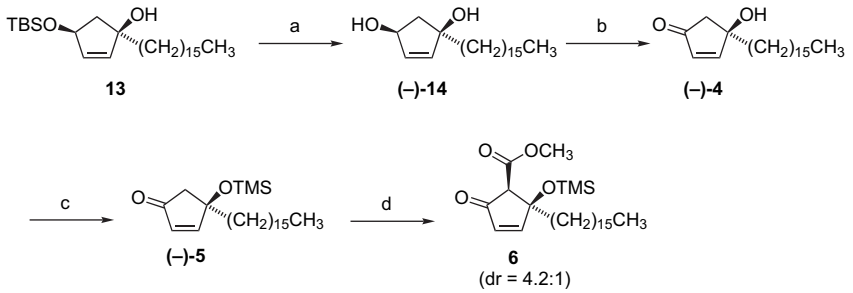
Since deprotection of TMS ether **6** could give optically active (−)-untenone A (**2**), deprotection of **6** was attempted (Scheme 6). First, treatment of **6** with TBAF in THF gave **2** as a racemic form ($[\alpha]_D^{23}$ ~0 (*c* 0.25, $CHCl_3$)). Although the formation of the acylic β-ketoester could not be observed in this reaction, the basic conditions would induce the retro-aldol reaction of the β′-hydroxy-β-ketoester and promote the racemization of **2**. Thus deprotection of **6** was performed under acidic conditions. Treatment of **6** with a catalytic amount of concd HCl in methanol gave optically active (−)-untenone A (**2**) in 94% yield. The optical rotation of our synthetic (−)-**2** ($[\alpha]_D^{23}$ −71.3 (*c* 0.94, $CHCl_3$)) was identical with those reported in the literature ($[\alpha]_D^{27}$ −73.3 (*c* 1.2, $CHCl_3$))[5c] by Asami et al., and $[\alpha]_D^{26}$ −79.7 (*c* 1.0, $CHCl_3$) by Honda et al.[3]

(−)-Plakevulin A (**1**) ($[\alpha]_D^{21}$ −25.7 (*c* 0.10, $CHCl_3$)) and (+)-untenone A (**2**) ($[\alpha]_D^{23}$ +72.2 (*c* 0.50, $CHCl_3$)) were prepared starting from **17**[5b] according to the same procedures (Scheme 7).

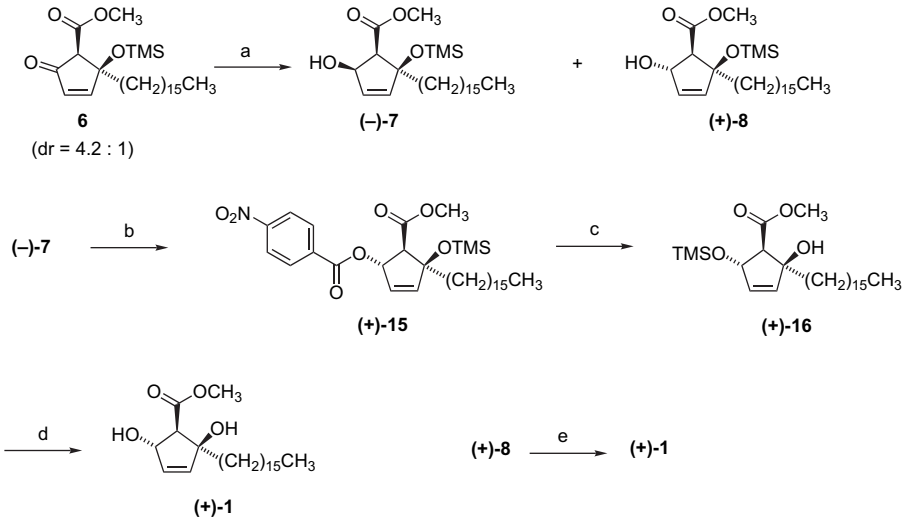
### 2.3. Preparation of (±)-untenone A, (±)-manzamenone A, and untenone A derivatives

In order to examine the structure–activity relationships, we prepared a number of untenone A derivatives.[9]

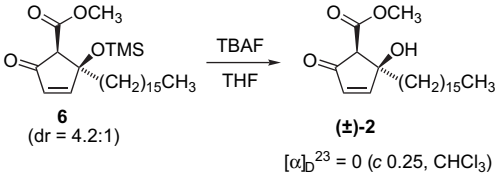
(±)-Untenone A (**2**) was prepared from (±)-**6**, from which in turn (±)-manzamenone A (**3**) was prepared by heating via a unique biogenetic pathway reported by Whitehead et al. (Scheme 8).[7]

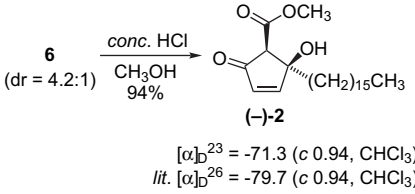


**Scheme 4**. Synthesis of the key intermediate **6**. (a) TBAF, THF, 84%; (b) Jones reagent, acetone, 77%; (c) TMSOTf, *i*-$Pr_2NEt$, $CH_2Cl_2$, 0 °C, 92% and (d) LDA, THF/HMPA, then $NCCO_2CH_3$, −42 °C, 69% (dr=4.2:1).

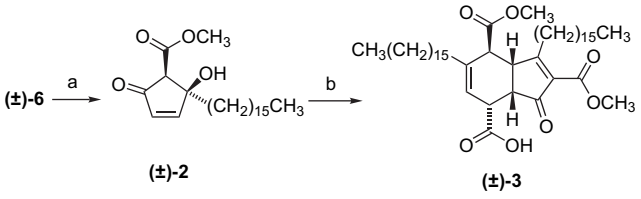



**Scheme 5**. Synthesis of (+)-plakevulin A (**1**). (a) DIBAL, $CH_2Cl_2$, −78 °C, 36% for (−)-**7** and 5% for (+)-**8**; (b) DIAD, $PPh_3$, *p*-nitrobenzoic acid, THF, 61%; (c) $NaOCH_3$, $CH_3OH$, 81%; (d) TBAF, THF, 73% and (e) TBAF, THF, 52%.

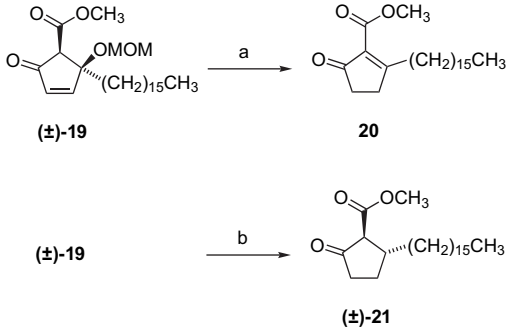



**Scheme 6**. Deprotection of TMS ether of **6**. (a) TBAF, THF and (b) concd HCl (cat), $CH_3OH$, 94%.

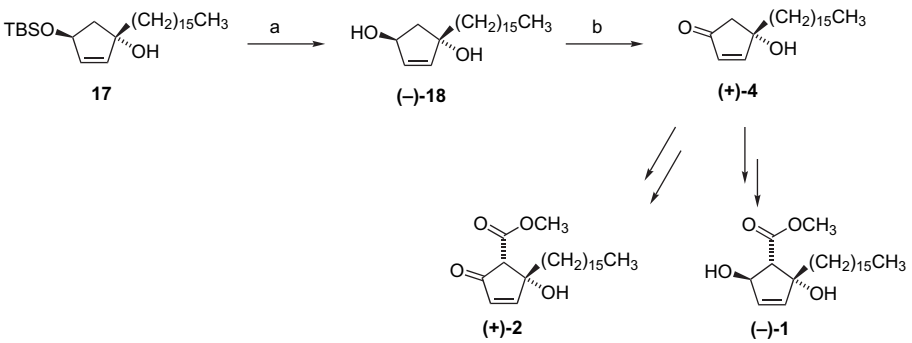



**Scheme 8**. Synthesis of (±)-**2** and (±)-**3**. (a) concd HCl, $CH_3OH$ and (b) △.




**Scheme 9**. Synthesis of (±)-**20** and (±)-**21**. (a) $H_2$, Pd/C, EtOAc, quant. and (b) $H_2$, $Pd(OH)_2$/C, EtOAc, quant.

Hydrogenation of the double bond and elimination of the methoxymethyloxy group occurred by treatment of (±)-**19**[5b] with 10% Pd on carbon under an $H_2$ atmosphere to yield **20** (Scheme 9). On the other hand, treatment of (±)-**19** with $Pd(OH)_2$ under an $H_2$ atmosphere afforded (±)-**21**. Compound (±)-**21** was produced by further hydrogenation and the isomerization of the β-ketoester. The stereochemistry of (±)-**21** was established by the NOESY experiment (Fig. 3). The NOESY correlations between H-3α and H-5, H-3α and H-6, and H-5 and H-6, and the NOESY correlation between H-3β and H-4 indicated the




**Scheme 7**. Synthesis of (−)-**1** and (+)-**2**. (a) TBAF, THF, 77% and (b) Jones reagent, acetone, 0 °C, 66%.

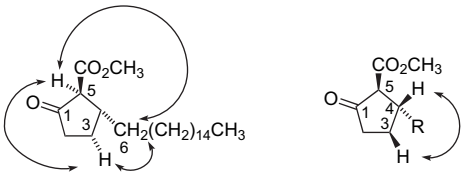



**Figure 3**. The NOESY correlations for (±)-**21**.

*anti*-relation for H-4/H-5. Reduction of the double bond of (±)-**19** was unsuccessful by hydrogenation or 1,4-reduction. Hydrogenation of (±)-**19** with Rh–$Al_2O_3$ and $PtO_2$ gave (±)-**21**. The use of other conditions ($NaBH_4$/MeOH, Mg/MeOH, and CuCl, $PhMe_2SiH$/DMF, etc.) gave complex mixture.

### 2.4. Structure–activity relationships of synthetic derivatives for inhibition of DNA polymerases

Synthetic (±)-**1**, (±)-**1a**, (±)-**11**, and (±)-**12** were tested with an enzyme inhibition assay for mammalian DNA polymerases α (pol α) and β (pol β). Table 2 shows the value of 50% inhibitory concentrations of these compounds. Compound (±)-**1** inhibited pol α ($IC_{50}$=61 μM) and weakly inhibited pol β ($IC_{50}$=179 μM), whereas the levulinyl ester (±)-**1a** did not influence pol α and pol β at concentrations lower than 200 μM. Interestingly, although (±)-**12** had no influence on pol α and pol β at concentrations lower than 200 μM, the levulinyl ester (±)-**11** inhibited the activity of pol α ($IC_{50}$=66 μM) and pol β ($IC_{50}$=132 μM). These results indicate that the stereochemistry and its functionality at C-1 greatly influenced the inhibitory activities against pol α and pol β.

**Table 2**. The $IC_{50}$ values for enzymatic inhibition of DNA polymerase α (pol α) and β (pol β) by (±)-**1**, (±)-**1a**, (±)-**11**, and (±)-**12**

| Compounds | $IC_{50}$(μM) | |
|---|---|---|
| | Pol α | Pol β |
| (±)-**1** | 66 | 179 |
| (±)-**1a** | >200 | >200 |
| (±)-**11** | 61 | 132 |
| (±)-**12** | >200 | >200 |

The inhibitory activities of (±)-**2**, (±)-**3**, (±)-**4**, (±)-**19**, **20**, and (±)-**21** against pol α, pol β, and TdT are summarized in Table 3. We found that synthetic (±)-untenone A (**2**) possessed selective inhibitory activity against the enzymes ($IC_{50}$=4.3 μM for pol α, $IC_{50}$=57 μM for pol β, and $IC_{50}$=16 μM for TdT). (±)-Manzamenone A (**3**) was found to have strong inhibitory activity against all of these enzymes in the micromolar range. The β-hydroxyketone (**4**) showed no inhibitory activity against pol α, pol β, and TdT. Methoxymethyl-protected untenone A (**19**) showed inhibitory activity against the enzymes in the submicromolar and micromolar range, but exhibited nonselective inhibitory activity against the enzymes when compared to (±)-**2**. Both the α,β-unsaturated β-ketoester (**20**) and the saturated deoxygenated derivative (**21**) showed weaker inhibitory activities against polymerases than untenone A (**2**). These results indicate that the methyl ester moiety and the substituents at C-4 affected the inhibitory activities against pol α, pol β, and TdT.

**Table 3**. The $IC_{50}$ values for enzymatic inhibition of DNA polymerase α (pol α) and β (pol β), and human terminal deoxynucleotidyl transferase (TdT) by (±)-**2**, (±)-**3**, (±)-**4**, (±)-**19**, **20**, and (±)-**21**

| Compounds | $IC_{50}$ (μM) | | |
|---|---|---|---|
| | Pol α | Pol β | TdT |
| (±)-**2** | 4.3 | 57 | 16 |
| (±)-**3** | 1.9 | 3.2 | 2.5 |
| (±)-**4** | >200 | >200 | >200 |
| (±)-**19** | 5.9 | 9.3 | 18 |
| **20** | 17 | 107 | 129 |
| (±)-**21** | 20 | 90 | 84 |

We newly carried out DNA polymerase assays using pol α and pol β in order to test the influence of the chirality of plakevulin A (**1**) and untenone A (**2**) on the inhibitory activities. Table 4 shows the inhibitory effects of (+)-**1**, (−)-**1**, (+)-**2**, and (−)-**2** against pol α and pol β. The inhibitory activities of (−)-**1** against these enzymes ($IC_{50}$=49 μM for pol α, $IC_{50}$=72 μM for pol β) were slightly stronger than those of (+)-**1** ($IC_{50}$=137 μM for pol α, $IC_{50}$=189 μM for pol β). In contrast, there are no significant differences in the inhibitory activities between (+)-**2** and (−)-**2**.

**Table 4**. The $IC_{50}$ values for enzymatic inhibition of DNA polymerase α (pol α) and β (pol β) by (+)-**1**, (−)-**1**, (+)-**2**, and (−)-**2**

| Compounds | $IC_{50}$(μM) | |
|---|---|---|
| | Pol α | Pol β |
| (+)-**1** | 137 | 189 |
| (−)-**1** | 49 | 72 |
| (+)-**2** | 13 | 91 |
| (−)-**2** | 19 | 54 |

## 3. Conclusion

We have achieved a total synthesis of the proposed structure of plakevulin A (**1a**). However, the $^1H$ and $^{13}C$ NMR spectral data of **1a** were different from those of natural plakevulin A. The chemical shifts of the proton and the carbon at C-1 of **1a** especially deviated downfield from those of natural plakevulin A. Thus **1a** was converted into the corresponding alcohol (**1**) by removal of the levulinyl ester. The NMR data of **1** was identical with that of the natural product.

We have prepared optically active plakevulin A (**1**) and untenone A (**2**) according to the modified protocol reported by Yamada et al. Compounds (+)-**1**, (−)-**1**, (+)-**2**, and (−)-**2** were prepared and tested with an enzyme inhibition assay for mammalian DNA polymerases α (pol α) and β (pol β). Several analogues were also prepared in order to examine the structure–activity relationships of **1** in the inhibition of DNA polymerases. We found that the methyl ester of **1** was important for the inhibitory activity and that the substituents at C-1 and C-4 greatly influenced the activity. Although the inhibitory activity of (−)-**1** against pol α and pol β was slightly more potent than that of (+)-**1**, there were no significant differences in the inhibitory activity between (+)-**2** and (−)-**2**. Among the synthetic analogues, manzamenone (**3**) showed the most potent activity against pol α, pol β, and TdT.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C NMR were recorded on a JEOL JNM-LD400, or on a BRUKER DXR400 or DRX600. Chemical shifts were reported in δ, parts per million (ppm), relative to TMS as an internal standard or calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a JASCO FT/IR-410 spectrometer. Mass spectra were obtained on API QSTAR Pulsar i spectrometer. Optical rotations were measured on a JASCO P-1030 digital polarimeter. Melting points were determined with Yanaco MP-3S melting point apparatus. Column chromatography was carried out on Fuji Silisia PSQ100B. Analytical thin-layer chromatography (TLC) was performed on precoated Merck silica gel 60 $F_{254}$ plates, and compounds were visualized by UV illumination (254 nm) or heating at 150 °C after spraying phosphomolybdic acid in ethanol. THF was distilled from sodium/benzophenone. $CH_2Cl_2$ was distilled from $P_2O_5$. HMPA and diisopropylamine were distilled from $CaH_2$. All other solvent and reagents were obtained from commercial sources and used without further purification. Organic extracts were dried over $Na_2SO_4$, filtered, and concentrated using a rotary evaporator. Involatile oils and solids were vacuum dried.

**4.1.1. 4-Hexadecyl-4-trimethylsiloxy-2-cyclopenten-1-one, (±)-5.** To a solution of (±)-**5** (637 mg, 1.98 mmol) and *i*-$Pr_2$NEt (690 μL, 3.96 mmol) in $CH_2Cl_2$ (20 mL) was added TMSOTf (390 μL, 2.18 mmol) at 0 °C and the mixture was stirred at 0 °C for 15 min. Then the mixture was quenched by the addition of satd aq $NaHCO_3$ and extracted with ether. The organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (10:1 hexane/EtOAc) to give TMS ether (703 mg, 90%) as a white solid. $^1$H NMR (600 MHz, $CDCl_3$) δ 7.44 (1H, d, *J*=5.7 Hz), 6.11 (1H, d, *J*=5.7 Hz), 2.50 (2H, m), 1.68 (2H, m), 1.31–1.25 (28H, br m), 0.88 (3H, t, *J*=6.9 Hz), 0.11 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.9, 166.9, 132.8, 81.3, 49.6, 41.9, 31.9, 29.9, 29.68 (×4), 29.65 (×2), 29.61, 29.55, 29.5, 29.4, 24.3, 22.7, 14.1, 2.1 (×3); IR (KBr) 2925, 2853, 1726, 1591, 1465, 1407, 1341, 1253, 1200, 1077, 938, 841, 756 cm$^{-1}$; HRMS calcd for $C_{24}H_{46}O_2NaSi$ ([M+Na]$^+$) 417.3159, found 417.3171.

**4.1.2. 4-Hexadecyl-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopenten-1-one, (±)-6.** To a solution of diisopropylamine (560 μL, 3.92 mmol) in THF (13 mL) was added *n*-BuLi (2.5 mL of a 1.58 M solution in hexane, 3.92 mmol) at 0 °C and the mixture was stirred at 0 °C for 10 min. The mixture was cooled to −78 °C. A solution of (±)-**5** (703 mg, 1.78 mmol) in THF/HMPA (10:1, 5 mL) was added to the mixture at −78 °C and the mixture was stirred at −78 °C for 80 min. Then methyl cyanoformate (340 μL, 4.27 mmol) was added and the mixture was stirred at −45 °C for 55 min. The mixture was quenched by the addition of satd $NH_4Cl$ and extracted with ether. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (4:1 hexane/EtOAc) to give methyl ester (505 mg, 63%) as a 4.2:1 diasteromeric mixture as colorless oil. $^1$H NMR (600 MHz, $CDCl_3$) major isomer: δ 7.46 (1H, d, *J*=5.8 Hz), 6.27 (1H, d, *J*=5.8 Hz), 3.69 (3H, s), 3.38 (1H, s), 1.87 (1H, m), 1.69 (1H, m), 1.35–1.25 (28H, br m), 0.88 (3H, t, *J*=6.8 Hz), 0.11 (9H, s), minor isomer: δ 7.55 (1H, d, *J*=5.8 Hz), 6.19 (1H, d, *J*=5.8 Hz), 3.76 (3H, s), 3.51 (1H, s), 1.78 (1H, m), 1.66 (1H, m), 1.35–1.25 (28H, br m), 0.88 (3H, t, *J*=6.8 Hz), 0.14 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) major isomer: δ 201.4, 167.6, 164.6, 133.5, 81.3, 62.0, 51.9, 41.6, 31.9, 29.7, 29.63 (×4), 29.60, 29.58, 29.54, 29.48, 29.4, 29.3, 24.1, 22.6, 14.1, 2.2 (×3), minor isomer: δ 200.6, 168.6, 165.9, 131.7, 83.6, 64.8, 52.1, 38.3, 31.9, 29.9, 29.7, 29.6 (×6), 29.5 (×3), 23.8, 22.6, 14.1, 1.9 (×3); IR (neat) 2925, 2853, 1750, 1718, 1464, 1436, 1340, 1315, 1252, 1151, 1103, 1051, 1009, 941, 757 cm$^{-1}$; HRMS calcd for $C_{26}H_{48}O_2NaSi$ ([M+Na]$^+$) 475.3214, found 475.3189.

**4.1.3. (1*RS*,4*SR*,5*RS*)-4-Hexadecyl-1-hydroxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (±)-7.** To a solution of (±)-**6** (200 mg, 0.44 mmol) in $CH_2Cl_2$ (5 mL) was added DIBAL (940 μL of a 0.95 M solution in $CH_2Cl_2$, 0.89 mmol) at −78 °C. After the mixture was stirred at −78 °C for 2.5 h, the mixture was diluted with $Et_2O$. Then 1.0 mL of MeOH, followed by Celite was added, and the mixture was stirred at rt for 1 h. The mixture was filtrated through Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (9:1→4:1 hexane/EtOAc) to give both (±)-**7** (82 mg, 41%) and (±)-**8** (12 mg, 6%) as colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 5.94 (1H, dd, *J*=5.6 Hz, 2.0 Hz), 5.84 (1H, d, *J*=5.6 Hz), 4.72 (1H, m), 4.08 (1H, d, *J*=9.5 Hz), 3.70 (3H, s), 3.30 (1H, d, *J*=7.1 Hz), 1.72 (1H, m), 1.58 (1H, m), 1.32–1.22 (28H, br m), 0.88 (3H, t, *J*=7.2 Hz), 0.09 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) 172.3, 136.9, 135.2, 87.9, 75.0, 56.7, 51.5, 42.5, 31.9, 29.8, 29.68 (×4), 29.65 (×2), 29.61, 29.57, 29.5, 29.3, 24.3, 22.7, 14.1, 2.2 (×3); IR (neat) 3511, 3018, 2926, 2854, 1717, 1466, 1438, 1415, 1360, 1253, 1176, 1099, 1067, 991, 843, 668 cm$^{-1}$; HRMS calcd for $C_{26}H_{50}O_4NaSi$ ([M+Na]$^+$) 477.3370, found 447.3380.

**4.1.4. (1*SR*,4*SR*,5*RS*)-4-Hexadecyl-1-hydroxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (±)-8.** $^1$H NMR (400 MHz, $CDCl_3$) δ 6.09 (1H, d, *J*=6.0 Hz), 5.97 (1H, dd, *J*=6.0 Hz, 2.4 Hz), 4.96 (1H, m), 4.03 (1H, d, *J*=4.0 Hz), 3.77 (3H, s), 3.07 (1H, d, *J*=5.6 Hz), 1.64 (2H, m), 1.32–1.25 (28H, br m), 0.88 (3H, t, *J*=7.2 Hz), 0.11 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) 173.5, 140.7, 132.7, 88.2, 74.4, 58.8, 51.7, 40.7, 31.9, 30.0, 29.7 (×6), 29.65, 29.6 (×2), 29.4, 23.9, 22.7, 14.1, 2.1 (×3); IR (neat) 3471, 3018, 2926, 2854, 1712, 1464, 1439, 1355, 1253, 1215, 1095, 843 cm$^{-1}$; HRMS calcd for $C_{26}H_{50}O_4NaSi$ ([M+Na]$^+$) 477.3370, found 447.3392.

**4.1.5. (1*SR*,4*SR*,5*RS*)-4-Hexadecyl-1-levuloyloxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (±)-9.** To a solution of (±)-**7** (3.3 mg, 7.3 μmol), levulinic acid (7.0 μL, 68.4 μmol) and $PPh_3$ (19.2 mg, 73.2 μmol) was added DIAD (40% in toluene, 3.7 μL, 7.32 μmol). The reaction mixture was stirred for 2 h. The resulting mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt 4:1) to afford (±)-**9** (2.0 mg, 52%) as a white solid. Mp=32–33 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 6.12 (1H, d, *J*=4.6 Hz), 5.93 (1H, d,

$J$=5.7 Hz), 5.91 (1H, d, $J$=5.7 Hz), 3.70 (3H, s), 2.95 (1H, d, $J$=4.6 Hz), 2.74 (2H, m), 2.55 (2H, m), 2.18 (3H, s), 1.79 (2H, br m), 1.34–1.26 (28H, br m), 0.88 (3H, t, $J$=6.0 Hz), 0.04 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.4, 172.3, 170.8, 138.8, 132.1, 87.9, 80.8, 59.0, 51.7, 42.1, 37.9, 31.9, 29.9, 29.9, 29.7 (×5), 29.7 (×2), 29.6, 29.6, 29.4, 27.9, 24.6, 22.7, 14.1, 2.0 (×3); IR (film) 3020, 2927, 2854, 1737, 1437, 1361, 1160, 1084, 846, 669 cm$^{-1}$; HRMS calcd for $C_{31}H_{56}O_6Na$ [(M+Na)$^+$] 575.3738, found 575.3766.

**4.1.6. (1*SR*,4*SR*,5*RS*)-4-Hexadecyl-4-hydroxy-1-levuloyloxy-5-methoxycarbonyl-2-cyclopentene (the proposed structure of plakevulin A), (±)-1a.** To a solution of (±)-**9** (5.5 mg, 9.9 μmol) in dry THF (0.5 mL) was added dropwise a solution of TBAF in THF (20 μL of 1.0 M solution in THF, 20 μmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. The resulting mixture was quenched with water, and extracted with $Et_2O$. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt=5:1 to 2:1) to afford (±)-**1a** (4.5 mg, 94%) as a white solid. Mp=45–47 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 6.04 (1H, ddd, $J$=4.4 Hz, 1.5 Hz, 0.8 Hz), 5.94 (1H, dd, $J$=5.4 Hz, 0.8 Hz), 5.91 (1H, dd, $J$=5.4 Hz, 1.5 Hz), 3.76 (3H, s), 2.96 (1H, d, $J$=4.4 Hz), 2.75 (2H, m), 2.56 (2H, m), 2.30 (1H, s), 2.18 (3H, s), 1.80 (2H, m), 1.34–1.26 (28H, br m), 0.88 (3H, t, $J$=6.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.3, 172.4, 171.8, 139.8, 131.5, 85.3, 80.9, 57.7, 52.2, 40.8, 37.8, 31.9, 29.9, 29.8, 29.7 (×5), 29.7 (×2), 29.6, 29.6, 29.4, 27.9, 24.2, 22.7, 14.1; IR (film) 3482, 3018, 2925, 2854, 1739, 1462, 1438, 1363, 1265, 1201, 1160, 1020, 759, 667 cm$^{-1}$; HRMS calcd for $C_{28}H_{48}O_6Na$ ([M+Na]$^+$) 503.3343, found 503.3307.

**4.1.7. (1*RS*,4*SR*,5*RS*)-4-Hexadecyl-1-levuloyloxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (±)-10.** To a solution of (±)-**7** (30 mg, 66 μmol) and levulinic acid (13.5 μL, 132 μmol) in 1,4-dioxane (0.7 mL) were added EDCI (25.3 mg, 132 μmol) and DMAP (0.8 mg, 6.6 μmol) at rt. The mixture was stirred at rt for 2 h. The resulting mixture was quenched with water, and extracted with $Et_2O$. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt=20:1 to 2:1) to afford (±)-**10** (30.3 mg, 83%) as white wax and the recovered (±)-**7** (3.8 mg, 13%). $^1$H NMR (600 MHz, $CDCl_3$) δ 6.01 (1H, d, $J$=5.8 Hz), 5.87 (1H, dd, $J$=5.8 Hz, 2.0 Hz), 5.61 (1H, br d, $J$=7.2 Hz), 3.64 (3H, s), 3.39 (1H, d, $J$=7.2 Hz), 2.73 (2H, m), 2.58 (2H, m), 2.18 (3H, s), 1.69 (1H, m), 1.58 (1H, m), 1.34–1.26 (28H, br m), 0.88 (3H, t, $J$=6.7 Hz), 0.10 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.5, 172.5, 168.7, 139.8, 129.9, 87.2, 75.9, 56.7, 51.2, 42.3, 37.8, 31.9, 29.8, 29.7 (×4), 29.6 (×3), 29.6, 29.6, 29.5, 29.3, 28.1, 24.3, 22.7, 14.1, 2.0 (×3); IR (film) 3022, 2926, 2854, 1744, 1464, 1436, 1359, 1252, 1158, 1098, 919, 843, 667 cm$^{-1}$; HRMS calcd for $C_{31}H_{56}O_6SiNa$ ([M+Na]$^+$) 575.3738, found 575.3777.

**4.1.8. (1*RS*,4*SR*,5*RS*)-4-Hexadecyl-4-hydroxy-1-levuloyloxy-5-methoxycarbonyl-2-cyclopentene, (±)-11.** To a solution of (±)-**10** (8.2 mg, 15 μmol) in dry THF (0.5 mL) was added TBAF (40 μL of 1.0 M solution in THF, 40 μmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The resulting mixture was quenched with water, and extracted with $Et_2O$. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (5:1→2:1 hexane/EtOAc) to afford (±)-**11** (3.5 mg, 49%) as a white solid. Mp=79–81 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 6.08 (1H, d, $J$=5.6 Hz), 5.90 (1H, dd, $J$=5.6 Hz, 2.1 Hz), 5.82 (1H, dd, $J$=6.9 Hz, 1.5 Hz), 4.06 (1H, s), 3.75 (3H, s), 3.22 (1H, dd, $J$=6.9 Hz, 1.0 Hz), 2.72 (2H, m), 2.55 (2H, t, $J$=6.5 Hz), 2.19 (3H, s), 1.65 (2H, m), 1.33–1.24 (28H, br m), 0.88 (3H, t, $J$=6.7 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 206.3, 172.0, 171.5, 142.2, 129.4, 83.4, 76.8, 53.9, 52.1, 40.4, 37.7, 31.9, 29.9, 29.8, 29.7 (×4), 29.6 (×2), 29.6, 29.6, 29.5, 29.4, 28.0, 24.1, 22.7, 14.1; IR (film) 3505, 3020, 2926, 2854, 1722, 1519, 1465, 1439, 1408, 1359, 1216, 1158, 1076, 1030, 929, 757, 669 cm$^{-1}$; HRMS calcd for $C_{28}H_{48}O_6Na$ ([M+Na]$^+$) 503.3343, found 503.3311.

**4.1.9. (±)-Plakevulin A (±)-1.** To a solution of (±)-**1a** (1.1 mg, 2.6 μmol) in dry pyridine (1.0 mL) was added a solution hydrazine monohydrate (2.0 μL, 41.2 μmol) in pyridine/AcOH (3:2, 1.0 mL). The reaction mixture was stirred for 20 min. The resulting mixture was quenched with water, and extracted with EtOAc. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (1:1 hexane/EtOAc) to afford (±)-**1** (0.9 mg, 92%) as a white solid. Mp=80–82 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 5.94 (1H, dd, $J$=5.7 Hz, 1.8 Hz), 5.84 (1H, dd, $J$=5.7 Hz, 1.5 Hz), 5.34 (1H, m), 3.79 (3H, s), 2.83 (1H, d, $J$=5.3 Hz), 2.45 (1H, s), 2.00 (1H, br s), 1.81 (2H, m), 1.37–1.22 (28H, br m), 0.88 (3H, t, $J$=6.9 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.6, 137.0, 135.7, 84.8, 78.2, 60.5, 52.1, 40.6, 31.9, 29.9, 29.7 (×5), 29.7 (×2), 29.6, 29.5, 29.4, 24.5, 22.7, 14.1; IR (film) 3445, 3019, 2927, 2855, 1724, 1520, 1465, 1439, 1374, 1041, 928, 759, 669 cm$^{-1}$; HRMS calcd for $C_{23}H_{42}O_4Na$ ([M+Na]$^+$) 405.2975, found 405.2972.

**4.1.10. (1*RS*,4*SR*,5*RS*)-4-Hexadecyl-1,4-dihydroxy-5-methoxycarbonyl-2-cyclopentene, (±)-12.** To a solution of (±)-**7** (8.9 mg, 19.5 μmol) in THF (2 mL) was added TBAF (30 μL of 1.0 M solution in THF, 30 μmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The resulting mixture was quenched with water, and extracted with $Et_2O$. The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/AcOEt 5:1 to 2:1) to afford (±)-**12** (4.8 mg, 64%) as white wax. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.09 (1H, dd, $J$=5.6 Hz, 2.4 Hz), 6.03 (1H, d, $J$=5.6 Hz), 4.82 (1H, m), 3.80 (3H, s), 3.50 (1H, s), 3.04 (1H, br d, $J$=8.0 Hz), 2.99 (1H, d, $J$=6.1 Hz), 1.73 (2H, m), 1.30–1.25 (28H, br m), 0.88 (3H, t, $J$=6.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.0, 140.0, 134.7, 83.9, 75.8, 55.0, 52.0, 39.3, 31.9, 29.9, 29.7 (×4), 29.6 (×2), 29.6, 29.6, 29.5, 29.3, 24.4, 22.7, 14.1; IR (film) 3440, 3014, 2925, 2854, 1718, 1464, 1440, 1357, 1214, 1176, 1064, 931, 759, 667 cm$^{-1}$; HRMS calcd for $C_{23}H_{42}O_4Na$ ([M+Na]$^+$) 405.2975, found 405.2989.

**4.1.11. (1*S*,4*R*)-(−)-4-Hexadecyl-1,4-dihydroxy-2-cyclopentene, (−)-14.** To a solution of **13** (2.6 g, 4.7 mmol) in THF (25 mL) was added TBAF (4.7 mL of a 1.0 M solution in THF, 4.7 mmol) at 0 °C and the mixture was stirred at rt for 30 min. Then the mixture was quenched by the addition of $H_2O$ and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (4:1 hexane/EtOAc) to give diol (1.3 g, 84%) as a white solid. Mp=79–80 °C; $[\alpha]_D^{23}$ −45.9 (*c* 0.80, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 5.91 (1H, dd, *J*=5.6 Hz, 2.0 Hz), 5.88 (1H, d, *J*=5.6 Hz), 4.67 (1H, m), 2.55 (2H, br s), 2.41 (1H, dd, *J*=14.3 Hz, 7.0 Hz), 1.73 (1H, d, *J*=14.3 Hz, 3.1 Hz), 1.58 (2H, m), 1.30–1.25 (28H, br m), 0.88 (3H, t, *J*=6.7 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 140.0, 134.9, 84.1, 75.3, 48.0, 40.5, 31.9, 30.0, 29.68 (×4), 29.65 (×3), 25.59, 29.57, 29.4, 24.3, 22.7, 14.1; IR (KBr) 3317, 2918, 2849, 1469, 1360, 1302, 1213, 1159, 1086, 1054, 995, 971, 935, 873, 825, 783, 722, 603 $cm^{-1}$; HRMS calcd for $C_{21}H_{40}O_2Na$ ([M+Na]$^+$) 347.2920, found 347.2916.

**4.1.12. (4*R*)-(−)-4-Hexadecyl-4-hydroxy-2-cyclopenten-1-one, (−)-4.** To a solution of (−)-**14** (503 mg, 1.55 mmol) in acetone (15 mL) was added the Jones reagent (0.5 mL) in portions. Then the mixture was quenched by the addition of 2-propanol (0.5 mL) and diluted with EtOAc and $H_2O$. The organic layer was separated and washed with $H_2O$, brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (3:1 hexane/EtOAc) to give (−)-**4** (383 mg, 77%) as a white solid. The product was recrystallized from $Et_2O$ to obtain colorless crystals. White solid, mp=52–53 °C; colorless crystal, mp=45–46 °C; $[\alpha]_D^{23}$ −54.5 (*c* 1.10, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, *J*=5.7 Hz), 6.09 (1H, d, *J*=5.7 Hz), 2.53 (1H, d, *J*=18.6 Hz), 2.41 (1H, d, *J*=18.6 Hz), 2.07 (1H, br s), 1.71 (2H, m), 1.35–1.23 (28H, br m), 0.85 (3H, t, *J*=6.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 206.9, 165.8, 133.3, 79.2, 48.8, 40.3, 31.9, 29.8, 29.7 (×3), 29.63 (×2), 29.61, 29.59, 29.5, 29.4, 29.3, 24.2, 22.7, 14.1; IR (KBr) 3418, 3017, 2925, 2854, 1715, 1466, 1404, 1339, 1215, 1067 $cm^{-1}$; HRMS calcd for $C_{21}H_{38}O_2Na$ ([M+Na]$^+$) 345.2764, found 345.2765.

**4.1.13. (4*R*)-(−)-4-Hexadecyl-4-trimethylsiloxy-2-cyclopenten-1-one, (−)-5.** To a solution of (−)-**4** (311 mg, 0.96 mmol) and *i*-$Pr_2NEt$ (480 μL, 2.75 mmol) in $CH_2Cl_2$ (5 mL) was added TMSOTf (250 μL, 1.38 mmol) at 0 °C and the mixture was stirred at 0 °C for 15 min. Then the mixture was quenched by the addition of $H_2O$ and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (10:1 hexane/EtOAc) to give (−)-**5** (351 mg, 92%) as a white solid. Mp=31–32 °C; $[\alpha]_D^{23}$ −16.0 (*c* 1.17, $CHCl_3$).

**4.1.14. 4-Hexadecyl-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopenten-1-one (6).** To a solution of diisopropylamine (250 μL, 1.76 mmol) in THF (5 mL) was added *n*-BuLi (1.1 mL of a 1.57 M solution in hexane, 1.73 mmol) at 0 °C and the mixture was stirred at 0 °C for 10 min. The mixture was cooled to −78 °C. A solution of (−)-**5** (309 mg, 0.78 mmol) in THF/HMPA (10:1, 4.4 mL) was added to the mixture at −78 °C and the mixture was stirred at −78 °C for 15 min. Then methyl cyanoformate (170 μL, 2.14 mmol) was added and the mixture was stirred at −45 °C for 2 h. The mixture was quenched by the addition of $H_2O$ and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (4:1 hexane/EtOAc) to give **6** (245 mg, 69%) as a 4.2:1 diasteromeric mixture as colorless oil. The $^1H$ NMR, $^{13}C$ NMR, and IR data of **6** were identical with those of (±)-**6**.

**4.1.15. (1*R*,4*S*,5*R*)-(−)-4-Hexadecyl-1-hydroxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (−)-7.** To a solution of **6** (125 mg, 0.28 mmol) in $CH_2Cl_2$ (5 mL) was added DIBAL (620 μL of a 0.94 M solution in $CH_2Cl_2$, 0.58 mmol) at −78 °C. After the mixture was stirred at −78 °C for 1 h, the mixture was diluted with $Et_2O$. Then 1.0 mL of MeOH, followed by Celite was added, and the mixture was stirred at rt for 1 h. The mixture was filtrated through Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (9:1→4:1 hexane/EtOAc) to give both (−)-**7** (45.5 mg, 36%) and (+)-**8** (6.8 mg, 5%) as colorless oil. $[\alpha]_D^{23}$ −12.7 (*c* 0.45, $CHCl_3$).

**4.1.16. (1*S*,4*S*,5*R*)-4-Hexadecyl-1-hydroxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (+)-8.** Colorless oil. $[\alpha]_D^{21}$ +54.0 (*c* 0.33, $CHCl_3$).

**4.1.17. (1*S*,4*S*,5*R*)-(+)-4-Hexadecyl-5-methoxycarbonyl-1-(4-nitrobenzoyl)-4-trimethylsiloxy-2-cyclopentene, (+)-15.** To a solution of (−)-**7** (30.1 mg, 66.2 μmol), *p*-nitrobenzoic acid (58.0 mg, 347 μmol) and $PPh_3$ (93.2 mg, 355 μmol) in THF (1.5 mL) was added DIAD (180 μL of a 40% solution in toluene, 356 μmol) at rt and the mixture was stirred at rt for 10 min. The mixture was quenched by the addition of $H_2O$ and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (30:1 hexane/EtOAc) to give (+)-**15** (24.2 mg, 61%) as a white solid. Mp=85–86 °C; $[\alpha]_D^{21}$ +117.3 (*c* 1.47, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.27 (2H, d, *J*=6.8 Hz), 8.17 (2H, d, *J*=6.8 Hz), 6.42 (1H, m), 6.07 (1H, dd, *J*=5.8 Hz, 1.9 Hz), 6.03 (1H, dd, *J*=5.8 Hz, 1.4 Hz), 3.75 (3H, s), 3.15 (1H, d, *J*=4.8 Hz), 1.84 (2H, m), 1.33–1.24 (28H, br m), 0.88 (3H, t, *J*=6.8 Hz), 0.09 (9H, s); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 170.2, 164.3, 150.6, 139.7, 135.4, 131.5, 130.8 (×2), 123.5 (×2), 87.9, 82.1, 59.1, 51.8, 42.1, 31.9, 29.9, 29.7 (×6), 29.64 (×2), 29.61, 29.3, 24.7, 22.7, 14.1, 2.0 (×3); IR (KBr) 2919, 2850, 1744, 1720, 1606, 1525, 1333, 1274, 1116, 968, 844, 721 $cm^{-1}$; HRMS calcd for $C_{33}H_{53}NO_7NaSi$ ([M+Na]$^+$) 626.3483, found 626.3510.

**4.1.18. (1*S*,4*S*,5*R*)-(±)-4-Hexadecyl-4-hydroxy-5-methoxycalbonyl-1-trimethylsiloxy-2-cyclopentene, (+)-16.** To a solution of (+)-**15** (26.5 mg, 43.9 μmol) in THF–MeOH (1/1, 3 mL) was added NaOMe (52.0 μL of a 1 M solution in MeOH, 52.0 μmol) at rt and the mixture was stirred at rt for 20 min. The mixture was quenched by the addition of $H_2O$ and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography

(5:1 hexane/EtOAc) to TMS ether (16.2 mg, 81%) as colorless oil. $[\alpha]_D^{23}$ +73.2 (*c* 1.0, $CHCl_3$). $^1H$ NMR (600 MHz, $CDCl_3$) δ 5.92 (1H, dd, *J*=5.8 Hz, 1.7 Hz), 5.80 (1H, dd, *J*=5.8 Hz, 1.7 Hz), 5.45 (1H, m), 3.71 (3H, s), 2.81 (1H, d, *J*=5.5 Hz), 2.21 (1H, br s), 1.81 (2H, m), 1.30–1.25 (28H, br m), 0.88 (3H, t, *J*=6.8 Hz), 0.02 (9H, s); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 171.4, 136.3, 136.2, 87.8, 77.7, 62.5, 51.6, 41.6, 31.9, 29.9, 29.69 (×5), 29.65 (×2), 29.6 (×2), 29.4, 24.9, 22.7, 14.1, 2.0 (×3); IR (film) 3444, 2925, 2854, 1734, 1463, 1438, 1359, 1250, 1216, 1082, 937, 844 $cm^{-1}$; HRMS calcd for $C_{26}H_{50}O_4NaSi$ ($[M+Na]^+$) 477.3370, found 477.3356.

**4.1.19. (+)-Plakevulin A (1).** To a solution of (+)-**18** (14.4 mg, 31.7 μmol) in THF (1.0 mL) was added TBAF (40.0 μL of 1.0 M solution in THF, 40.0 μmol) and the mixture was stirred at rt for 1 h. The mixture was quenched by the addition of $H_2O$ and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (2:1 hexane/EtOAc) to give (+)-plakevulin A (8.9 mg, 73%) as colorless wax. The product was recrystallized from hexane/EtOAc to obtain white solid. Colorless wax, mp=61–62 °C; White solid, mp=73–74 °C; $[\alpha]_D^{21}$ +27.1 (*c* 0.55, $CHCl_3$). The $^1H$ NMR, $^{13}C$ NMR, and IR data of (+)-**1** were identical with those of (±)-**1**.

**4.1.20. (−)-Untenone A (2).** To a solution of **6** (18.7 mg, 0.041 mmol) in MeOH (1 mL) was added one drop of concd HCl (ca. 10 μL) at rt and the mixture was stirred at rt for 15 min. The mixture was quenched by the addition of $H_2O$ and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (9:1 hexane/EtOAc with 1% AcOH) to give (−)-untenone A (**2**) (14.7 mg, 94%) as colorless wax. The product was recrystallized from hexane to obtain white solid. Colorless wax, mp=~30 °C; White solid, mp=60–62 °C; $[\alpha]_D^{23}$ −71.3 (*c* 0.94, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, *J*=5.7 Hz), 6.19 (1H, d, *J*=5.7 Hz), 3.80 (3H, s), 3.65 (1H, br s), 3.47 (1H, s), 1.81 (1H, m), 1.70 (1H, m), 1.32–1.25 (28H, br m), 0.88 (3H, t, *J*=6.9 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 200.0, 169.1, 167.1, 132.3, 79.9, 60.8, 52.9, 40.4, 31.9, 29.74, 29.67 (×4), 29.64, 29.62, 29.58, 29.5, 29.4, 29.3, 23.8, 22.7, 14.1; IR (neat) 3451, 2919, 2850, 1740, 1712, 1467, 1437, 1321, 1256, 1154, 1035, 817, 763, 721 $cm^{-1}$; HRMS calcd for $C_{23}H_{41}O_4Na$ ($[M+Na]^+$) 381.3004, found 381.3012.

**4.1.21. (1*S*,4*S*)-(−)-4-Hexadecyl-1,4-dihydroxy-2-cyclopentene, (−)-18.** To a solution of **17** (326 mg, 0.74 mmol) in THF (6 mL) was added TBAF (0.92 mL of a 1.0 M solution in THF, 0.92 mmol) at 0 °C and the mixture was stirred at rt for 7 h. Then the mixture was quenched by the addition of $H_2O$ and extracted with EtOAc. The organic layer was washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (4:1 hexane/EtOAc) to give (−)-**18** (185 mg, 77%) as a white solid. Mp=83 °C; $[\alpha]_D^{23}$ −28.7 (*c* 0.68, $CHCl_3$). $^1H$ NMR (600 MHz, $CDCl_3$) δ 5.91 (1H, dd, *J*=5.6 Hz, 2.0 Hz), 5.87 (1H, dd, *J*=5.6 Hz, 1.2 Hz), 5.04 (1H, m), 2.30 (1H, dd, *J*=14.0 Hz, 6.8 Hz), 1.81 (1H, dd, *J*=14.0 Hz, 4.0 Hz), 1.73–1.63 (4H, m), 1.30–1.26 (28H, br m), 0.88 (3H, t, *J*=6.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 139.6, 135.9, 85.1, 76.1, 48.1, 41.6, 31.9, 30.0, 29.7 (×6), 29.64 (×2), 29.58, 29.3, 24.4, 22.7, 14.1; IR (KBr) 3330, 2919, 2850, 1465, 1406, 1346, 1268, 1190, 1160, 1126, 1103, 1045, 915, 867, 783, 722 $cm^{-1}$; HRMS calcd for $C_{21}H_{40}O_2Na$ ($[M+Na]^+$) 347.2920, found 347.2913.

**4.1.22. (4*S*)-(+)-4-Hexadecyl-4-hydroxy-2-cyclopenten-1-one, (+)-4.** To a solution of (−)-**18** (505 mg, 1.55 mmol) in acetone (30 mL) was added the Jones reagent (0.6 mL) in portions. The mixture was stirred at rt for 30 min. Then the mixture was quenched by the addition of 2-propanol (1.0 mL) and diluted with EtOAc and $H_2O$. The organic layer was separated and washed with $H_2O$, brine, dried ($Na_2SO_4$), and concentrated. The residue was purified by silica gel column chromatography (3:1 hexane/EtOAc) to give (+)-**4** (332 mg, 66%) as a white solid. The product was recrystallized from $Et_2O$ to obtain colorless crystals. Mp=45–46 °C; $[\alpha]_D^{20}$ +51.9 (*c* 1.10, $CHCl_3$).

**4.1.23. (4*S*)-(+)-4-Hexadecyl-4-trimethylsiloxy-2-cyclopenten-1-one, (+)-5.** White solid, mp=30–31 °C; $[\alpha]_D^{21}$ +16.1 (*c* 1.27, $CHCl_3$).

**4.1.24. (1*S*,4*R*,5*S*)-(+)-4-Hexadecyl-1-hydroxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (+)-7.** Colorless oil; $[\alpha]_D^{22}$ +12.7 (*c* 0.67, $CHCl_3$).

**4.1.25. (1*R*,4*R*,5*S*)-4-Hexadecyl-1-hydroxy-5-methoxycarbonyl-4-trimethylsiloxy-2-cyclopentene, (−)-8.** Colorless oil; $[\alpha]_D^{21}$ −52.4 (*c* 0.10, $CHCl_3$).

**4.1.26. (1*R*,4*R*,5*S*)-(−)-4-Hexadecyl-5-methoxycarbonyl-1-(4-nitrobenzoyl)-4-trimethylsiloxy-2-cyclopentene, (−)-15.** White solid, mp=82–83 °C; $[\alpha]_D^{19}$ −111.7 (*c* 0.55, $CHCl_3$).

**4.1.27. (1*R*,4*R*,5*S*)-(−)-4-Hexadecyl-4-hydroxy-5-methoxycalbonyl-1-trimethylsiloxy-2-cyclopentene, (−)-16.** Colorless oil; $[\alpha]_D^{21}$ −73.3 (*c* 0.25, $CHCl_3$).

**4.1.28. (−)-Plakevulin A (1).** Colorless wax, mp=60–62 °C; white soild, mp=70–71 °C; $[\alpha]_D^{21}$ −25.7 (*c* 0.10, $CHCl_3$).

**4.1.29. (+)-Untenone A (2).** White solid, mp=60–62 °C; $[\alpha]_D^{23}$ +72.2 (*c* 0.50, $CHCl_3$).

**4.1.30. (±)-Manzamenone A (3).** Compound (±)-**2** (20 mg, 47 μmol) was heated at ~70 °C for 24 h. The residue was purified by PTLC (hexane/EtOAc/AcOH 150:60:1) to give (±)-**3** (3.7 mg, 20%). $^1H$ NMR (600 MHz, $CDCl_3$) δ 6.18 (1H, br s), 3.88 (3H, s), 3.62 (1H, m), 3.55 (3H, s), 3.51 (1H, d, *J*=5.9 Hz), 3.20 (1H, dd, *J*=7.7 Hz, *J*=6.2 Hz), 3.13 (1H, m), 2.93 (1H, t, *J*=8.3 Hz), 2.45 (1H, m), 2.19 (2H, m), 1.60–1.26 (56H, br m), 0.88 (6H, t, *J*=6.6 Hz).

**4.1.31. 2-Methoxycarbonyl-3-hexadecyl-2-cyclopenten-1-one (20).** A solution of (±)-**19** (2.5 mg, 5.9 μmol) and 10% Pd on carbon (0.7 mg) in EtOAc (1 mL) was stirred at rt under an $H_2$ atmosphere for 14.5 h. The mixture was filtrated through Celite and washed with EtOAc. The solvent was removed under a reduced pressure. The residue was

purified by silica gel column chromatography (4:1 hexane/EtOAc) to give **20** (1.8 mg, 100%) as colorless oil. $^1$H NMR (600 MHz, $CDCl_3$) δ 3.84 (3H, s), 2.76 (2H, t, *J*=7.9 Hz), 2.68 (2H, m), 2.49 (2H, m), 1.57 (4H, m), 1.36 (1H, m), 1.26–1.32 (23H, br m), 0.88 (3H, t, *J*=7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 203.8, 189.0, 163.8, 51.8, 34.9, 32.7, 31.9, 30.4, 29.7 (×7), 29.6, 29.6, 29.5, 29.4, 29.3, 27.7, 22.7, 14.1; IR (film) 3020, 2926, 2854, 1739, 1714, 1620, 1465, 1437, 1361, 1295, 1259, 1216, 1155, 1026, 758, 667 cm$^{-1}$; HRMS calcd for $C_{23}H_{40}O_3Na$ ([M+Na]$^+$) 387.2869, found 387.2868.

**4.1.32. (2*RS*,3*SR*)-2-Methoxycarbonyl-3-hexadecylcyclopentanone, (±)-21.** A solution of (±)-**19** (8.4 mg, 20 μmol) and 20% $Pd(OH)_2$ on carbon (2.3 mg) in EtOAc (1 mL) was stirred at rt under an $H_2$ atmosphere for 26 h. The mixture was filtrated through Celite and washed with EtOAc. The solvent was removed under a reduced pressure. The residue was purified by silica gel column chromatography (4:1 hexane/EtOAc) to give (±)-**21** (7.1 mg, 100%) as a white solid. Mp=38–41 °C. $^1$H NMR (600 MHz, $CDCl_3$) δ 3.76 (3H, s), 2.83 (1H, d, *J*=11.2 Hz), 2.57 (1H, m), 2.42 (1H, dd, *J*=8.3 Hz, 18.7 Hz), 2.32 (1H, m), 2.23 (1H, m), 1.54 (1H, m), 1.47 (1H, m), 1.43 (1H, m), 1.36 (1H, m), 1.31–1.27 (27H, br m), 0.88 (3H, t, *J*=6.9 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 212.1, 170.1, 61.9, 52.4, 41.5, 38.5, 35.0, 31.9, 29.7 (×7), 29.6, 29.6, 29.5, 29.4, 27.4, 27.2, 22.7, 14.1; IR (film) 3021, 2927, 2855, 1754, 1726, 1463, 1439, 1216, 1129, 927, 759, 669 cm$^{-1}$; HRMS calcd for $C_{23}H_{42}O_3Na$ ([M+Na$^+$]) 389.3026, found 389.3039.

### 4.2. DNA polymerase assay[13]

Calf pol α was purified by immuno-affinity column chromatography as described previously.[14] Recombinant rat pol β was purified based on the method described by Date et al.[15] Recombinant human TdT was purified as described by Ibe et al.[16] The synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) at various concentrations and sonicated for 1 min. Five micro liters of these compounds in 40% DMSO were mixed with 10 μl of 2× reaction mixture (100 mM Tris–HCl (pH 7.5), 10 mM $MgCl_2$, 2 mM dithiothreitol, 15% glycerol, 250 μg/ml activated DNA, 100 μM each of dATP, dGTP, and dCTP, and 0.2 μM [$^3$H]dTTP) and 5 μl of each enzyme (0.01 units). These mixtures were incubated on ice for 10 min, then at 37 °C for 60 min. The amount of incorporated [$^3$H]dTMP into activated DNA without inhibitors was considered 100%. One unit of the activity was defined as the amount of enzyme that catalyzes the incorporation of 1 nmol of deoxyribonucleotide triphosphates into template DNA in 60 min at 37 °C.

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# Convenient synthesis of linear pyrano[3,2-*g*]-, [2,3-*g*]- and angular pyrano[3,2-*f*]coumarins from 4[(1,1-dimethyl-2-propynyl)oxy]phenol☆

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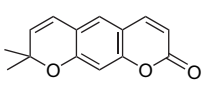
**Abstract**—An easy preparation of new 4-alkoxycarbonyl angular and linear pyranocoumarins starting from 4-[(1,1-dimethyl-2-propynyl)-oxy]phenol and their transformation to the known coumarins xanthyletin, 8,8-dimethylpyrano[3,2-*f*]chromen-3(8*H*)-one and 7,7-dimethyl-pyrano[2,3-*g*]chromen-2(7*H*)-one is described.


## 1. Introduction

Several linear and angular pyranocoumarins, like xanthyletin (**I**) and seselin (**II**) have been isolated from natural sources.[1–5] These compounds are known to possess useful biological activities.[3–6] Thus, xanthyletin shows[4] antifungal, insecticidal, anticancer, and anti-HIV activities, while seselin is used as a photoactive drug for skin disorders.[5] For the syntheses of these compounds various methods have been developed.[4–11]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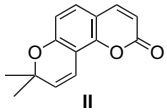
II

Thus, the 7-(1,1-dimethyl-prop-2-ynyl)ethers of coumarins, when heated, at reflux in *N*,*N*-dimethylaniline, gave the angular pyranocoumarins with cyclization taking place at the more reactive 8-position. If the 8-position is substituted however, the corresponding 8-substituted linear pyranocoumarins are obtained.[6–8] Thermal [3,3]-sigmatropic rearrangement of 6-prop-2-ynyloxycoumarins also resulted in the efficient synthesis of angular pyrano[3,2-*f*]chromen-2(7*H*)-ones.[9] Angular pyranocoumarins were also obtained from both 5- and 7-hydroxycoumarins and 1,1-diethoxy-3-methyl-2-butene,[10] while seselin and seselin derivatives were conveniently prepared in a two-step approach from 2,4-dihydroxybenzaldehyde and 2,4-dihydroxyacetophenone, using Claisen rearrangement and Wittig reaction.[5] 6-Hydroxy-2,2-dimethyl-2*H*-chromen-7-carbaldehyde and 7-hydroxy-2,2-dimethyl-2*H*-chromen-6-carbaldehyde, prepared earlier by the formylation of the corresponding 6-methoxy- and 7-methoxy-chromene derivatives and subsequent demethylation, were effectively converted into the corresponding linear pyranocoumarins by refluxing with *N*,*N*-dimethylacetamide dimethylacetal.[11]

4-Alkoxycarbonylcoumarins have been prepared earlier,[12,13] mainly by our group, from the reaction of *o*-quinones with alkoxycarbonylmethylene(triphenyl)phosphoranes ($Ph_3P{=}CHCOOR$) via an initial Wittig monoolefination to the corresponding *o*-quinonemethide, which by further Michael addition of a second ylide species followed by Hofmann elimination of $Ph_3P$, and finally by δ-lactonization gives rise to the corresponding coumarins. Recently Yavari and co-workers reported[14] that reactions of phenols with DMAD in the presence of $Ph_3P$ lead to the corresponding 4-methoxycarbonylcoumarins via an initial addition of $Ph_3P$ to the acetylenic ester and a concominant protonation of the reactive 1:1 adduct, followed by electrophilic attack of the vinyltriphenylphosphonium cation formed to the aromatic ring, in the *ortho* position relative to the strongly activating PhO-group.

Brown and co-workers in 1990 reported[15] the synthesis of 4-[(1,1-dimethyl-2-propynyl)oxy]phenol **1** from hydroquinone, which by refluxing in *o*-xylene afforded 2,2-dimethylchromen-6-ol **2**. Oxidation of **2** with Fremy's salt gave 2,2-dimethyl-2*H*-chromene-6,7-dione (**3**).

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*Keywords*: Pyranocoumarins; Xanthyletin; Phenols; DMAD; $Ph_3P$; Wittig reaction; δ-Lactonization; Dealkoxycarbonylation.

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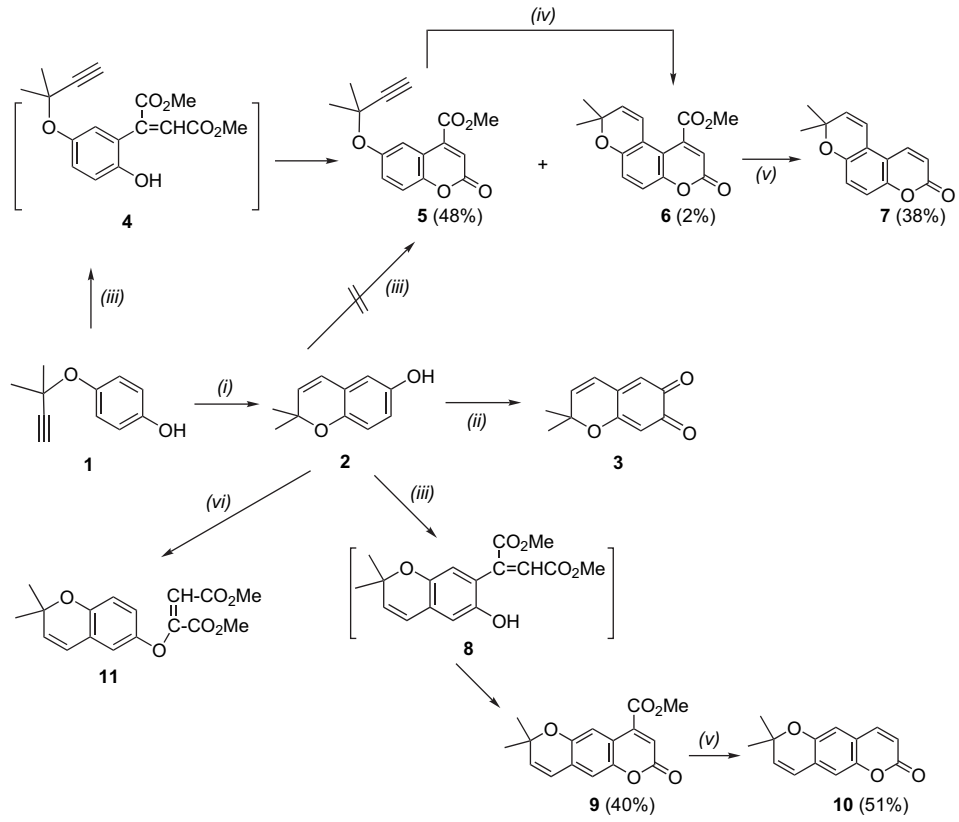
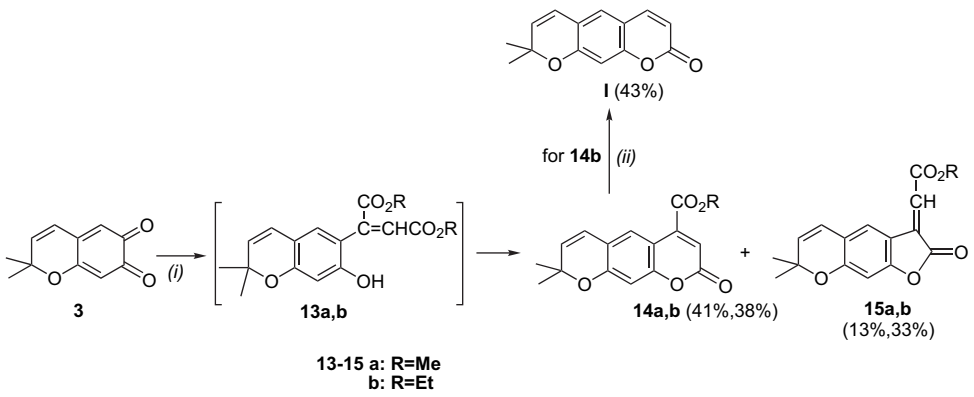



**Scheme 1**. Reagents and conditions: (i) Ref. 15, *o*-xylene, reflux, $N_2$ (91%); (ii) Ref. 15, Fremy's salt (68%); (iii) $Ph_3P$, DCM, DMAD (at −5 °C), reflux; (iv) *o*-xylene, reflux (77%); (v) Cu, quinoline, $N_2$, 175–180 °C, 19 h and (vi) DMAD, $ZnCl_2$, $N_2$, 100 °C, 1.5 h (23%).




**Scheme 2**. Reagents and conditions: (i) $Ph_3P$=CHCOOR (**12a**: R=Me, **b**: R=Et), DCM, rt, $N_2$, 30 min and (ii) Cu, quinoline, $N_2$, 175–180 °C, 19 h.

As a continuation of our investigation on the syntheses of coumarin derivatives,[13] we now report the easy preparation of the new coumarin derivatives **6**, **9**, and **14a**,**b** from the compounds **1**, **2**, and **3**, respectively. The reactions studied and the products obtained are depicted in Schemes 1–2.

## 2. Results and discussion

Treatment of phenol **1** with DMAD in the presence of $Ph_3P$ in refluxing DCM for two days, and separation of the reaction mixture by column chromatography afforded methyl 6-[(1,1-dimethyl-2-propynyl)oxy]-2-oxo-2*H*-chromene-4-carboxylate (**5**) and methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano[3,2-*f*]chromene-1-carboxylate (**6**) in 48% and 2% yields, respectively. Compound **5** by refluxing in *o*-xylene for 20 h gave coumarin **6** in 77% yield (Scheme 1). Obviously product **5** was obtained by δ-lactonization of the intermediate **4** and gave the angular coumarin **6** by further cyclization.[9]

When compound **1** was previously cyclized to phenol **2** according to the lit. 15 and the latter was then subjected to a similar treatment with $Ph_3P$ and DMAD in refluxing DCM for five days, ethyl 7,7-dimethyl-2-oxo-2,7-dihydropyrano[2,3-*g*]chromene-4-carboxylate (**9**) was obtained in 40% yield. The linear coumarin **9** was obviously produced by further δ-lactonization of the intermediate **8**. Both key intermediates **4** and **8** are formed via an electrophilic attack of the vinyltriphenylphosphonium cation[14] on the aromatic

ring *ortho* to the –OH substituent of **1** and **2**, respectively. In contrast to the formation of **4** from the symmetrically substituted phenol **1**, the formation of **8** can be attributed to the attack of the vinyltriphenylphosphonium cation to the less sterically hindered 7-position (in comparison to the 5-position) of the non-symmetric phenol **2**.

We considered as an alternative path for the preparation of linear pyranocoumarins the initial transformation of phenol **2** to the known[15] quinone **3** and the reaction[12,13] of the latter with the phosphoranes $Ph_3P{=}CHCOOR$ **12a**,**b** (Scheme 2). Treatment of quinone **3** with $Ph_3P{=}CHCOOCH_3$ (**12a**) at room temperature afforded methyl 8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano[3,2-*g*]chromene-4-carboxylate (**14a**) (41%) along with methyl 2-[7,7-dimethyl-2-oxo-7*H*-furo[3,2-*g*]-chromen-3(2*H*)-ylidene]acetate (**15a**) (13%) via the δ- and γ-lactonization, respectively, of the intermediate **13a**. Similarly, the reaction of **3** with $Ph_3P{=}CHCOOC_2H_5$ (**12b**) gave compounds **14b** and **15b** in 38% and 33% yield, respectively. The formation of intermediate **13** instead of **8** can be predicted from the lower electrophilicity of the C-7 C=O, due to the +R effect of the pyran ring O-atom, since this intermediate is formed by the initial Wittig monoolefination of the C-6 C=O of **3**, followed by Michael addition of a second ylide and Hofmann elimination of $Ph_3P$.[11,12] The IR spectra of compounds **15a**,**b** exhibited the characteristic[13a] absorption at $\nu_{max}$ ~1790 $cm^{-1}$ for a five-member lactone carbonyl.

We also studied the reaction of phenol **2** with DMAD in the presence of $ZnCl_2$, which resulted in the formation of dimethyl 2-[(2,2-dimethyl-2*H*-chromen-6-yl)oxy]-2-butenedioate (**11**) in 23% yield, but no cyclization product was isolated.

The proposed structures of all the new pyranocoumarins **6**, **9**, and **14a**,**b** were in good agreement with their analytical and spectral data ($^1H$ NMR, $^{13}C$ NMR, IR, and MS) and they are unequivocally proved via their transformation, by heating in quinoline and Cu powder, into the known 8,8-dimethylpyrano[3,2-*f*]chromen-3(8*H*)-one[9,10] (**7**) (38%), 7,7-dimethylpyrano[2,3-*g*]chromen-2(7*H*)-one[11] (**10**) (51%), and 8,8-dimethyl-2*H*,8*H*-pyrano[3,2-*g*]chromen-2-one[11] (**I**) [xanthyletin, 43% (from **14b**)], respectively. The yields for the preparation of these coumarins are comparable to the yields of the earlier preparation.[4–11]

The above mentioned synthetic approaches demonstrate their utility for the synthesis of different linear and angular pyranocoumarins, using the same starting material, depending on the reaction conditions.

## 3. Experimental

### 3.1. General

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer 1310 spectrophotometer as Nujol mulls. NMR spectra were recorded on a Bruker AM 300 (300 MHz and 75 MHz for $^1H$ and $^{13}C$, respectively) using $CDCl_3$ as solvent and TMS as an internal standard. *J* values are reported in Hertz. Mass spectra were determined on a VG-250 spectrometer at 70 eV under Electron Impact (EI) conditions. High-resolution mass spectra (HRMS) were recorded on an Ionspec mass spectrometer under Matrix-Assisted Laser Desorption-Ionization Fourier Transform Mass Spectrometer (MALDI-FTMS) conditions with 2,5-dihydroxybenzoic acid (DHB) as the matrix. Microanalyses were performed on a Perkin–Elmer 2400-II Element analyzer. Silica gel no. 60, Merck A.G. has been used for column chromatography. Compounds **1**, **2**, and **3** were prepared according to the lit. 15.

**3.1.1. Procedure for the synthesis of methyl 6-[(1,1-dimethyl-2-propynyl)oxy]-2-oxo-2*H*-chromene-4-carboxylate (5) and methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano[3,2-*f*]chromene-1-carboxylate (6).** 4-[(1,1-Dimethyl-2-propynyl)oxy]phenol **1** (0.6 g, 3.41 mmol) and $Ph_3P$ (0.893 g, 3.41 mmol) were dissolved in DCM (15 ml). A solution of DMAD (0.484 g, 0.418 ml, 3.41 mmol) in DCM (10 ml) was added dropwise over 10 min at −5 °C and the orange solution was heated under reflux for two days. Evaporation of the solvent and separation by column chromatography (hexane/DCM 1:1) followed by PTLC (silica gel, DCM) afforded **5** (0.465 g, 48%) and **6** (15 mg, 2%).

**3.1.1.1. Methyl 6-[(1,1-dimethyl-2-propynyl)oxy]-2-oxo-2*H*-chromene-4-carboxylate (5).** Yellow crystals, mp 76–78 °C (DCM/hexane); IR (Nujol) $\nu$ ($cm^{-1}$): 3230, 1725, 1705, 1600, 1550; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.67 (s, 6H), 2.63 (s, 1H), 4.00 (s, 3H), 6.97 (s, 1H), 7.29 (d, *J*=8.9 Hz, 1H), 7.43 (dd, *J*= 2.9 and 8.9 Hz, 1H), 8.18 (d, *J*=2.9 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 29.4, 53.1, 73.4, 74.7, 85.4, 117.4, 118.8, 119.7, 123.8, 126.7, 142.0, 150.1, 152.0, 160.1, 164.2; MS *m/z*: 286 ($M^+$, 14), 271 (28), 221 (38), 220 (37), 219 (52), 192 (56), 160 (56), 134 (74), 67 (100). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 66.92; H, 4.98.

**3.1.1.2. Methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano-[3,2-*f*]chromene-1-carboxylate (6).** Yellow crystals, mp 98–100 °C (DCM/hexane); IR (Nujol) $\nu$ ($cm^{-1}$): 1720, 1705, 1600, 1555; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.46 (s, 6H), 3.96 (s, 3H), 5.73 (d, *J*=9.8 Hz, 1H), 6.22 (d, *J*= 9.8 Hz, 1H), 6.52 (s, 1H), 7.06 (d, *J*=8.9 Hz, 1H), 7.17 (d, *J*=8.9 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75 Hz) $\delta$: 26.9, 53.2, 75.5, 111.6, 116.8, 117.1, 117.6, 118.9, 121.7, 131.5, 144.9, 149.2, 150.1, 159.5, 167.0; MS *m/z*: 286 ($M^+$, 20), 271 (100), 243 (16), 211 (10), 184 (8), 156 (4), 128 (4). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 67.35; H, 5.12.

**3.1.2. Procedure for the preparation of methyl 8,8-dimethyl-3-oxo-3,8-dihydropyrano[3,2-*f*]chromene-1-carboxylate (6).** A degassed solution of coumarin **5** (0.209 g, 0.73 mmol) in *o*-xylene (40 ml) under an Argon atmosphere was heated at reflux for 20 h. The solvent was evaporated and the residue was separated by PTLC (silica gel, DCM) and gave **6** (0.161 g, 77%).

**3.1.3. Procedure for the synthesis of methyl 7,7-dimethyl-2-oxo-2,7-dihydropyrano[2,3-*g*]chromene-4-carboxylate (9).** 2,2-Dimethylchromen-6-ol (**2**) (0.35 g, 2 mmol) and $Ph_3P$ (0.524 g, 2 mmol) were dissolved in DCM (10 ml). A solution of DMAD (0.284 g, 0.246 ml, 2 mmol) in DCM (5 ml) was added dropwise over 10 min period at −5 °C

and the solution was heated under reflux for five days. Evaporation of the solvent and separation by column chromatography (hexane/DCM 1:1) resulted to **9** (0.23 g, 40%); yellow crystals, mp 181–182 °C (DCM/hexane); IR (Nujol) $\nu$ ($cm^{-1}$): 1705, 1690, 1605, 1520; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.46 (s, 6H), 3.99 (s, 3H), 5.87 (d, $J$=9.8 Hz, 1H), 6.38 (d, $J$=9.8 Hz, 1H), 6.87 (s, 1H), 6.97 (s, 1H), 7.61 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 27.9, 53.1, 77.7, 112.7, 113.8, 115.8, 118.7, 121.2, 125.8, 135.7, 142.1, 149.1, 149.5, 160.3, 164.3; MS *m/z*: 286 ($M^+$, 15), 272 (11), 271 (100), 241 (18), 156 (10), 128 (12), 91 (10). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.11; H, 4.93. Found: C, 67.15; H, 4.96.

**3.1.4. Procedure for the synthesis of dimethyl 2-[(2,2-dimethyl-2*H*-chromen-6-yl)oxy]-2-butenodioate (11).** DMAD (0.69 g, 0.6 ml, 4.88 mmol) was added to a mixture of 2,2-dimethylchromen-6-ol (**2**) (0.5 g, 2.84 mmol) and anhydrous $ZnCl_2$ (0.387 g, 2.84 mmol) and the mixture was heated under an Argon atmosphere at 100 °C for 90 min. After cooling the mixture was partitioned in ethyl acetate (10 ml) and 10% HCl (10 ml). The organic layer was separated, washed with $H_2O$ (10 ml), dried by anhydrous $Na_2SO_4$, separated by column chromatography (hexane/DCM 1:2) and gave **11** (0.208 g, 23%); colorless crystals, mp 65–66 °C (ethyl acetate/hexane); IR (Nujol) $\nu$ ($cm^{-1}$): 1725, 1690, 1640, 1255, 1195; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.41 (s, 6H), 3.72 (s, 3H), 3.73 (s, 3H), 5.64 (d, $J$=10.2 Hz, 1H), 6.25 (d, $J$=10.2 Hz, 1H), 6.50 (s, 1H), 6.62 (d, $J$=2.5 Hz, 1H), 6.69 (d, $J$=8.9 Hz, 1H), 6.70 (dd, $J_1$=2.5 Hz, $J_2$=8.9 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 27.7, 51.9, 52.9, 76.1, 113.9, 114.1, 116.6, 116.9, 121.9, 122.0, 131.9, 148.8, 150.3, 150.4, 162.8, 164.0; MS *m/z*: 316 ($M^+$, 11), 304 (20), 303 (100), 161 (9), 144 (17), 132 (8), 115 (12), 91 (8). HRMS calcd for $C_{17}H_{18}O_6$ $[M]^+$ 318.1097, found: 318.1094.

**3.1.5. General procedure for the preparation of the coumarins 14a,b and the furanones 15a,b.** A solution of *o*-quinone **3** (1 mmol) and ylides **12a**,**b** (2.2 mmol) in dry DCM (50 ml) was stirred under an Argon atmosphere at room temperature for 1 h. The solvent was evaporated in a rotary evaporator and the residue was subjected to column chromatography (silica gel, hexane/ethyl acetate 15:1) to give products **15a**,**b** and **14a**,**b**.

**3.1.5.1. Methyl 8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano-[3,2-*g*]chromene-4-carboxylate (14a).** Yellow crystals (from EtOAc/hexane); mp 186–187 °C; yield 41%; IR (Nujol) $\nu$ ($cm^{-1}$): 1725, 1675, 1605, 1545; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.47 (s, 6H), 3.99 (s, 3H), 5.70 (d, $J$=10.2 Hz, 1H), 6.36 (d, $J$=10.2 Hz, 1H), 6.74 (s, 2H), 7.87 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 28.2, 53.0, 77.9, 104.5, 109.5, 115.6, 118.7, 121.1, 123.9, 131.2, 142.0, 155.8, 157.2, 160.4, 164.6; MS *m/z*: 286 ($M^+$, 10), 272 (17), 271 (81), 244 (10), 243 (11), 184 (7), 156 (11), 128 (14), 91 (100). HRMS calcd for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.0914, found: 287.0910.

**3.1.5.2. Methyl 2-[7,7-dimethyl-2-oxo-7*H*-furo[3,2-*g*]-chromen-3(2*H*)-ylidene]acetate (15a).** Yellow crystals (from EtOAc/hexane); mp 129–131 °C; yield 13%; IR (Nujol) $\nu$ ($cm^{-1}$): 1795, 1702, 1625, 1598; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.46 (s, 6H), 3.86 (s, 3H), 5.62 (d, $J$=10.2 Hz, 1H), 6.37 (d, $J$=10.2 Hz, 1H), 6.55 (s, 1H), 6.70 (s, 1H), 8.30 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 28.4, 29.7, 52.2, 78.3, 99.8, 113.6, 117.1, 120.2, 121.6, 126.8, 129.4, 133.5, 157.7, 158.9, 166.0, 168.2; MS *m/z*: 286 ($M^+$, 14), 272 (17), 271 (100), 243 (10), 184 (7), 156 (9), 128 (10), 115 (7). HRMS calcd for $C_{16}H_{15}O_5$ $[M+H]^+$ 287.0914, found: 287.0910.

**3.1.5.3. Ethyl 8,8-dimethyl-2-oxo-2*H*,8*H*-pyrano[3,2-*g*]-chromene-4-carboxylate (14b).** Yellow crystals (from $Et_2O$/hexane); mp 151–152 °C; yield 38%; IR (Nujol) $\nu$ ($cm^{-1}$): 1720, 1690, 1605, 1550; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.42 (t, $J$=7.6 Hz, 3H), 1.47 (s, 6H), 4.44 (q, $J$=7.6 Hz, 2H), 5.70 (d, $J$=10.2 Hz, 1H), 6.37 (d, $J$=10.2 Hz, 1H), 6.74 (s, 2H), 7.88 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 14.1, 28.4, 62.3, 77.9, 104.5, 109.6, 115.5, 118.7, 121.2, 124.0, 131.2, 142.4, 155.8, 157.2, 160.6, 164.1; MS *m/z*: 300 ($M^+$, 46), 285 (100), 257 (49), 229 (8), 213 (8), 185 (42), 156 (12), 128 (16). Anal. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.86; H, 5.34.

**3.1.5.4. Ethyl 2-[7,7-dimethyl-2-oxo-7*H*-furo[3,2-*g*]-chromen-3(2*H*)-ylidene]acetate (15b).** Yellow crystals (from EtOAc/hexane); mp 138–140 °C; yield 33%; IR (Nujol) $\nu$ ($cm^{-1}$): 1788, 1705, 1600, 1575; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 1.37 (t, $J$=7.6 Hz, 3H), 1.47 (s, 6H), 4.31 (q, $J$=7.6 Hz, 2H), 5.61 (d, $J$=10.2 Hz, 1H), 6.37 (d, $J$=10.2 Hz, 1H), 6.55 (s, 1H), 6.70 (s, 1H), 8.30 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$: 14.2, 28.4, 29.7, 61.2, 78.2, 99.7, 113.6, 117.7, 120.8, 121.6, 126.8, 129.4, 133.3, 157.6, 158.8, 165.6, 168.3; MS *m/z*: 300 ($M^+$, 14), 285 (100), 259 (14), 258 (30), 257 (27), 229 (10), 213 (12), 185 (45), 156 (22), 128 (55), 115 (29), 69 (60). HRMS calcd for $C_{17}H_{17}O_5$ $[M+H]^+$ 301.1070, found: 301.1060.

**3.1.6. General procedure for the dealkoxycarbonylation of the coumarin derivatives 6, 9, and 14b.** A mixture of coumarin derivative **6** or **9** or **14b** (0.32 mmol) and copper powder (0.66 mmol) in dry quinoline (5 ml) was heated under an Argon atmosphere at 175–180 °C for 19 h. After cooling, ethyl acetate (50 ml) was added, the copper powder was filtered and the residue was treated with 5% HCl (50 ml). The water layer was washed with ethyl acetate (50 ml) and the combined organic layers were washed with water (50 ml) and dried over anhydrous $Na_2SO_4$. The solvent was evaporated in a rotary evaporator and the residue was subjected to column chromatography (silica gel, DCM) to give the coumarin derivatives **7**[9,10] (38%), **10**[11] (51%), and **I**[11] (43%).

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# Indirect electrochemical oxidation of piperidin-4-ones mediated by sodium halide-base system

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**Abstract**—Indirect electrochemical oxidation of 1-*N*-subsituted piperidin-4-ones in methanol in an undivided cell in the presence of sodium iodide/sodium methoxide system leads to the corresponding α-hydroxyketals in 50–80% substance yield (50–65% current yield). 2,2,6,6-Tetramethylpiperidin-4-one under the same conditions forms a mixture of methyl 2,2,5,5-tetramethyl-3-pyrrolidinecarboxylate and methyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate in 70% substance yield (60–70% current yield) via electrochemically induced Favorskii rearrangement.


## 1. Introduction

The oxidation of ketones is a known method for preparing carboxylic acids and their derivatives, bifunctional compounds such as α-hydroxyketones, diketones and other useful intermediates in organic synthesis.[1] The formation of adipic acid from cyclohexanone is an important industrial process. α-Hydroxyketones are significant 'building blocks' in the construction of natural products and fine chemicals.[2,3] In the case of aryl alkyl ketones, the corresponding α-hydroxyketones and α-hydroxyketals are convenient compounds for synthesis of the pharmacologically active 2-arylalkanoic acids.[4,5]

Due to the considerable progress in the electrochemistry of organic compounds in the last decades, the electrosynthesis became a highly competitive method in modern organic chemistry.[6,7] However, in the case of the electrochemical oxidation of ketones, only some examples of the procedures, which could ensure product-selectivity are known.

The direct electrochemical oxidation of ketones led to the formation of a mixture of acids, saturated and unsaturated hydrocarbons, carbon monoxide and dioxide.[8–11] Remote non selective oxidative functionalization of aliphatic ketones was observed when electrooxidation was carried out in acetonitrile or trifluoroacetic acid as a result of the subsequent transformation of the initially produced cation radical $R^1R^2C{=}O^{+\bullet}$.[12,13]

In some oxidative transformations of ketones, such as in the haloform reaction, the α-halogenation of ketones is an important step.[14] So for certain cases, the selective indirect electrooxidation of ketones with the electrochemically generated halides is also possible. Thus, the electrocatalytic variant of the haloform reaction–the procedure to prepare carboxylic acid esters by the electrooxidation of methyl alkyl and methyl aryl ketones in methanol in the presence of alkali metal bromides is well known.[15]

The NaI/NaOH mediatory system is also known for the effective indirect electrochemical oxidation of carbonyl compounds. Using this mediatory system aryl alkyl ketones are oxidized into the corresponding α-hydroxyketals.[16] Electrolysis of alkyl benzyl ketones in methanol in an undivided cell in the presence of the NaI/NaOH system induces a process similar to the Favorskii rearrangement of α-haloalkyl benzyl ketones to produce methyl arylalkanecarboxylates.[17] Electrolysis of dialkyl ketones under the same conditions involves a process analogous to the Favorskii rearrangement of α,α-dihalodialkyl ketones giving rise to methyl esters of α,β-unsaturated carboxylic acids.[18,19]

It has been found that the result of the indirect electrochemical oxidation of cyclic ketones in methanol in an undivided cell in the presence of sodium halide or sodium halide-base system depends on the ring size of ketone. Cyclopentanone affords 2,2-dimethoxycyclopentanone, while cyclohexanone gives rise to 2,2-dimethoxycyclohexanol. Cyclic

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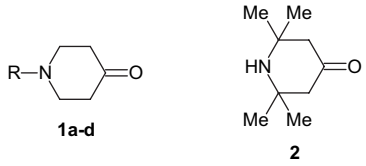
ketones with higher ring size after α,α-dihalogenation undergo the electrochemically induced Favorskii rearrangement with the formation of methyl cycloalkenecarboxylates containing in the ring one carbon less than starting ketone. So the simple electrocatalytic system can distinguish the ring size of cyclic ketones.[20,21]

Recently we have found that electrolysis of 4-substituted cyclohexanones in methanol in the presence of sodium halides in an undivided cell results in the stereoselective formation of *cis*-5-substituted-2,2-dimethoxycyclohexanols.[22]

Continuing our studies on the electrocatalytic and indirect electrooxidation of ketones[15–22] we have accomplished indirect electrochemical oxidation of substituted piperidin-4-ones **1a–d** and **2** in the presence of sodium halides as mediators and in the presence of mediatory systems sodium halide-base (Scheme 1).




**Scheme 1**.

## 2. Results and discussion

In the present study we report our results on the indirect electrochemical oxidation of substituted piperidin-4-ones **1a–d** and **2** (Tables 1–4). It has been found that electrooxidation of *N*-substituted 4-piperidinones **1a–d** in methanol in the presence of sodium halides as mediators led to the formation of 1-substituted 4,4-dimethoxypiperidine-3-ols **3a–d** (Scheme 2) (Table 1).

Thus the general result of the indirect electrochemical oxidation of *N*-substituted piperidin-4-ones **1a–d** is similar to the result of indirect electrochemical oxidation of cyclohexanone **4**[20,21] and 4-substituted cyclohexanones[22] (Scheme 3).

But there is a difference in the conditions of the electrooxidation. In the indirect electrooxidation of cyclohexanone[21]

**Table 2**. Electrooxidation of 2,2,6,6-tetramethylpiperidin-4-one **2** in methanol[a]

| No. | Ketone | Mediator | Base equivalent | Product, yield %[b] | Current yield %[c] |
|---|---|---|---|---|---|
| 1 | **2** | NaBr | — | **6a**, 18; **7a**, 28 | 37 |
| 2 | **2** | NaBr | 0.1 MeONa | **6a**, 29; **7a**, 42 | 57 |
| 3 | **2** | NaBr | 0.3 MeONa | **6a**, 42; **7a**, 34 (59) | 55 |
| 4 | **2** | NaBr | 0.5 MeONa | **6a**, 36; **7a**, 29 (57) | 50 |
| 5 | **2** | NaBr | 0.8 NaONa | **6a**, 32; **7a**, 21 | 37 |
| 6 | **2** | NaBr | 1.0 MeONa | **6a**, 28; **7a**, 15 | 29 |
| 7 | **2** | NaI | — | **6a**, 23; **7a**, 5 | 17 |
| 8 | **2** | NaI | 0.1 MeONa | **6a**, 43; **7a**, 8 | 30 |
| 9 | **2** | NaI | 0.3 MeONa | **6a**, 52; **7a**, 14 | 40 |
| 10 | **2** | NaI | 0.5 MeONa | **6a**, 59; **7a**, 26 (71) | 56 |
| 11 | **2** | NaI | 0.8 MeONa | **6a**, 53; **7a**, 29 (68) | 56 |
| 12 | **2** | NaI | 1.0 MeONa | **6a**, 38; **7a**, 45 (69) | 64 |
| 13 | **2** | NaI | 3.0 MeONa | **6a**, 29; **7a**, 58 (73) | 73 |

[a] Ketone (10 mmol), 10 mmol of mediator, 20 ml of MeOH, Fe-cathode, C-anode, current density 200 mA/cm$^2$, 4 F/mol electricity passed, 30 °C, conversion of **2** (95–100%).
[b] Determined by gas chromatography and NMR spectra, in parenthesis–isolated yields for the mixture of **6a** and **7a**.
[c] For the mixture of **6a** and **7a**.

**Table 3**. Electrooxidation of 2,2,6,6-tetramethylpiperidin-4-one **2** in ethanol[a]

| No. | Ketone | Mediator | Base equivalent | Product, yield %[b] | Current, yield %[c] |
|---|---|---|---|---|---|
| 1 | **2** | NaI | — | **6b**, 36 | 18 |
| 2 | **2** | NaI | 0.1 EtONa | **6b**, 53 (40) | 27 |
| 3 | **2** | NaI | 0.3 EtONa | **6b**, 65 (51); **7b**, 2 | 35 |
| 4 | **2** | NaI | 0.5 EtONa | **6b**, 44; **7b**, 11 | 33 |

[a] Ketone (10 mmol), 10 mmol of NaI, 20 ml of EtOH, Fe-cathode, C-anode, current density 200 mA/cm$^2$, 4 F/mol electricity passed, 30 °C, conversion of **2** (95–100%).
[b] Determined by gas chromatography and NMR spectra, in parenthesis–isolated yields for **6b**.
[c] For **6b** or the mixture of **6b** and **7b**.

**Table 4**. Electrooxidation of 3,3,5,5-tetramethylcyclohexanone **8** in methanol[a]

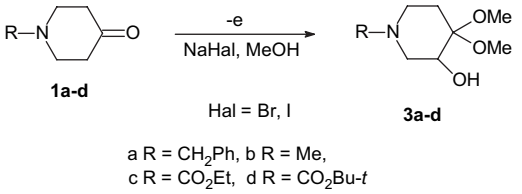
| No. | Ketone | Base equivalent | Product, yield %[b] | Current yield %[c] |
|---|---|---|---|---|
| 1 | **8** | — | **9** 7; **10** 53 (38); **11** 15 | 72 |
| 2 | **8** | 0.5 MeONa | **9** 12; **10** 34 (18); **11** 29 (17) | 69 |
| 3 | **8** | 1 MeONa | **9** 17 (11); **10** 13; **11** 46 (31) | 68 |

[a] Ketone (10 mmol), 10 mmol of NaI, 20 ml of MeOH, Fe-cathode, C-anode, current density 200 mA/cm$^2$, electricity passed 4 F/mol, 30 °C, conversion of **8** (95–100%).
[b] Determined by gas chromatography and NMR spectra, in parenthesis–isolated yields.
[c] For the mixture of **9**, **10** and **11**.

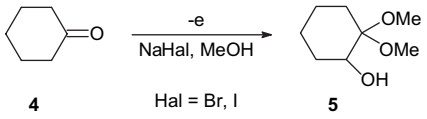
**Table 1**. Electrooxidation of *N*-substituted piperidin-4-ones **1a–d**[a]

| No. | Ketone | R | Mediator | Base equivalent | Electricity passed, F/mol | Product, yield %[b] | Current yield % |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | $CH_2Ph$ | NaBr | — | 6 | **3a**, 45 | 15 |
| 2 | **1a** | $CH_2Ph$ | NaI | — | 4.5 | **3a**, 56 | 25 |
| 3 | **1a** | $CH_2Ph$ | NaI | 0.3 NaOH | 4 | **3**a, 67 | 34 |
| 4 | **1a** | $CH_2Ph$ | NaI | 0.5 NaOH | 4 | **3a**, 74 (59) | 37 |
| 5 | **1a** | $CH_2Ph$ | NaI | 1.0 NaOH | 4 | **3a**, 61 | 31 |
| 6 | **1a** | $CH_2Ph$ | NaI | 0.5 MeONa | 3 | **3a**, 86 (71) | 57 |
| 7 | **1a** | $CH_2Ph$ | NaBr | 0.5 MeONa | 3 | **3a**, 66 | 44 |
| 8 | **1b** | Me | NaI | 0.5 MeONa | 3 | **3b**, 94 (81) | 65 |
| 9 | **1c** | $CO_2Et$ | NaI | 0.5 MeONa | 3 | **3c**, 69 (55) | 46 |
| 10 | **1d** | $CO_2Bu$-*t* | NaI | 0.5 MeONa | 3 | **3d**, 67 (52) | 45 |

[a] Ketone (10 mmol), 10 mmol of mediator, 20 ml of MeOH, Fe-cathode, C-anode, current density 200 mA/cm$^2$, 30 °C, conversion of **1a–d** (98–100%).
[b] Determined by gas chromatography and NMR spectra, in parenthesis–isolated yields.



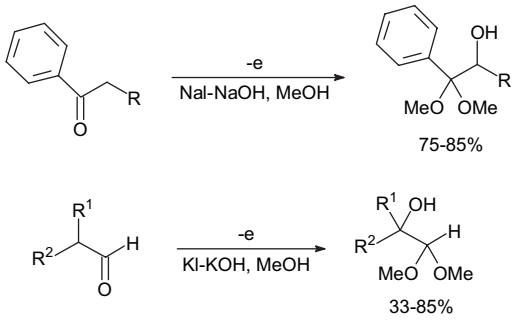

**Scheme 2**.




**Scheme 3**.

or 4-substituted cyclohexanones[22] into α-hydroxyketals of type **5**, there is no significant difference between the use of NaI or NaBr as a mediator and it is not necessary to use base additive to ensure good current efficiency.

As it follows from the data of Table 1, NaI is more efficient as mediator when compared with NaBr for the indirect electrooxidation of **1a–d** into α-hydroxyketals **3a–d**. In the case of NaOH as additive the best results were obtained with 0.5 equiv of NaOH. The next improvement of the conditions for the indirect electrochemical oxidation of **1a** was achieved using 0.5 equiv of MeONa. Under these optimal conditions **3a** was obtained in 86% substance and 57% current yields. Earlier only NaOH was used as additive for the electrooxidation of carbonyl compounds into corresponding α-hydroxyketals. Aryl alkyl ketones were successfully electrooxidized in the presence of NaI as mediator and 0.1 equiv of NaOH;[16] analogous transformation of aliphatic aldehydes was performed in the presence of NaI and 0.4 equiv of NaOH[23](Scheme 4):

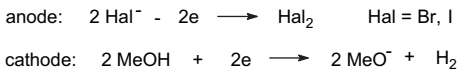



**Scheme 4**.

Earlier oxidation of **1a** by iodine/KOH (0 °C, 2.5 h)[24] resulted in **3a** formation in 50% yield and **3b** was obtained by oxidation of **1b** with iodobenzenediacetate[25] in MeOH/KOH (36 h) in 32% yield.

Taking into consideration the above results and the data on the mechanism of the electrocatalytic oxidation of cyclohexanone and 4-substituted cyclohexanones with sodium halide as mediator the following mechanism of the electrochemical oxidation of *N*-substituted piperidin-4-ones **1a–d** into α-hydroxyketals **3a–d** in the presence of sodium halide/NaOMe system is suggested.

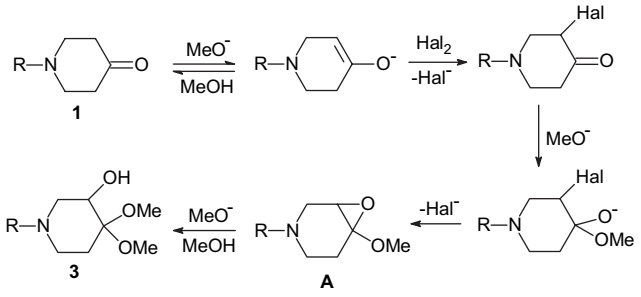
The reactions at the electrodes, which take place during the process, are shown below (Scheme 5):




**Scheme 5**.

The formation of iodine or bromine at the anode is a well-known process and the corresponding colour was observed when the electrolysis was conducted without stirring the reaction mixture, as well as evolution of hydrogen at the cathode.

Further bromination of enolate anion of **1** takes place in solution with following addition of methoxide anion to the carbonyl group and intramolecular substitution of halogen with the formation of intermediate epoxide (**A**). Then the attack of another methoxide anion leads to epoxide ring opening, and finally to formation of **3** (Scheme 6).

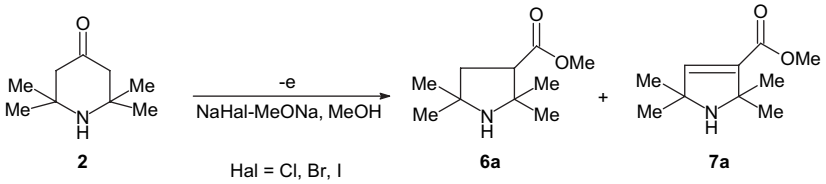



**Scheme 6**.

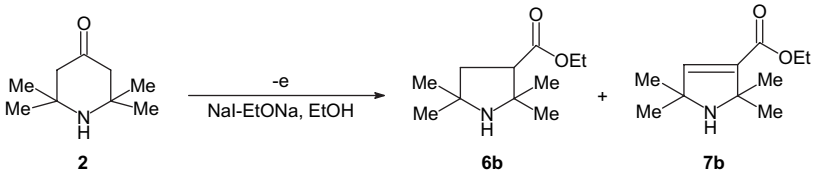
Sodium iodide gives better results for the indirect electrochemical oxidation of ketone **1** into α-hydroxyketal **3** compared to sodium bromide as bromine generated at anode is more effective for competitive oxidation of methoxide anions.

Taking into consideration that the indirect electrochemical oxidation of *N*-substituted piperidin-4-ones **1a–d** is similar to the result of indirect electrochemical oxidation of cyclohexanone **4** and leads to *N*-substituted 4,4-dimethoxypiperidine-3-ols **3a–d**, it was strange for us to find in recent preliminary communication that 2,2,6,6-tetramethylpiperidin-4-one **2** under conditions of the indirect electrochemical oxidation in methanol in the presence of sodium halides and 2.5 equiv of MeONa undergoes the electrochemically induced Favorskii rearrangement with the formation of mixtures of methyl 2,2,5,5-tetramethylpyrrolidine-3-carboxylate **6a** and methyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **7a**[26] (Scheme 7).

Indirect electrochemical oxidation of **2** in the presence of NaCl under our conditions without base or in the presence of 0.5 equiv of MeONa resulted in the formation of a complex mixture of compounds. The combined yields of esters **6** and **7** were less than 10% by GC and NMR data. The results of the electrochemical oxidation of **2** in the presence of NaI and NaBr in methanol are given in the Table 2.




**Scheme 7**.




**Scheme 8**.

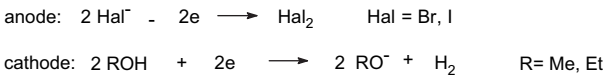
As it follows from the data of Table 2, NaI is more efficient mediator when compared with NaBr for the indirect electrooxidation of cyclic ketone **2** into the mixture of the cyclic esters **6a** and **7a**. Nevertheless, NaBr as mediator with 0.3 or 0.5 equiv of MeONa also led to good results. The best yields for the mixture of cyclic esters **6a** and **7a** were obtained using NaI–0.5 and more equivalents of MeONa mediatory system. Under these conditions cyclic esters **6a** and **7a** were isolated in 70% yield. The ratio of **6a** and **7a** changes from 2:1 to 1:2 with the increase of MeONa quantity from 0.5 to 3.0 equiv. Hydrogenation of the mixture of **6a** and **7a** in autoclave on Pd/C catalyst (5% Pd) in methanol resulted in formation of **6a** in quantitative yield.

What are the main differences of the electrooxidation **2** in MeOH under our conditions from those published earlier?[26] (**1**) The electrooxidation of **2** in the presence of NaCl in our case has no selectivity. (**2**) In the electrooxidation of **2** in the presence of NaBr under our conditions, the optimal quantity of MeONa is 0.3–0.5 equiv (ratio **6a/7a**, 4:3); earlier 2.6 equiv of MeONa (ratio **6a/7a**, 2:3). (**3**) In the electrooxidation of **2** in the presence of NaI under our conditions, the optimal quantity of MeONa is 0.5–3.0 equiv (whereas ratio **6a/7a** changes from 2:1 to 1:2), earlier 2.6 equiv of MeONa (ratio **6a/7a**, 1:1). (**4**) And the last but not least, current yields for the mixture of **6a** and **7a** in our case comprise 50–70%, the twice improvement on the earlier reported 30% yields.[26]

Indirect electrochemical oxidation of **2** in the presence of NaI in ethanol was found to be more selective process, in this case **6b** was isolated from the reaction mixture directly after electrolysis (Scheme 8) (Table 3).

Taking into consideration the results of the electrocatalytic oxidation of **2** and the data on the mechanism of the electrocatalytic oxidation of cyclic ketones with sodium halide as mediator,[12] the following mechanism of the indirect electrochemical oxidation of **2** in the presence of sodium halide/NaOR system is suggested.

The reactions at the electrodes, which take place during the process, are shown below (Scheme 9):




**Scheme 9**.

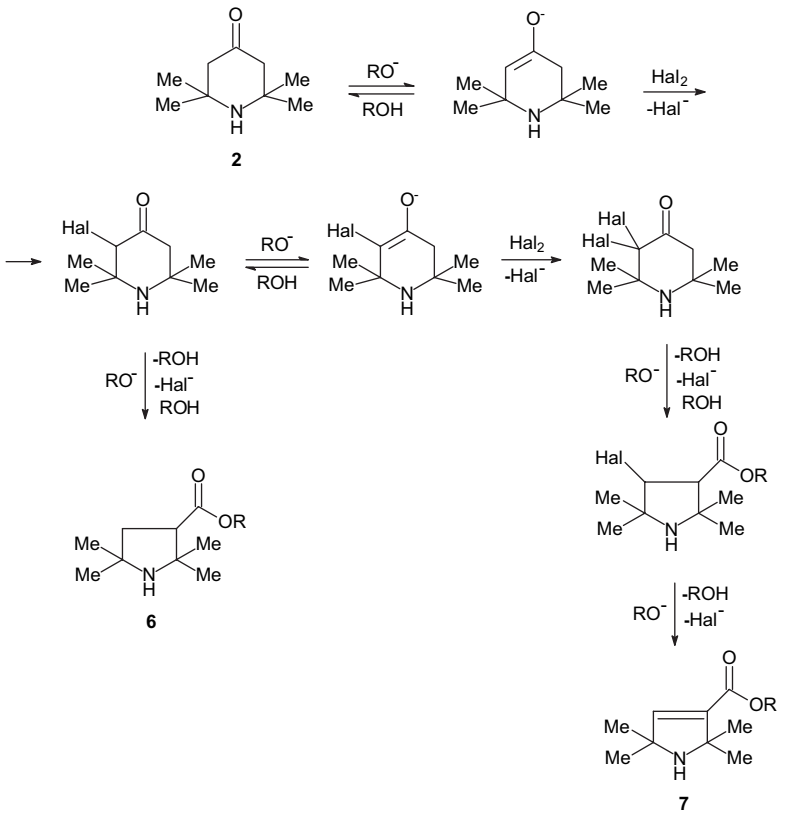
Further bromination and dibromination of enolate anion of **2** take place in solution, followed by proton abstraction with methoxide anion and Favorskii rearrangement[27] while the attack of methoxide anion on the carbonyl group is blocked by steric hindrance of the four methyl substituents (Scheme 10).

To determine an influence of tetramethyl substitution on the result of the electrocatalytic oxidation of the 6-membered cyclic ketones, the electrocatalytic oxidation of 3,3,5,5-tetramethylcyclohexanone has been studied (Table 4).

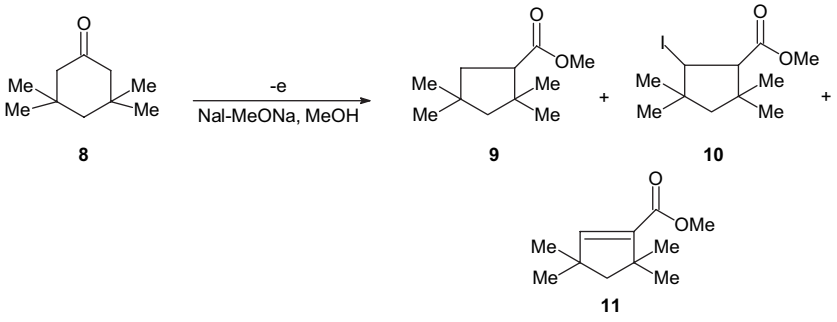
It was found that the result of electrocatalytic oxidation of 6-membered tetramethyl ketone **8** (Scheme 11) is very similar to the oxidation of 6-membered azatetramethyl ketone **2** and quite different from the electrocatalytic oxidation of cyclohexanone where only corresponding α-hydroxyketal was obtained.[21] The steric hindrance for the elimination of the iodine substituent in the ester **10** is even more stronger than in the corresponding ester formed from ketone **2** (according to the mechanism shown in Scheme 10), since only a part of iodoester **10** was converted into unsaturated ester **11** under conditions studied. Thus the steric influence of four methyl substituents is the main reason for the change in route of the indirect electrochemical oxidation of tetramethylpiperidinone **2** compare to *N*-substituted piperidin-4-ones **1a–d**.

## 3. Conclusion

To summarize, we have found that electrolysis with NaI/MeONa mediatory system in an undivided cell affords under mild conditions in methanol electrochemical oxidation of 1-*N*-substituted piperidin-4-ones into corresponding α-hydroxyketals in 50–80% yields. Under the similar conditions 2,2,6,6-tetramethylpiperidin-4-one in methanol was



**Scheme 10**.



**Scheme 11**.

transformed into the mixture of methyl 2,2,5,5-tetramethylpyrrolidine-3-carboxylate and methyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate in 70% overall yield or in ethanol directly into ethyl 2,2,5,5-tetramethyl-3-pyrrolidinecarboxylate in 40–50% yields as the result of the electrochemically induced Favorskii rearrangement. The simple two-step procedure, i.e., electrolysis and further hydrogenation affords methyl 2,2,5,5-tetramethyl-3-pyrrolidinecarboxylate in 70% yield. These methods require the use of common and commercially available reagents, inexpensive apparatus and an undivided cell. The techniques for electrolysis and isolation of the reaction products are simple and convenient to use both under laboratory conditions and in large-scale apparatus.

## 4. Experimental

### 4.1. General

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. GC analysis was carried out on LKhM-80 chromatograph with a flame-ionization detector. Columns: (1) fused-silica capillary column HP-1 (5 m×0.53 mm×2.65 μm) and (2) glass column 3 m× 3 mm with 10% FFAP on Chromaton N-Super (0.13–0.16 mm). $^1$H NMR spectra were run for solutions in $CDCl_3$ and recorded with Bruker AM-300 and Bruker DRX-500 spectrometers. Chemical shifts are presented in $\delta$ scale with tetramethylsilane (TMS) used as an internal standard.

### 4.2. General electrolysis procedure

A solution of ketone (10 mmol), sodium halide (10 mmol) and base (type of the base and amount used are specified in the corresponding Tables 1–4) in methanol or ethanol (20 ml) was electrolyzed in an undivided cell equipped with C-anode and Fe-cathode at 30 °C under constant current density 200 mA/cm$^2$ until the quantity of the electricity indicated in tables was passed. The reaction mixture was neutralized by dilute HCl, the solvent was then removed, and the reaction mixture was extracted with ether, washed with solution of $Na_2S_2O_3$ in water, then with water, and dried over $Na_2SO_4$. Solvent was removed and then products were isolated by sublimation (**3a** and **3b**), vacuum distillation (mixture of **6a** and **7a**, **6b**) or column chromatography on silica gel (eluent: hexane/ethyl acetate 1:1–10:1) (**3c**, **3d**, **9**, **10** and **11**). Mixtures of **6a** and **7a** were converted into **6a** by hydrogenation.

### 4.3. General hydrogenation procedure

Mixtures of **6a** and **7a** (0.5 g–2.0 g) in 20 ml of MeOH in the presence of 0.12 g, 5% Pd/C catalyst was hydrogenated in steel autoclave equipped with magnetic stirrer (500 rounds per minute) under 20 bar of hydrogen pressure during 5 h. Conversion of **7a** into **6a** was controlled by GC analysis on 11 m×0.25 mm Supelco SP™ 2380 capillary column (column temperature 120 °C). After 5 h compound **7a** was fully converted into **6a** with quantitative yield. The catalyst was filtered off, and after solvent removing **6a** was isolated.

**4.3.1. 1-Benzyl-4,4-dimethoxypiperidine-3-ol (3a).**[23,28] Yield 1.78 g (71%) [exp. 6, Table 1], white solid, mp 89–90 °C, $^1$H NMR ($CDCl_3$): $\delta$ 1.75–2.0 (m, 2H), 2.12–2.25 (m, 1H), 2.50–2.56 (m, 1H), 2.65–2.75 (m, 1H), 2.74 (s, 1H, OH), 2.83–2.90 (m, 1H), 3.22 (s, 3H, $OCH_3$), 3.28 (s, 3H, $OCH_3$), 3.57 (s, 2H, $CH_2Ph$), 3.70–3.74 (m, 1H, CH–O), 7.25–7.38 (m, 5H, Ph). $^{13}$C NMR ($CDCl_3$): $\delta$ 27.8 ($CH_2$), 47.5 ($OCH_3$), 47.6 ($OCH_3$), 49.2 ($CH_2$), 56.1 ($CH_2$), 61.9 ($CH_2$), 66.8 (OCH), 98.9 [$C(OCH_3)_2$], 127.0, 128.2, 128.8, 137.8 (Ph). MS (70 eV) *m*/*z* (relative intensity %): 251 (M$^+$, 12), 236 (14), 220 (23), 202 (15), 188 (10), 142 (6), 120 (21), 91 (100), 65 (15), 42 (17). IR (KBr): $\nu_{max}$ 3450, 2912, 2832, 1584, 1452, 1340, 1212, 1132, 1076, 948.

**4.3.2. 1-Methyl-4,4-dimethoxypiperidine-3-ol (3b).** Yield 1.41 g (81%), white solid, mp 108–109 °C [lits.[29,30] 109–110 °C], $^1$H NMR ($CDCl_3$): $\delta$ 1.80–1.94 (m, 2H), 2.05–2.13 (m, 1H), 2.25 (s, 3H, $CH_3$), 2.38–2.43 (m, 1H), 2.58–2.65 (m, 1H), 2.76–2.81 (m, 1H), 2.85 (s, 1H, OH), 3.19 (s, 3H, $OCH_3$), 3.25 (s, 3H, $OCH_3$), 3.71–3.75 (m, 1H, CH–O). $^{13}$C NMR ($CDCl_3$): $\delta$ 27.5 ($CH_2$), 45.5 ($CH_3$), 47.5 ($OCH_3$), 47.6 ($OCH_3$), 51.6 ($CH_2$), 58.2 ($CH_2$), 66.9 (OCH), 98.5 [$C(OCH_3)_2$]. MS (70 eV) *m*/*z* (relative intensity %): 175 (M$^+$, 24), 160 (23), 144 (29), 126 (31), 112 (20), 100 (7), 87 (45), 70 (11), 58 (49), 44 (100). IR (KBr): $\nu_{max}$ 3136, 2944, 2772, 1468, 1360, 1292, 1152, 1116, 1068, 948.

**4.3.3. Ethyl 3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (3c).**[28] Compound **3c** was isolated by column chromatography (eluent: hexane/ethyl acetate 1:1), yield 1.28 g (55%), colourless oil, $^1$H NMR ($CDCl_3$): $\delta$ 1.22 (t, 3H, *J*=7.1 Hz), 1.65–1.88 (m, 2H), 2.65 (s, 1H, OH), 2.94–3.18 (m, 2H), 3.20 (s, 3H, $OCH_3$), 3.22 (s, 3H, $OCH_3$), 3.72–3.90 (m, 3H), 4.18 (q, 2H, *J*=7.1 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.3 ($CH_3$), 27.0 ($CH_2$), 40.2 ($CH_2$), 46.3 ($CH_2$), 47.4 ($OCH_3$), 47.6 ($OCH_3$), 61.1 ($OCH_2$), 66.33 (OCH), 98.84 [$C(OCH_3)_2$], 156.10 (C=O). MS (70 eV) *m*/*z* (relative intensity %): 233 (M$^+$, 20), 218 (8), 204 (16), 202 (11), 173 (15), 160 (18), 156 (21), 144 (43), 101 (57), 88 (100), 56 (67), 42 (98). IR (KBr): $\nu_{max}$ 3460, 2944, 2832, 1685, 1436, 1272, 1228, 1120, 1076, 940.

**4.3.4. *tert*-Butyl 3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate (3d).**[23] Compound **3d** was isolated by column chromatography (eluent: hexane/ethyl acetate 1:1), yield 1.35 g (52%), colourless oil, $^1$H NMR ($CDCl_3$): $\delta$ 1.40 (s, 9H), 1.71–1.86 (m, 2H), 2.65 (s, 1H, OH), 2.95 (m, 1H), 3.15 (s, 3H, $OCH_3$), 3.18 (s, 3H, $OCH_3$), 3.29 (m, 1H), 3.61–3.73 (m, 3H). $^{13}$C NMR ($CDCl_3$): $\delta$ 28.1 ($CH_3$), 28.4 ($CH_2$), 42.2 ($CH_2$), 47.5 ($OCH_3$), 47.6 ($OCH_3$), 48.47 ($CH_2$), 65.86 (OCH), 79.12 (C–O), 99.92 [$C(OCH_3)_2$], 154.56 (C=O). MS (70 eV) *m*/*z* (relative intensity %): 261 (M$^+$, 2), 204 (5), 188 (2), 160 (4), 146 (14), 101 (15), 89 (24), 57 (100), 43 (66). IR (KBr): $\nu_{max}$ 3400, 2944, 2832, 1692, 1428, 1368, 1172, 1120, 1076, 940.

**4.3.5. Methyl 2,2,5,5-tetramethyl-3-pyrrolidinecarboxylate (6a).**[31,32] Yield 1.26 g (70%) [two-step procedure: electrolysis (exp.10, Table 2) and hydrogenation], colourless oil, bp 96–99 °C (14 Torr), [lit.[33] bp 86 °C (10.5 Torr)], $^1$H NMR ($CDCl_3$): $\delta$ 1.10 (s, 3H, $CH_3$), 1.22 (s, 3H, $CH_3$), 1.31 (s, 3H, $CH_3$), 1.40 (s, 3H, $CH_3$), 1.91 (dd, 1H, $J_1$=7.3 Hz, $J_2$=13.1 Hz), 2.19 (dd, 1H, $J_1$=11.5 Hz, $J_2$=13.1 Hz), 2.88 (dd, 1H, $J_1$=7.3 Hz, $J_2$=11.5 Hz), 3.65 (s, 3H, $OCH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ 25.9 ($CH_3$), 30.8 ($CH_3$), 31.0 ($CH_3$), 31.3 ($CH_3$), 42.4 ($CH_2$), 51.2 ($OCH_3$), 54.7 (CH), 57.5 (C), 62.0 (C), 173.2 (C=O). MS (70 eV) *m*/*z* (relative intensity %): 185 (M$^+$, 4), 170 (100), 154 (11), 138 (14), 124 (10), 110 (45), 99 (33), 84 (24), 58 (98). IR (KBr): $\nu_{max}$ 2964, 2930, 2872, 1736, 1464, 1436, 1368, 1288, 1188, 1148.

**4.3.6. Methyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (7a).**[26,32] Compound **7a** was obtained by method as described in Ref. 34. 70% Yield, colourless oil, bp 110–112 °C (15 Torr) [lit.[34] bp 56–58 °C (1.3 Torr)], $^1$H NMR ($CDCl_3$): $\delta$ 1.29 (s, 6H), 1.40 (s, 6H), 3.71 (s, 3H, $OCH_3$), 6.60 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 29.7 ($CH_3$), 29.8 ($CH_3$), 51.0 ($OCH_3$), 63.2 (C), 65.7 (C), 139.0 (C=), 148.9 (CH=), 164.3 (C=O). MS (70 eV) *m*/*z* (relative intensity %): 183 (M$^+$, 25), 168 (100), 152 (18), 136 (43), 122 (30), 108 (82), 94 (49), 67 (45). IR (KBr): $\nu_{max}$ 2964, 2928, 2872, 1730, 1632, 1436, 1368, 1328, 1148, 1064.

**4.3.7. Ethyl 2,2,5,5-tetramethyl-3-pyrrolidinecarboxylate (6b).**[35] Compound **6b** was isolated by reaction mixture distillation (exp. 3, Table 3), 1.01 g (51%) colourless oil, bp 114–116 °C (15 Torr) [lit.[35] bp 217 °C (748 Torr)], $^1$H NMR ($CDCl_3$): $\delta$ 1.07 (s, $CH_3$), 1.20 (s, $CH_3$), 1.25 (t, 3H, *J*=7.1 Hz), 1.29 (s, $CH_3$), 1.39 (s, $CH_3$), 1.89 (dd, 1H, $J_1$=7.3 Hz, $J_2$=13.0 Hz), 2.15 (dd, 1H, $J_1$=11.6 Hz, $J_2$=13.0 Hz), 2.85 (dd, 1H, $J_1$=7.3 Hz, $J_2$=11.6 Hz), 4.05–4.20 (m, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.1 ($CH_3$), 25.9 ($CH_3$), 30.9 ($CH_3$), 31.1 ($CH_3$), 31.4 ($CH_3$), 42.4 ($CH_2$), 54.9 (CH), 57.5 (C), 60.0 ($OCH_2$), 62.0 (C), 172.73

(C═O). MS (70 eV) *m/z* (relative intensity %): 199 ($M^+$, 3), 184 (100), 154 (14), 138 (12), 124 (6), 110 (39), 99 (24), 84 (18), 58 (50). IR (KBr): $\nu_{max}$ 2968, 2932, 1736, 1464, 1368, 1284, 1256, 1184, 1148, 1064.

**4.3.8. Ethyl 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (7b).**[36] Compound **7b** was obtained by method as described in Ref. 34. 55% Yield, colourless oil, bp 120–122 °C (12 Torr) [lit.[36] bp 212 °C (740 Torr)], $^1$H NMR ($CDCl_3$): $\delta$ 1.26 (s, 6H), 1.30 (t, 3H, $J$=7.2 Hz), 1.41 (s, 6H), 4.22 (q, 2H, $J$=7.2 Hz), 6.65 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.2 ($CH_3$), 29.9 ($2CH_3$), 30.1 ($2CH_3$), 59.9 ($OCH_2$), 63.2 (C), 65.9 (C), 139.4 (C═), 148.6 (CH═), 163.9 (C═O). MS (70 eV) *m/z* (relative intensity %): 197 ($M^+$, 2), 182 (100), 152 (21), 136 (15), 122 (10), 109 (66), 94 (18), 58 (11). IR (KBr): $\nu_{max}$ 2928, 2868, 1720, 1632, 1468, 1360, 1328, 1160, 1060.

**4.3.9. Methyl 2,2,4,4-tetramethylcyclopentanecarboxylate (9).** Compound **9** was isolated by column chromatography (exp. 3, Table 4) (eluent: hexane/ethyl acetate 8:1) 0.20 g (11%), colourless oil, $^1$H NMR ($CDCl_3$): $\delta$ 0.85 (s, 3H), 0.95 (s, 3H), 1.04 (s, 3H), 1.13 (s, 3H), 1.41 (s, 2H), 1.65 (dd, 1H, $J_1$=7.3 Hz, $J_2$=13.0 Hz), 1.95 (dd, 1H, $J_1$=11.7 Hz, $J_2$=13.0 Hz), 2.63 (dd, 1H, $J_1$=7.3 Hz, $J_2$=11.7 Hz), 3.59 (s, 3H, $OCH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ 25.8 (q), 30.6 (q), 31.0 (q), 31.2 (q), 36.3 (s), 42.5 (s), 42.9 (t), 50.9 (q), 54.0 (t), 56.6 (d), 174.2 (s). MS (70 eV) *m/z* (relative intensity %): 184 ($M^+$, 7), 169 (24), 153 (8), 137 (11), 123 (61), 109 (100), 95 (92), 83 (97), 56 (30). IR (KBr): $\nu_{max}$ 2956, 2930, 2868, 1736, 1464, 1436, 1256, 1192, 1172, 1064. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.56; H, 11.05.

**4.3.10. Methyl 5-iodo-2,2,4,4-tetramethylcyclopentanecarboxylate (10).** Compound **10** was isolated by column chromatography (exp. 1, Table 4) (eluent: hexane/ethyl acetate 10:1) 1.17 g (38%), pink oil, $^1$H NMR ($CDCl_3$): 0.91 (s, 3H), 1.05 (s, 3H), 1.13 (s, 3H), 1.27 (s, 3H), 1.52 (d, 1H, $J$=13.2 Hz), 1.71 (d, 1H, $J$=13.3 Hz), 3.11 (d, 1H, $J$=12.4 Hz), 3.72 (s, 3H, $OCH_3$), 4.29 (d, 1H, $J$=12.4 Hz). $^{13}$C NMR ($CDCl_3$): $\delta$ 27.7 ($CH_3$), 28.1 ($CH_3$), 29.2 ($CH_3$), 31.6 ($CH_3$), 41.4 (C), 41.9 (CH), 48.1 (C), 51.3 ($CH_2$), 51.6 ($OCH_3$), 63.8 (CH), 172.1 (C═O). MS (70 eV) *m/z* (relative intensity %): 310 ($M^+$, 6), 279 (7), 251 (3), 237 (11), 183 ($M^+$–I, 43), 167 (6), 151 (26), 123 (100), 109 (16), 97 (40). IR (KBr): $\nu_{max}$ 2960, 2932, 2868, 1740, 1460, 1436, 1372, 1256, 1192, 1168. Anal. Calcd for $C_{11}H_{19}IO_2$: C, 42.60; H, 6.17; I, 40.91. Found: C, 42.46; H, 6.03; I, 40.77.

**4.3.11. Methyl 3,3,5,5-tetramethyl-1-cyclopentene-1-carboxylate (11).** Compound **11** was isolated by column chromatography (exp. 3, Table 4) (eluent: hexane/ethyl acetate 8:1) 0.56 g (31%), colourless oil, $^1$H NMR ($CDCl_3$): 1.08 (s, 6H), 1.21 (s, 6H), 1.67 (s, 2H), 3.65 (s, 3H, $OCH_3$), 6.40 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 29.2 (q), 29.4 (q), 35.1 (s), 45.6 (s), 50.8 (q), 55.4 (t), 139.8 (s), 152.1 (d), 165.4 (s). MS (70 eV) *m/z* (relative intensity %): 182 ($M^+$, 18), 167 (33), 151 (7), 135 (15), 120 (20), 107 (100), 93 (22), 65 (25). IR (KBr): $\nu_{max}$ 2960, 2930, 2869, 1720, 1628, 1436, 1340, 1304, 1192, 1060. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.35; H, 9.81.

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# Chemoselective annulation of 1,3-dithiin, -thiazine and -oxathiin rings on thiazoles using a green protocol

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**Abstract**—Tandem Knoevenagel and Michael reactions of 3-arylrhodanines, aromatic aldehydes and ammonium *N*-aryldithiocarbamates diastereoselectively yield dithioesters, thiazol-5-ylmethyl *N*-aryldithiocarbamates, under solvent-free microwave irradiation conditions in a one-pot procedure. Under the same conditions, the dithioesters are chemoselectively and expeditiously annulated with montmorillonite K-10 clay, $Li^+$-montmorillonite clay and $I_2$ to give thiazolo-1,3-dithiins, -thiazines and -oxathiins, respectively.


## 1. Introduction

Recently, a number of oxathiin, thiazine and dithiin derivatives have been reported to exhibit antiviral activity against human immunodeficiency virus type 1 (HIV-1), poliovirus type 1 (PV-1), coxsackie B virus type 3 (CoxB-3), vesicular stomatitis virus (VSV) and herpes simplex virus type 1 (HSV-1).[1] Moreover, dithiocarbamates have been extensively investigated for their fungitoxicity and many of these, viz., maneb, mancozeb, ziram, thiram and vapam, have attained major recognition as agricultural fungicides.[2,3] Compounds bearing the dithiocarbamate group, as part of a heterocyclic structure have been relatively less studied although some of these compounds, e.g., rhodanines and mylone are known to display useful pesticidal properties.[4,5] The thiazole nucleus is a well-known active core of various bioactive molecules. Thus, heterocyclic systems resulting from the annulation of oxathiin, thiazine and dithiin rings on biologically versatile thiazole nuclei provide an attractive scaffold that can be utilised for exploiting chemical diversity and generating drug-like screening libraries to generate lead candidates.

One-pot multi-component reactions (MCRs) have emerged as an improved synthetic strategy for drug discovery processes, [6–12] because multi-step synthesis produces considerable amounts of environmentally unfavourable wastes predominantly due to complex isolation procedures that often involve expensive, toxic and hazardous solvents after each step.

The application of microwave (MW) irradiation as a non-conventional energy source for activation of reactions, in general and under solvent-free conditions in particular, has now gained popularity over the usual homogeneous and heterogeneous reactions. It provides chemical processes with special attributes, such as enhanced reaction rates, higher yields of pure products, better selectivity, improved ease of manipulation, rapid optimisation of reactions in parallel and several ecofriendly advantages in the context of green chemistry.[13–20] The application of MW irradiation has recently been extended to modern drug discovery processes,[21,22] and has proved successful in the formation of carbon–heteroatom and carbon–carbon bonds.[23,24]

Considering the above reports and the recently reported results concerning MW accelerated Ugi three-component coupling (3cc) reactions,[25–27] in addition to continuing our work on new solvent-free cyclisation procedures,[28–32] we devised a solvent-free MW-activated expeditious synthesis of thiazolo-1,3-dithiins **5**, -thiazines **6** and -oxathiins **7** via one-pot Knoevenagel and Michael reactions (Scheme 1).

## 2. Results and discussion

After some preliminary experimentation, it was found that the envisaged synthesis (Scheme 1) was successful on intermittent MW irradiation of an intimate mixture of 3-arylrhodanines **1**, aromatic aldehydes **2** and ammonium *N*-aryldithiocarbamates **3** under solvent-free conditions for the time specified in Table 1, followed by heterocyclisations

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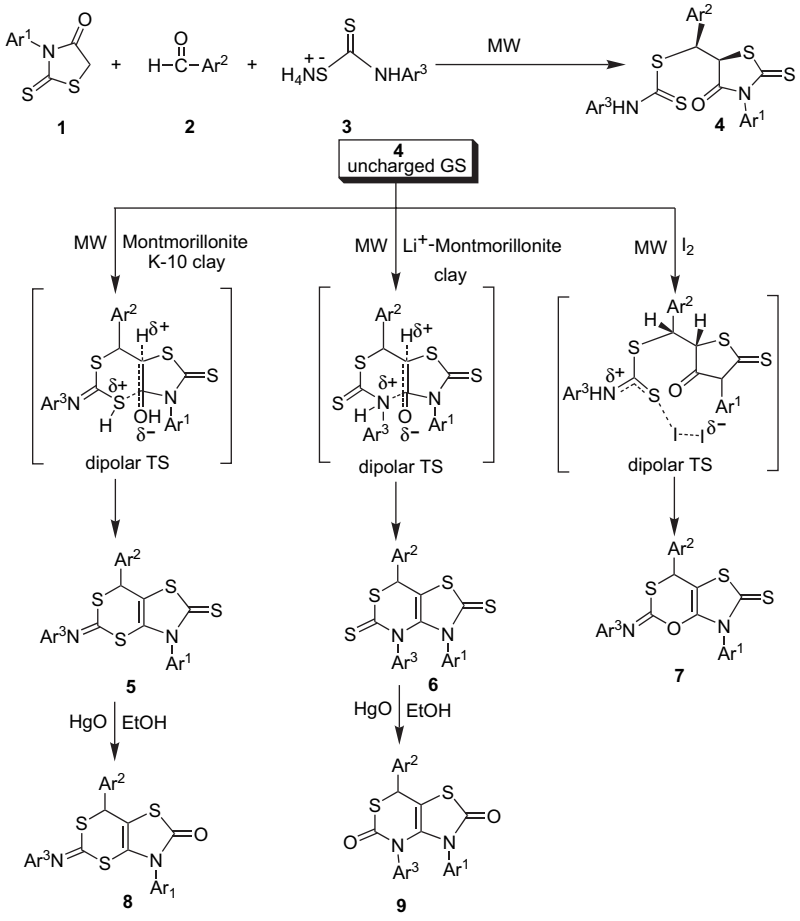


| 4- 7 | $Ar^1$ | $Ar^2$ | $Ar^3$ |
|---|---|---|---|
| a | Ph | 4-$ClC_6H_4$ | Ph |
| b | Ph | 4-$MeOC_6H_4$ | Ph |
| c | 2-$MeC_6H_4$ | Ph | 2-$MeC_6H_4$ |
| d | 2-$MeC_6H_4$ | 4-$ClC_6H_4$ | 2-$MeC_6H_4$ |
| e | 2-$MeC_6H_4$ | 4-$MeOC_6H_4$ | 2-$MeC_6H_4$ |

**Scheme 1**.

of the resulting dithioesters **4** with montmorillonite K-10 clay, $Li^+$-montmorillonite, or $I_2$ under the same conditions. Isolation and purification by recrystallisation from ethanol afforded the desired products **4–7** in 77–89% yield (Table 1).

For comparative purposes, the final temperature of the reaction mixture was recorded immediately after the MW irradiation for 2 min and was found to reach about 90 °C. Reactions were also carried out using a thermostated oil bath at the same temperature (90 °C) as the MW-activated method, but for a longer (optimised) period of time (Table 1) to ascertain whether the MW method improved the yield or simply increased the conversion rates. It was found that significantly lower yields (42–52%) were obtained using the oil baths rather compared to the MW-activated method (Table 1). This observation may be rationalised by considering the formation of a dipolar transition state (TS) from an uncharged ground state (GS) in these reactions (Scheme 1). The greater stabilisation of more polar TS by dipole–dipole interactions with the electric field of microwaves as compared to the less polar GS, may reduce the activation energy ($\Delta G^{\neq}$), resulting in rate enhancement.[17]

Compounds **5–7** were synthesised from the same precursors **4** by intramolecular chemoselective heterocyclizations (Scheme 1). The isomeric compounds **5** and **6** clearly differ in their IR spectra; **5** exhibited a strong band attributed to C=N (1635 $cm^{-1}$), whereas **6** was devoid of this band. Further, the representative compounds **5a** and **6a** were converted into their -6-one and -2,5-dione analogs **8a** and **9a**, respectively, on treatment with HgO. This conversion, involving desulfurisation of the exocyclic sulfur, provides chemical evidence for the assigned structures of the isomeric **5a** and **6a** as the desulfurated products **8a** and **9a** are not isomeric.

**Table 1**. Solvent-free microwave-activated synthesis of products **4–7**

| Product | Time | | Yield (%)[a] | | mp (°C)[b] |
|---|---|---|---|---|---|
| | MW (min)[c] | Thermal (h)[d] | MW | Thermal | |
| **4a** | 6 | 2 | 88 | 51 | 118–120 |
| **4b** | 6 | 3 | 79 | 43 | 127–128 |
| **4c** | 4 | 2 | 82 | 42 | 133–135 |
| **4d** | 4 | 2 | 87 | 46 | 138–139 |
| **4e** | 6 | 3 | 80 | 43 | 130–131 |
| **5a** | 12 | 3 | 89 | 52 | 139–140 |
| **5b** | 10 | 3 | 80 | 47 | 143–144 |
| **5c** | 10 | 5 | 83 | 48 | 148–150 |
| **5d** | 12 | 4 | 85 | 50 | 150–152 |
| **5e** | 12 | 4 | 80 | 42 | 145–146 |
| **6a** | 10 | 5 | 88 | 45 | 154–156 |
| **6b** | 10 | 4 | 81 | 43 | 159–160 |
| **6c** | 12 | 3 | 82 | 42 | 153–154 |
| **6d** | 12 | 3 | 85 | 48 | 164–166 |
| **6e** | 10 | 4 | 78 | 45 | 162–163 |
| **7a** | 10 | 5 | 87 | 51 | 158–159 |
| **7b** | 10 | 5 | 83 | 48 | 167–168 |
| **7c** | 8 | 4 | 80 | 43 | 175–176 |
| **7d** | 8 | 5 | 85 | 48 | 152–153 |
| **7e** | 10 | 3 | 77 | 43 | 170–171 |

[a] Yield of isolated and purified products.
[b] All compounds gave C, H and N analyses within ±0.35% and satisfactory spectral (IR, $^1$H NMR, $^{13}$C NMR and EIMS) data.
[c] Microwave irradiation time (power = 100 W).
[d] Time for oil-bath heating at 90 °C.

## 3. Conclusion

In summary, we have developed a green protocol for an expeditious synthesis of various potentially, pharmaceutically and agrochemically useful thiazolo-1,3-dithiins, -thiazines and -oxathiins starting from readily available simple substrates employing solvent-free MW irradiation conditions.

## 4. Experimental

### 4.1. General

Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 993 IR spectrophotometer, $^1$H NMR spectra were recorded on a Bruker WM-40 C (400 MHz) FT spectrometer in DMSO-$d_6$ using TMS as internal reference. $^{13}$C NMR spectra were recorded on the same instrument at 100 MHz using the same solvent and internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyser. A CEM Discover Focused Microwave Synthesis System operating at 2450 MHz was used at an output of 100 W for all the experiments. All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

### 4.2. (3-Arylperhydro-4-oxo-2-thioxothiazol-5-yl)arylmethyl *N*-aryldithiocarbamates 4. General procedure

An intimate mixture of a 3-arylrhodanine **1** (2.0 mmol), an aromatic aldehyde **2** (2.0 mmol) and an ammonium *N*-aryldithiocarbamate **3** (2.0 mmol) were taken in a 20 mL vial and subjected to MW irradiation at 100 W in a CEM Discover microwave system for 2 min. The reaction mixture was then thoroughly mixed outside the MW oven for 2 min and again irradiated for another 2 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time of 4–6 min (Table 1). After completion of the reaction as indicated by TLC (hexane/AcOEt, 8:2, v/v), water (10 mL) was added to the reaction mixture and stirred well. The yellowish precipitate thus obtained was washed with water to give the crude product, which was recrystallised from ethanol to afford a diastereomeric mixture (>96:<4). The crude product ratios were >95:<5 as determined by $^1$H NMR spectroscopy. The product on second recrystallisation from ethanol furnished an analytically pure sample of a single diastereomer **4** (Table 1). Comparison of the *J* values to that reported in the literature,[33–38] led to the assignment of cis stereochemistry for **4**, as the coupling constant ($Jcyclic_{SCH}$, $acyclic_{SCH}$=5 Hz) of the major isomer was lower than that for the minor trans diastereomer ($Jcyclic_{SCH}$, $acyclic_{SCH}$=10 Hz).

**4.2.1. Compound 4a.** White needles (88%), mp 118–120 °C. IR (KBr) $\nu_{max}$ 3147, 3025, 1700, 1602, 1580, 1451, 1055 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 5.94 (d, 1H, *J*=5 Hz, acyclic SCH), 6.05 (d, 1H, *J*=5 Hz, cyclic SCH), 7.13–8.02 (m, 14H$_{arom}$), 9.30 (br s, 1H, NH, exchanges with D$_2$O). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 43.6, 79.0, 126.6, 127.2, 127.8, 129.5, 130.2, 130.9, 131.7, 132.5, 133.2, 133.8, 134.4, 135.1, 173.7, 192.9, 195.8. Mass (*m*/*z*): 500, 502 (M, M+2). Anal. Calcd for $C_{23}H_{17}ClN_2OS_4$: C, 55.13; H, 3.42; N, 5.59%. Found: C, 57.43; H, 3.34; N, 5.34%.

**4.2.2. Compound 4b.** White needles (79%), mp 127–128 °C. IR (KBr) $\nu_{max}$ 3143, 3022, 1705, 1601, 1575, 1445, 1050 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 3.70 (s, 3H, OMe), 5.91 (d, 1H, *J*=5 Hz, acyclic SCH), 6.08 (d, 1H, *J*=5 Hz, cyclic SCH), 7.03–7.99 (m, 14H$_{arom}$), 9.28 (br s, 1H, NH, exchanges with D$_2$O). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 43.5, 55.3, 79.3, 125.9, 126.8, 127.5, 128.2, 129.0, 129.7, 130.3, 131.0, 131.6, 132.3, 133.0, 133.8, 173.5, 192.5, 195.7. Mass (*m*/*z*): 496 (M$^+$). Anal. Calcd for $C_{24}H_{20}N_2O_2S_4$: C, 58.04; H, 4.06; N, 5.64%. Found: C, 58.37; H, 3.86; N, 5.46%.

**4.2.3. Compound 4c.** White needles (82%), mp 133–135 °C. IR (KBr) $\nu_{max}$ 3140, 3020, 1707, 1600, 1580, 1450, 1057 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.29 (s, 6H, 2×Me), 5.89 (d, 1H, *J*=5 Hz, acyclic SCH), 6.11 (d, 1H, *J*=5 Hz, cyclic SCH), 7.13–8.11 (m, 13H$_{arom}$), 9.35 (br s, 1H, NH, exchanges with D$_2$O). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.3, 21.4, 43.1, 79.8, 125.3, 125.9, 126.6, 127.2, 128.8, 128.5, 129.1, 129.8, 130.4, 131.0, 131.8, 132.6, 133.3, 134.0, 134.7, 135.2, 173.4, 192.5, 195.4. Mass (*m*/*z*): 494 (M$^+$). Anal. Calcd for $C_{25}H_{22}N_2OS_4$: C, 60.70; H, 4.48; N, 5.66%. Found: C, 61.01; H, 4.29; N, 5.89%.

**4.2.4. Compound 4d.** White needles (87%), mp 138–139 °C. IR (KBr) $\nu_{max}$ 3142, 3026, 1702, 1605, 1587, 1455, 1058 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.32 (s, 6H, 2×Me), 5.90 (d, 1H, *J*=5 Hz, acyclic SCH), 6.07 (d, 1H, *J*=5 Hz, cyclic SCH), 7.03–8.12 (m, 12H$_{arom}$), 9.30 (br s, 1H, NH, exchanges with D$_2$O). $^{13}$C NMR

(DMSO-$d_6$/TMS) $\delta$: 20.5, 21.6, 43.7, 80.0, 125.5, 126.1, 126.7, 127.4, 128.0, 128.6, 129.3, 130.0, 130.6, 131.3, 131.9, 132.5, 133.1, 133.8, 134.5, 135.2, 173.3, 192.8, 195.7. Mass (*m*/*z*): 528, 530 (M, M+2). Anal. Calcd for $C_{25}H_{21}ClN_2OS_4$: C, 56.74; H, 4.00; N, 5.29%. Found: C, 56.99; H, 3.89; N, 5.48%.

**4.2.5. Compound 4e.** White needles (80%), mp 130–131 °C. IR (KBr) $\nu_{max}$ 3147, 3028, 1706, 1608, 1579, 1449, 1051 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.37 (s, 6H, 2×Me), 3.68 (s, 3H, OMe), 5.85 (d, 1H, $J$=5 Hz, acyclic SCH), 6.01 (d, 1H, $J$=5 Hz, cyclic SCH), 7.01–8.11 (m, 12H$_{arom}$), 9.28 (br s, 1H, NH, exchanges with $D_2O$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.4, 21.5, 43.5, 55.1, 79.6, 125.4, 126.1, 126.7, 127.4, 127.9, 128.5, 129.2, 129.9, 130.5, 131.8, 132.4, 133.1, 133.7, 134.4, 135.1, 135.8, 173.2, 192.7, 195.5. Mass (*m*/*z*): 524 (M$^+$). Anal. Calcd for $C_{26}H_{24}N_2O_2S_4$: C, 59.51; H, 4.61; N, 5.34%. Found: C, 59.79; H, 4.48; N, 5.54%.

### 4.3. 3,7-Diaryl-5-(arylamino)-2,3,5,7-tetrahydrothiazolo[4,5-*d*][1,3]dithiin-2-thiones 5. General procedure

Thoroughly mixed dithioesters **4** (2.0 mmol) and montmorillonite K-10 clay (0.2 g) were taken in a 20 mL vial and subjected to intermittent MW irradiation at 100 W at the intervals of 2 min for the total irradiation time of 10–12 min (Table 1). After completion of the reaction as indicated by TLC (hexane/AcOEt, 8:2, v/v), water (10 mL) was added to the reaction mixture and stirred well. The yellowish precipitate thus obtained was washed with water to give the crude product, which was recrystallised from ethanol to afford analytically pure sample of **5**.

**4.3.1. Compound 5a.** Yellowish needles (89%), mp 139–140 °C. IR (KBr) $\nu_{max}$ 3025, 1635, 1604, 1585, 1456, 1060 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 4.45 (s, 1H, Ar-CH), 7.13–7.95 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 42.5, 80.5, 126.7, 127.4, 128.0, 128.6, 129.3, 130.1, 130.7, 131.5, 132.3, 133.0, 133.6, 134.3, 158.5, 159.8, 192.5. Mass (*m*/*z*): 482, 484 (M, M+2). Anal. Calcd for $C_{23}H_{15}ClN_2S_4$: C, 57.18; H, 3.13; N, 5.80%. Found: C, 57.47; H, 3.34; N, 5.49%.

**4.3.2. Compound 5b.** Yellowish needles (80%), mp 143–144 °C. IR (KBr) $\nu_{max}$ 3021, 1631, 1603, 1584, 1455, 1058 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 3.73 (s, 3H, OMe), 4.41 (s, 1H, Ar-CH), 7.11–7.93 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 42.4, 54.9, 81.3, 126.6, 127.3, 128.1, 128.7, 129.4, 130.1, 130.8, 131.6, 132.2, 132.9, 133.5, 134.2, 158.4, 159.6, 192.3. Mass (*m*/*z*): 478 (M$^+$). Anal. Calcd for $C_{24}H_{18}N_2OS_4$: C, 60.22; H, 3.79; N, 5.85%. Found: C, 59.87; H, 3.88; N, 5.65%.

**4.3.3. Compound 5c.** Yellowish needles (83%), mp 148–150 °C. IR (KBr) $\nu_{max}$ 3020, 1630, 1598, 1579, 1449, 1056 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.30 (s, 6H, 2×Me), 4.43 (s, 1H, Ar-CH), 7.15–7.89 (m, 13H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.3, 21.5, 42.2, 79.9, 125.4, 126.0, 126.6, 127.3, 128.0, 128.6, 129.4, 130.0, 130.7, 131.3, 131.9, 132.7, 133.3, 134.0, 134.6, 135.2, 158.1, 159.8, 192.5. Mass (*m*/*z*): 476 (M$^+$). Anal. Calcd for $C_{25}H_{20}N_2S_4$: C, 62.99; H, 4.23; N, 5.88%. Found: C, 62.72; H, 4.09; N, 5.98%.

**4.3.4. Compound 5d.** Yellowish needles (85%), mp 150–152 °C. IR (KBr) $\nu_{max}$ 3024, 1633, 1605, 1581, 1451, 1059 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.33 (s, 6H, 2×Me), 4.48 (s, 1H, Ar-CH), 7.10–7.91 (m, 12H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.2, 21.7, 42.4, 81.4, 125.3, 126.0, 126.7, 127.4, 128.1, 128.7, 129.3, 130.0, 130.8, 131.4, 132.0, 132.7, 133.4, 134.1, 134.7, 135.3, 157.9, 160.0, 192.8. Mass (*m*/*z*): 510, 512 (M, M+2). Anal. Calcd for $C_{25}H_{19}ClN_2S_4$: C, 58.74; H, 3.75; N, 5.48%. Found: C, 57.79; H, 3.58; N, 5.67%.

**4.3.5. Compound 5e.** Yellowish needles (80%), mp 145–146 °C. IR (KBr) $\nu_{max}$ 3021, 1631, 1601, 1580, 1448, 1061 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.31 (s, 6H, 2×Me), 3.70 (s, 3H, OMe), 4.42 (s, 1H, Ar-CH), 7.09–7.95 (m, 12H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.3, 21.6, 42.3, 54.8, 80.8, 125.5, 126.1, 126.7, 127.3, 128.0, 128.7, 129.4, 130.0, 130.6, 131.2, 131.9, 132.5, 133.2, 133.8, 134.4, 135.1, 158.8, 159.9, 192.6. Mass (*m*/*z*): 506 (M$^+$). Anal. Calcd for $C_{26}H_{22}N_2OS_4$: C, 61.63; H, 4.38; N, 5.53%. Found: C, 61.90; H, 4.23; N, 5.31%.

### 4.4. 3,4,7-Triaryl-2,3,4,5,7-pentahydrothiazolo[4,5-*d*]-[1,3]thiazine-2,5-dithiones 6. General procedure

An intimate mixture of dithioesters **4** (2.0 mmol) and Li$^+$-montmorillonite clay (0.2 g) was taken in a 20 mL vial and intermittently irradiated at the intervals of 2 min in a CEM Discover MW system at 100 W for the total irradiation time of 10–12 min (Table 1). To obtain analytically pure sample of compounds **6**, the same procedure was adopted as described for **5**.

**4.4.1. Compound 6a.** Yellowish needles (88%), mp 154–156 °C. IR (KBr) $\nu_{max}$ 3027, 1605, 1585, 1445, 1057 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 4.39 (s, 1H, Ar-CH), 7.02–7.91 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 42.1, 78.9, 125.8, 126.6, 127.3, 128.0, 128.8, 129.7, 130.4, 131.1, 131.9, 132.8, 133.6, 134.9, 151.9, 191.5, 192.3. Mass (*m*/*z*): 482, 484 (M, M+2). Anal. Calcd for $C_{23}H_{15}ClN_2S_4$: C, 57.18; H, 3.13; N, 5.80%. Found: C, 56.83; H, 3.25; N, 5.56%.

**4.4.2. Compound 6b.** Yellowish needles (81%), mp 159–160 °C. IR (KBr) $\nu_{max}$ 3021, 1598, 1583, 1451, 1051 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 3.75 (s, 3H, OMe), 4.43 (s, 1H, Ar-CH), 7.13–7.95 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 42.0, 54.7, 80.2, 125.7, 126.5, 127.3, 128.0, 128.8, 129.7, 130.4, 131.1, 131.9, 132.8, 133.6, 134.9, 151.9, 191.5, 192.3. Mass (*m*/*z*): 478 (M$^+$). Anal. Calcd for $C_{24}H_{18}N_2OS_4$: C, 60.22; H, 3.79; N, 5.85%. Found: C, 60.57; H, 3.64; N, 5.61%.

**4.4.3. Compound 6c.** Yellowish needles (82%), mp 153–154 °C. IR (KBr) $\nu_{max}$ 3022, 1601, 1579, 1450, 1053 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.32 (s, 6H, 2×Me), 4.37 (s, 1H, Ar-CH), 7.05–7.98 (m, 13H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.1, 21.3, 41.5, 78.8, 125.4, 126.0, 126.7, 127.3, 127.9, 128.6, 129.4, 130.0, 130.6, 131.2, 131.9, 132.5, 133.1, 133.8, 134.6, 135.0, 151.8, 191.5, 192.2. Mass (*m*/*z*): 476 (M$^+$). Anal. Calcd for $C_{25}H_{20}N_2S_4$: C, 62.99; H, 4.23; N, 5.88%. Found: C, 62.69; H, 4.11; N, 5.68%.

**4.4.4. Compound 6d.** Yellowish needles (85%), mp 164–166 °C. IR (KBr) $\nu_{max}$ 3026, 1604, 1584, 1448, 1059 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.31 (s, 6H, 2×Me), 4.42 (s, 1H, Ar-CH), 7.09–7.85 (m, 12H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.6, 21.5, 41.9, 81.0, 125.3, 125.9, 126.5, 127.2, 127.8, 128.5, 129.1, 129.8, 130.5, 131.1, 131.8, 132.4, 133.0, 133.7, 134.3, 135.0, 151.6, 191.7, 192.4. Mass (*m*/*z*): 510, 512 (M, M+2). Anal. Calcd for $C_{25}H_{19}ClN_2S_4$: C, 58.74; H, 3.75; N, 5.48%. Found: C, 58.36; H, 3.85; N, 5.73%.

**4.4.5. Compound 6e.** Yellowish needles (78%), mp 162–163 °C. IR (KBr) $\nu_{max}$ 3020, 1602, 1580, 1446, 1052 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.28 (s, 6H, 2×Me), 3.72 (s, 3H, OMe), 4.36 (s, 1H, Ar-CH), 7.11–7.88 (m, 12H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.4, 21.4, 41.7, 54.6, 81.1, 125.4, 126.1, 126.7, 127.3, 127.9, 128.6, 129.3, 130.0, 130.6, 131.3, 132.0, 132.6, 132.8, 133.6, 134.3, 135.0, 151.7, 191.6, 192.3. Mass (*m*/*z*): 506 (M$^+$). Anal. Calcd for $C_{26}H_{22}N_2OS_4$: C, 61.63; H, 4.38; N, 5.53%. Found: C, 61.30; H, 4.51; N, 5.73%.

### 4.5. 3,7-Diaryl-5-(arylamino)-2,3,5,7-tetrahydrothiazolo[4,5-*e*][1,3]oxathiin-2-thiones 7. General procedure

Thoroughly mixed dithioesters **4** (2 mmol) and $I_2$ (0.56 g) were taken in a 20 mL vial and subjected to intermittent MW irradiation at 100 W at the intervals of 2 min for the total irradiation time of 8–10 min (Table 1). To obtain analytically pure sample of compounds **7**, the same procedure was adopted as described for **5**.

**4.5.1. Compound 7a.** Yellowish needles (87%), mp 158–159 °C. IR (KBr) $\nu_{max}$ 3025, 1639, 1605, 1586, 1455, 1058 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 4.39 (s, 1H, Ar-CH), 7.03–7.85 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 42.7, 79.5, 125.9, 126.6, 127.4, 128.2, 128.9, 129.7, 130.5, 131.4, 132.1, 132.9, 133.7, 134.6, 161.2, 162.9, 191.8. Mass (*m*/*z*): 466, 468 (M, M+2). Anal. Calcd for $C_{23}H_{15}ClN_2OS_3$: C, 59.15; H, 3.24; N, 6.00%. Found: C, 60.10; H, 3.39; N, 5.78%.

**4.5.2. Compound 7b.** Yellowish needles (83%), mp 167–168 °C. IR (KBr) $\nu_{max}$ 3022, 1635, 1601, 1578, 1448, 1056 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 3.79 (s, 3H, OMe), 4.51 (s, 1H, Ar-CH), 7.32–7.95 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 42.5, 55.2, 81.2, 125.8, 126.5, 127.5, 128.3, 129.2, 130.1, 130.9, 131.7, 132.5, 133.2, 133.9, 134.7, 161.0, 162.7, 191.7. Mass (*m*/*z*): 462 (M$^+$). Anal. Calcd for $C_{24}H_{18}N_2O_2S_3$: C, 62.31; H, 3.92; N, 6.06%. Found: C, 62.66; H, 3.79; N, 6.26%.

**4.5.3. Compound 7c.** Yellowish needles (80%), mp 175–176 °C. IR (KBr) $\nu_{max}$ 3020, 1635, 1603, 1581, 1449, 1053 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.27 (s, 6H, 2×Me), 4.44 (s, 1H, Ar-CH), 7.05–7.99 (m, 13H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.3, 21.4, 42.2, 80.0, 125.3, 125.9, 126.6, 127.3, 128.0, 128.7, 129.4, 130.0, 130.6, 131.2, 131.9, 132.5, 133.2, 133.8, 134.4, 135.2, 160.9, 162.5, 191.3. Mass (*m*/*z*): 460 (M$^+$). Anal. Calcd for $C_{25}H_{20}N_2OS_3$: C, 65.19; H, 4.38; N, 6.08%. Found: C, 65.38; H, 4.22; N, 5.90%.

**4.5.4. Compound 7d.** Yellowish needles (85%), mp 152–153 °C. IR (KBr) $\nu_{max}$ 3026, 1633, 1599, 1585, 1445, 1054 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.36 (s, 6H, 2×Me), 4.52 (s, 1H, Ar-CH), 7.19–7.81 (m, 12H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.5, 21.7, 42.9, 81.3, 125.4, 126.0, 126.7, 127.3, 127.9, 128.5, 129.2, 129.8, 130.5, 131.1, 131.7, 132.3, 133.0, 133.6, 134.3, 134.9, 169.8, 162.7, 191.5. Mass (*m*/*z*): 494, 496 (M, M+2). Anal. Calcd for $C_{25}H_{19}ClN_2OS_3$: C, 60.65; H, 3.87; N, 5.66%. Found: C, 60.34; H, 3.72; N, 5.87%.

**4.5.5. Compound 7e.** Yellowish needles (77%), mp 170–171 °C. IR (KBr) $\nu_{max}$ 3023, 1636, 1600, 1580, 1451, 1056 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 2.29 (s, 6H, 2×Me), 3.82 (s, 3H, OMe), 4.48 (s, 1H, Ar-CH), 6.99–7.85 (m, 12H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 20.2, 21.5, 42.7, 54.8, 79.9, 125.2, 125.8, 126.4, 127.1, 127.7, 128.3, 129.0, 129.6, 130.3, 130.9, 131.6, 132.2, 133.5, 133.8, 134.1, 134.8, 161.5, 162.6, 191.7. Mass (*m*/*z*): 490 (M$^+$). Anal. Calcd for $C_{26}H_{22}N_2O_2S_3$: C, 63.64; H, 4.52; N, 5.71%. Found: C, 61.90; H, 4.40; N, 5.46%.

### 4.6. Conversion of 5a and 6a into their 2-one and 2,5-dione analogs 8a and 9a, respectively

Compounds **5a** (2.0 mmol) and HgO (4.0 mmol) were refluxed in ethanol (25 mL) for 13 h.[39] The precipitated HgS was filtered off, and the filtrate was concentrated and cooled to furnish **8a**, which was recrystallised from ethanol as white needles. Compound **9a** was similarly prepared from **6a** and recrystallised from ethanol.

**4.6.1. Compound 8a.** Yellowish needles, mp 138 °C. IR (KBr) $\nu_{max}$ 3024, 1705, 1638, 1604, 1585, 1451 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 4.49 (s, 1H, Ar-CH), 7.03–7.95 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 41.9, 80.9, 126.2, 126.8, 127.6, 128.5, 129.3, 130.0, 130.6, 131.3, 132.1, 132.7, 133.6, 134.5, 158.4, 160.0, 164.9. Mass (*m*/*z*): 466, 468 (M, M+2). Anal. Calcd for $C_{23}H_{15}ClN_2OS_3$: C, 59.15; H, 3.24; N, 6.00%. Found: C, 59.50; H, 3.13; N, 5.79%.

**4.6.2. Compound 9a.** Yellowish needles, mp 182–183 °C. IR (KBr) $\nu_{max}$ 3022, 1707, 1676, 1605, 1580, 1448 cm$^{-1}$. $^1$H NMR (DMSO-$d_6$/TMS) $\delta$: 4.50 (s, 1H, Ar-CH), 7.12–7.98 (m, 14H$_{arom}$). $^{13}$C NMR (DMSO-$d_6$/TMS) $\delta$: 43.7, 80.5, 126.3, 126.9, 127.7, 128.5, 129.4, 130.2, 130.9, 131.6, 132.5, 133.5, 133.9, 134.9, 152.1, 165.3, 166.2. Mass (*m*/*z*): 450, 452 (M, M+2). Anal. Calcd for $C_{23}H_{15}ClN_2O_2S_2$: C, 61.26; H, 3.35; N, 6.21%. Found: C, 6098; H, 3.49; N, 5.99%.

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# Monosubstituted thermotropic ferrocenomesogens containing heterocyclic pyrazole

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**Abstract**—The synthesis and mesomorphic properties of two series of ferrocenyl derivatives, 5-[4-(4-alkoxylbenzyloxy)phenyl]-3-(4-ferrocenylphenyl)-1*H*-pyrazoles **1a** and 3-[4-(4-ferrocenylbenzyloxy)phenyl]-5-(4-alkoxylphenyl)-1*H*-pyrazoles **1b** are reported. Compounds **1a** exhibited either nematic (N) or smectic A (SmA) phases, whereas compounds **1b** formed N/SmC or SmA/SmC phases depending on the terminal carbon length. The formation of SmC phases in compounds **1b** was attributed to better molecular interaction between layers since the ferrocenyl unit was remotely located one phenyl ring away from pyrazole core. In contrast, their precursors, ferrocenyl β-diketonates, were in fact non-mesogenic. A less bent shape formed by ferrocenyl pyrazoles than ferrocenyl β-diketones was believed to be responsible for the formation of observed mesophases. The crystal and molecular structure of 3-[4-(4-ferrocenylbenzyloxy)phenyl]-5-(4-hexyloxyphenyl)-1*H*-pyrazole (**1b**; $n$=6) was determined by means of X-ray structural analysis. It crystallizes in the triclinic space group $p$-1, with $a$=11.0725(5) Å, $b$=12.5514(5) Å, $c$=14.2085(6) Å, and $Z$=2. The molecular arrangement was quite consistent with the layer structure observed by powder X-ray diffractometer. The cyclic voltammogram measured for **1** and **2** ($n$=16) indicated that incorporation of pyrazole group hardly influenced the electrochemical behavior of the ferrocenyl moiety.


## 1. Introduction

An increasing number of novel ferrocenomesogens or metallomesogens[1–2] derived from a ferrocenyl core have been reported and investigated since the first ferrocenyl Schiff bases exhibiting a nematic mesophase were synthesized and characterized by Malthête and Billard[3] in 1976. Most mesogenic ferrocenes[4,5] are structurally classified as monosubstituted,[5] 1,1′- or 1,3-disubstituted[4d] compounds. The molecular shapes resulting from the ferrocenomesogens were grouped[5a] as L-, S-, U-, and T-shape depending on the substitution and/or the position. Among them monosubstituted derivatives constitute the majority, which were also reviewed by Imrie.[5a] A ferrocenyl group located in the terminal position often resulted in a mono-molecular L-shape. A large distance of ca. 3.3 Å between the two Cp rings led to an unfavorable *l*/*d* ratio, and these two Cp rings often weakened the molecular interaction between the layers. On the other hand, a better geometric anisotropy was obtained by increasing the overall molecular length. Therefore, monoferrocenomesogens often contained a minimum of three phenyl groups. In a few examples, an extended S-shape evidenced by X-ray crystal structure[6] generated by two interlocked molecules in neighboring layers was used to explain the improved mesomorphic behavior. Most monosubstituted ferrocenomesogens gave rise to N, SmA, and/or SmC phases. The N phase was favored and often observed due to the repulsive steric effects of the ferrocenyl core because the resulting L-shape[6] molecules exhibited a reduced ability of the molecules to pack in more regular layers. The first ferrocenyl Schiff base derivatives with a chiral center exhibiting a TGBA/blue[7] phase apart from SmC*, SmA, and N* phase transformations are also known. A new type of mesogenic fullerene–ferrocene dyads[8] was prepared in 2004, and these compounds were found to exhibit enantiotropic SmA and organize into a partial bilayer structure. However, examples exhibiting a columnar phase[9] are relatively limited. The formation of hexagonal columnar phases by use of H-bonding interactions was demonstrated in tetracatenar covalent and bis-ferrocene derivatives.

Although metallomesogenic/mesogenic β-diketonates as their precursors have long been noted, compounds[10] derived from purely β-diketonates or pyrazoles are limited. Examples of ionic columnar metallomesogens[11] formed by three-coordinated copper(I) complexes were previously reported by this group. Other examples of novel structures formed

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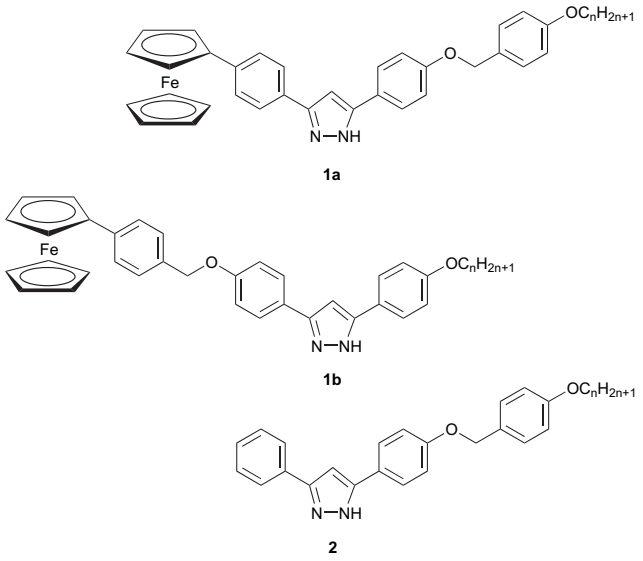
by trigold(I) pyrazoles[12] exhibiting columnar phases were also reported by Serrano[13] and Kim.[14] In this investigation, we report the synthesis and mesomorphic properties of the mesogenic ferrocenyl-based pyrazoles.

## 2. Results and discussion

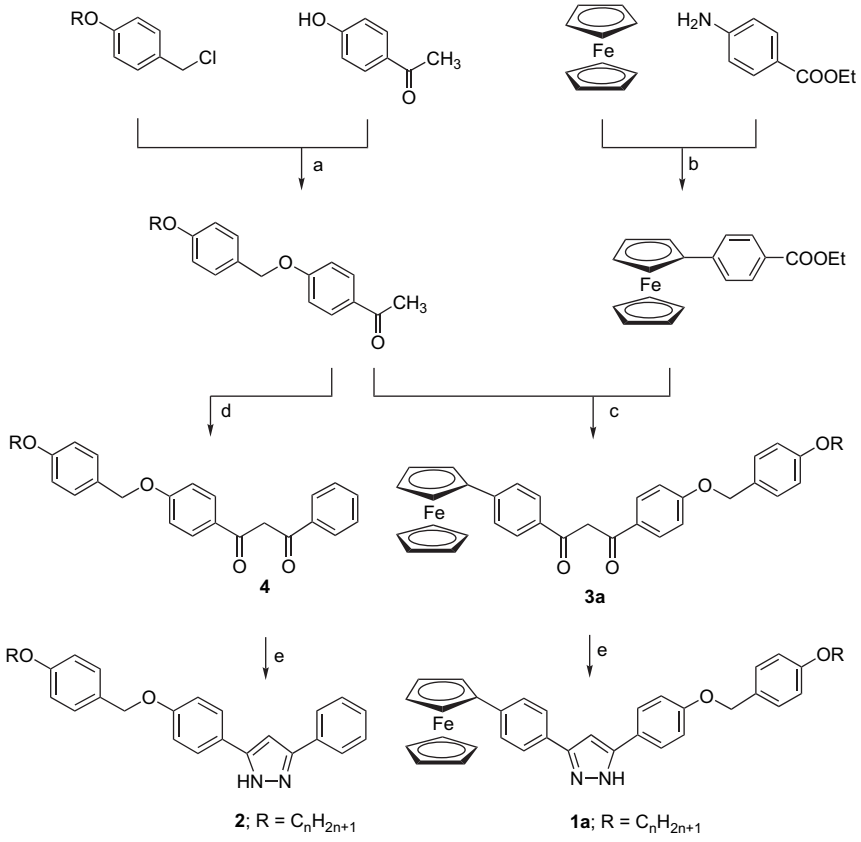
### 2.1. Synthesis and characterization

The pyrazole derivatives were similarly prepared according to the literatures[11,13b] with minor modifications. The synthetic pathways followed to generate compounds **1a** and **1b** are summarized in Schemes 1 and 2. Ethyl 4-ferrocenylbenzoate was prepared by the reaction of ferrocene, ethyl 4-aminobenzoate, and sodium nitrite with a yield of ca. 34–40%. The β-diketones, isolated as deep red solids, were prepared by the reaction of methyl acetophenones and ethyl 4-ferrocenylbenzoate in the presence of NaH and 1,2-dimethoxyethane or THF. The reaction of β-diketones and hydrazine monohydrate in refluxing THF/EtOH gave pyrazole as yellow-to-orange solids. The compounds were characterized by $^{1}H$, $^{13}C$ NMR spectroscopy and elemental analysis. The ratio of different tautomers in β-diketonates was determined by $^{1}H$ NMR spectroscopy. Two singlets at ca. 6.75–6.95 and 16.9–17.2 ppm were assigned to the proton of –CH═C and the enol–OH group, and the integration of each singlet was different depending on the solvent. However, the total integration of the two peaks was equal to two protons. A very broad peak at ca. 10.0–10.7 ppm assigned to the –NH proton in the pyrazoles[13b] was not observed for compounds **1a** and **1b**.

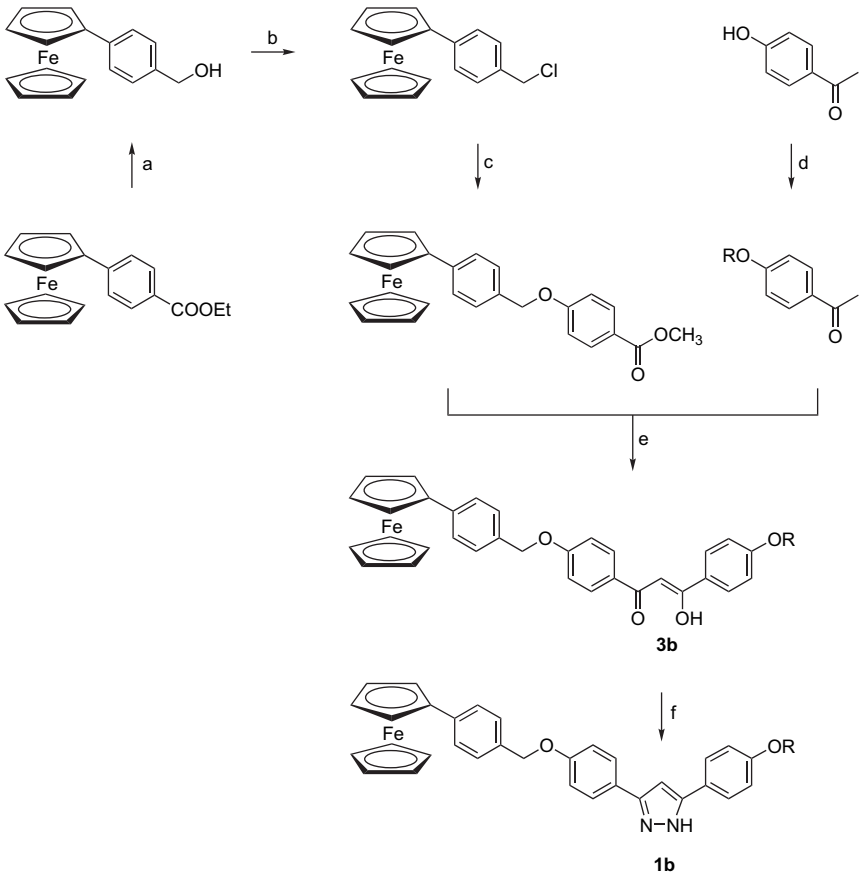



### 2.2. Single crystal structure 3-[4-(4-ferrocenylbenzyloxy)phenyl]-5-(4-hexyloxyphenyl)-1*H*-pyrazole (1b; *n*=6)

A single crystal grown from $CH_2Cl_2/CH_3OH$ suitable for X-ray crystallography was obtained by diffusion technique.




**Scheme 1**. Reagents and conditions: (a) $K_2CO_3$ (1.30 equiv), KI, refluxed in $CH_3COCH_3$, 48 h; (b) $NaNO_2$ (1.10 equiv), $CH_3COONa$ (1.10 equiv), 10% $H_2SO_4$, stirred at 0 °C in $CH_2Cl_2$, 4 h; (c) NaH (6.0 equiv), refluxed in THF, 24 h; (d) methyl benzoate (1.0 equiv), NaH (6.0 equiv), refluxed in THF, 24 h; (e) $N_2H_4 \cdot H_2O$ (3.30 equiv), refluxed in dry THF/ethanol, 2 h.




**Scheme 2**. Reagents and conditions: (a) $LiAlH_4$ (2.0 equiv), stirred at 0 °C in THF, then warmed up to rt, 24 h; (b) $SOCl_2$ (10.0 equiv), stirred in THF at rt, 4 h; (c) methyl 4-hydroxyacetophene (1.0 equiv), $K_2CO_3$ (1.30 equiv), KI, refluxed in $CH_3COCH_3$, 48 h; (d) RBr (1.0 equiv), $K_2CO_3$ (2.0 equiv), KI, refluxed in $CH_3COCH_3$, 48 h; (e) NaH (6.0 equiv), refluxed in THF, 24 h; (f) $N_2H_4 \cdot H_2O$ (3.30 equiv), refluxed in dry THF/absolute ethanol, 2 h.

Attempts to obtain a single crystal from $CH_2Cl_2$ were unsuccessful, which indicated that $CH_3OH$ might play an important role in the crystal packing. The molecular structure with numbering scheme is shown in Figure 1. The unit cell is triclinic and the molecular geometry is fully extended and linear (Fig. 2). The overall molecular shape is described as elongated L-shape, and the molecular length measured ca. 29.10 Å. The two cyclopentadienyl rings were slightly staggered in conformation. Looking down from the top ring, the two cyclopentadienyl rings were rotated by ca. 10.63°–12.92°, which indicated that the conformation is between fully eclipsed and fully staggered. Three aromatic rings except for the second one from the Cp ring were in fact considered as parallel with the Cp ring. The torsion angles between the substituted cyclopentadienyl ring and the other four aromatic rings were calculated as ~2.39°, ~29.26°, ~0.41°, and ~8.05°, respectively. The torsion angle of the second phenyl ring with the pyrazole ring (C22–C21–C24–N1) was measured as ~31.67°. A view of the crystal packing in the unit cell is presented in Figure 2 and reveals that the molecules are packed in a parallel arrangement within the layers. The molecules were arranged parallel to each other in an extended fashion in a head-to-tail/tail-to-head format, and the closest distance between the two molecules was 2.605 Å, as shown in Figure 3. A CH–π stacking interaction (3.725 Å) within the layer was also possible. The distance of H-bonding interaction between N-atom on the pyrazole and the O-atom on the methanol was measured as 2.099 Å. This molecular arrangement was quite consistent with the layered structure observed by powder XRD.

## 2.3. Mesogenic properties

The phase behavior of these compounds was characterized and studied by differential scanning calorimetry (DSC) and polarized optical microscopy. The thermal behavior of

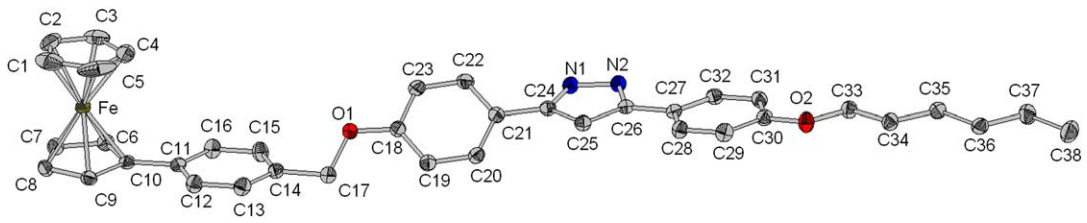



**Figure 1**. An ORTEP drawing for **1b** ($n$=6) with the numbering scheme. The thermal ellipsoids of the non-hydrogen atoms are drawn at the 50% probability level. It crystallizes in the triclinic space group $P$-1, with $a$=11.0725(5) Å, $b$=12.5514(5) Å, $c$=14.2085(6) Å, and $Z$=2.

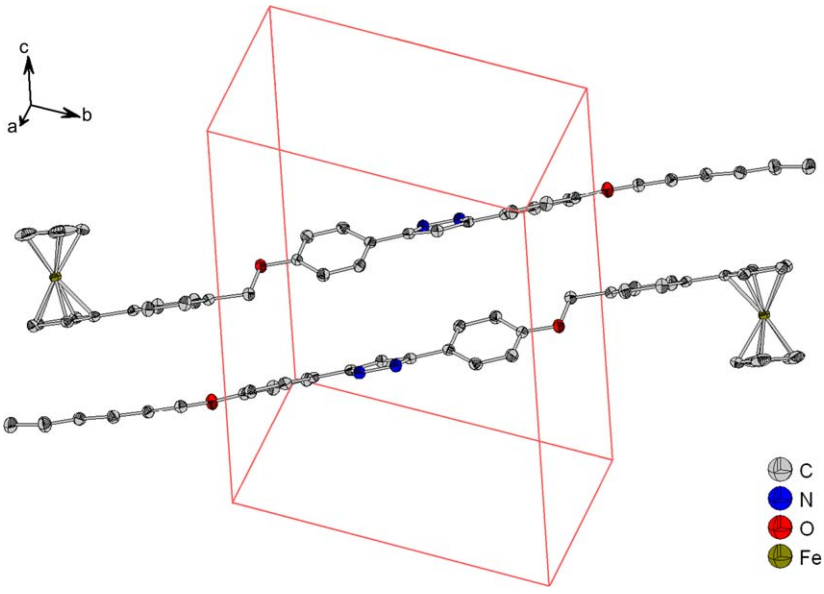



**Figure 2**. The crystal packing in the unit cell showing the two parallel molecules.

ferrocenyl pyrazoles **1a** and **1b** is summarized in Tables 1 and 2. All compounds **1a**–**1b** exhibited mesomorphic properties. Compounds **1a** with shorter alkyl chains exhibited a monotropic N phase ($n$=6, 8) or monotropic SmA phases ($n$=10), however, an enantiotropic SmA phase was observed for other compounds **1a** with longer terminal chains ($n$=12, 14, 16). The optical texture of N or SmA phase was observed by optical microscope (Fig. 4). The N phase exhibited Schlieren textures, whereas the SmA phase appeared as a focal-conic fan texture with a large area of homeotropic domains. The clearing temperatures were insensitive to the terminal chain length, and ranged between 182.2 and 188.7 °C. The insensitivity of the clearing temperatures to chain length indicated that the formation of the mesophase was not controlled and/or determined by the dispersive force of terminal chains. The temperature ranges of mesophases were quite narrow, ca. 8.0–13.9 °C on heating cycle or ca. 14.0–33.8 °C on cooling cycle. The enthalpies of I→N transition were relatively low in the values of 1.40–1.94 kJ/mol, and the enthalpies of I→SmA transition ranged from 3.87 to 5.22 kJ/mol. The narrow range of mesophase temperature indicated that the mesophase was not kinetically stable, which revealed the important role of the ferrocenyl core in the molecular packing. Ferrocenyl moiety as a relatively steric core led to the molecular packing ineffective. In contrast, all their precursor β-diketones were in fact non-mesogenic. The difference observed in the formation of mesophases formed by these two types of compounds was probably attributed to complementary molecular shapes required to be mesogenic. Pyrazoles are comparatively less bent shape

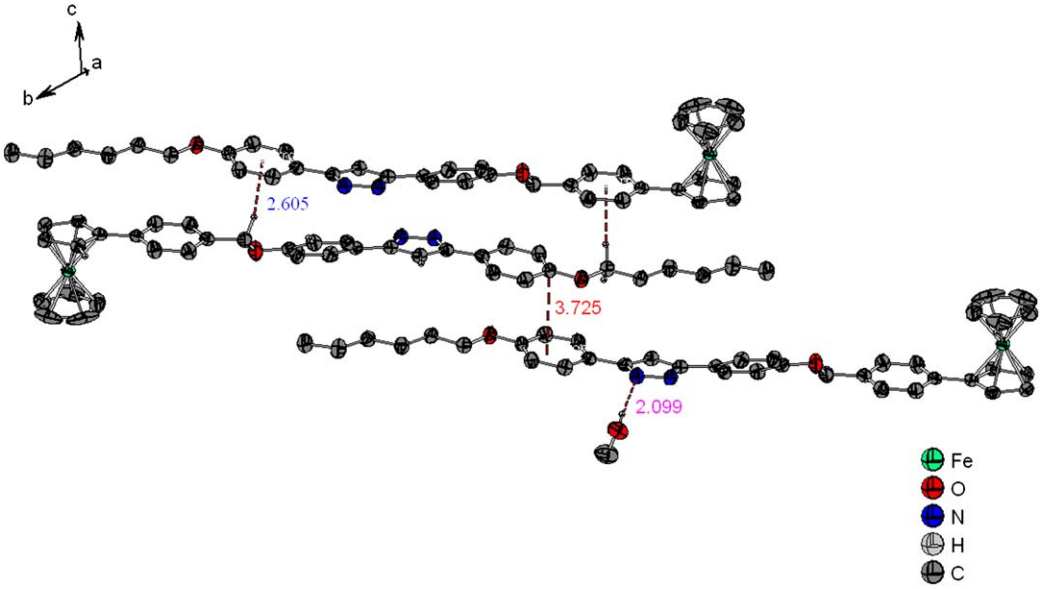



**Figure 3**. Some crystallographic data. (a) 2.605 Å; the π–CH interaction; (b) 3.725 Å; the π–π interaction; and (c) 2.099 Å; H-bond bonding between the O-atom on the $CH_3OH$ and N-atom on the pyrazole ring.

**Table 1**. The phase transition temperatures and the enthalpies of compounds **1a** and **2**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a**; $n$ = 6 | | | Cr | 162.5 (31.6) | 186.2 (35.7) | N | 179.2 (1.40) | | Iso |
| 8 | | | Cr | 163.7 (35.0) | 188.7 (43.6) | N | 177.7 (1.94) | | Iso |
| 10 | | | Cr | 156.9 (32.7) | 182.2 (41.7) | SmA | 178.1 (4.45) | | Iso |
| 12 | | | Cr | 151.3 (29.4) | 175.2 (30.5) | SmA | 183.2 (3.88) | | Iso |
| 14 | $Cr_1$ | 143.2 (8.23) 146.6 (8.24) | $Cr_2$ | 150.7 (21.2) | 173.1 (22.5) | SmA | 184.5 (5.05) | 187.0 (5.25) | Iso |
| 16 | $Cr_1$ | 140.7 (14.6) 146.0 (14.7) | $Cr_2$ | 151.1 (27.9) | 171.7 (30.0) | SmA | 182.0 (5.22) | 183.2 (5.42) | Iso |
| **2**; $n$ = 6 | | | Cr | 130.1 (18.2) | 155.5 (18.4) | SmA | 176.3 (5.15) | 178.3 (5.29) | Iso |
| 12 | | | Cr | 119.3 (27.5) | 142.6 (27.7) | SmA | 181.5 (6.47) | 184.6 (7.13) | Iso |
| 16 | | | Cr | 113.3 (29.3) | 136.7 (29.5) | SmA | 182.6 (7.71) | 184.2 (7.58) | Iso |

$n$ represents the number of carbons in the alkoxy chain. K is crystal phase; SmA is smectic A phase; N is nematic phase; Iso is isotropic.

**Table 2**. The phase temperatures and enthalpies of compounds **1b** and **4**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1b**; $n$ = 6 | $Cr_1$ | 113.2 (11.5) 114.9 (1.63) | $Cr_2$ | | 195.7 (45.6) | SmC | 173.7 (1.07) | N | 192.2 (2.25) 197.0[a] | | Iso |
| 8 | $Cr_1$ | 117.3 (13.9) 158.5 (0.33) | $Cr_2$ | 176.6 (17.4) | | SmC | 191.7 (0.41) 176.3 (0.30) | N | 186.6 (0.71) 193.0[a] | | Iso |
| 10 | $Cr_1$ | 111.9 (13.0) 133.2 (1.47) | $Cr_2$ | 175.0 (29.8) | | SmC | 188.3 (2.45) 178.8 (1.37) | N | 186.9 (2.63) 192.0[a] | | Iso |
| 12 | $Cr_1$ | 68.4 (7.34) | $Cr_2$ | 120.4 (19.4) 168.5 (24.4) | | SmC | 181.1 (1.89) 174.1 (0.51) | N | 180.6 (0.46) 188.0[a] | | Iso |
| 14 | $Cr_1$ | 69.6 (5.12) | $Cr_2$ | 114.3 (25.5) 168.0 (30.0) | | SmC | 183.1 (4.72) 169.1 (0.34) | SmA | 180.5 (4.2) 186.0[a] | | Iso |
| 16 | $Cr_1$ | 68.8 (3.83) 82.5 (6.18) | $Cr_2$ | 112.8 (21.2) 168.2 (25.5) | | SmC | 166.7[a] 182.5 (4.45) | SmA | 176.2 (3.24) 184.0[a] | | Iso |
| **4**; $n$ = 10 | | | | | | | | Cr | 76.2 (23.1) 140.5 (39.0) | | Iso |
| 12 | | | | | | | | Cr | 73.9 (21.7) 120.1 (38.5) | | Iso |
| 14 | | | | | | | | Cr | 80.9 (41.8) 122.4 (42.3) | | Iso |

[a] Determined by optical microscope. SmC is smectic phase. Also see Table 1 for term definitions.

than their precursor β-deketones, required for the formation of calamitic mesogens.

To better understand the effect of steric ferrocenyl group on the formation of mesophases, compounds **2** without the ferrocenyl moiety incorporated were also prepared and their mesomorphic properties were studied. The thermal behavior of compounds **2** ($n$=6, 12, 16) is listed in Table 1. The effect of incorporating ferrocenyl moieties is very marked. Instead of the monotropic behavior observed in compounds **1a** ($n$=6, 8), all compounds **2** ($n$=6, 12, 16) formed enantiotropic phases. SmA phases (see Fig. 5) were all observed. The clearing temperatures ranged from ca. 178.3 to 184.6 °C, similar to those in compounds **1a** containing the

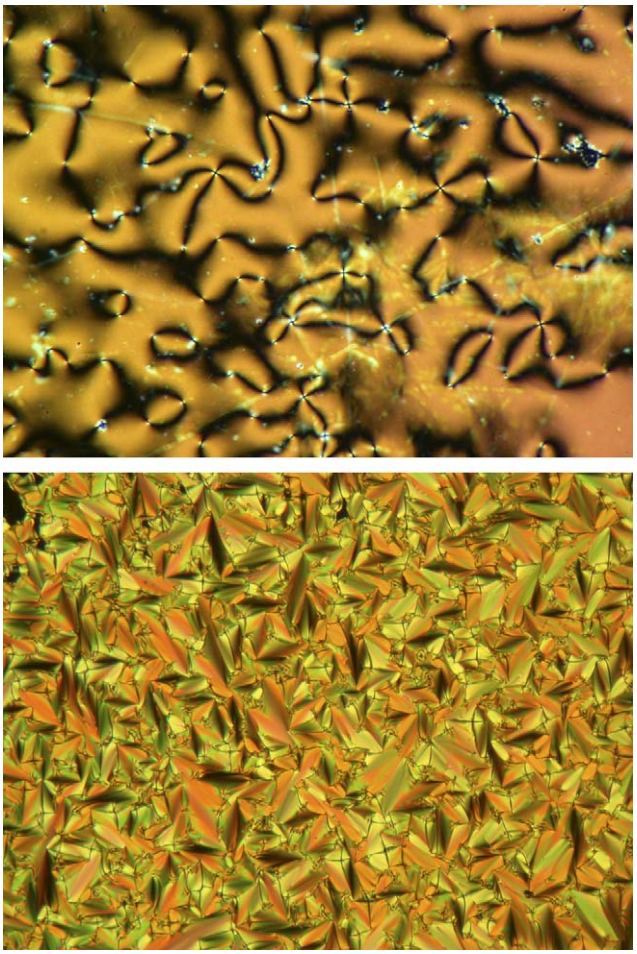


**Figure 4**. Optical textures of N phase at 174 °C (top plate) observed by **1a** ($n$=8) and SmA phase at 110 °C (bottom plate) observed by **1a** ($n$=12).

same carbon chain length. The clearing temperature was shown to be less influenced by the presence of a steric ferrocenyl group. However, the temperature range of SmA phases observed on cooling cycle was measured at ca. 46.2–69.3 °C, which was relatively much wider than that for compounds **1a**. In contrast, the range of mesophase temperatures increased with the carbon chain length ($\Delta T$=46.2 °C, 62.2 °C, and 69.3 °C for $n$=6, 12, and 16). The mesophase formed by compounds **2** is apparently more kinetically stable than that by compounds **1a**. Therefore, the results indicated that the steric ferrocenyl unit played an important role in the formation of mesophase in this type of ferrocenyl pyrazole.

Variable temperature powder XRD diffractometer was used to confirm the structure of the mesophases. A diffraction pattern for compounds **1a** ($n$=16) at 178 °C is given in Figure 6, which was characteristic of the SmA phase. The $d$-spacing of 36.73 Å corresponded to the layer distance, and was close to 34.25 Å, the molecular length estimated for compound **1a**.

In order to improve the mesophase, we also prepared a series of compounds **1b**. Compounds **1b** were structurally similar to compounds **1a**, however, pyrazole ring in **1b** was one benzyl group further away from the –Cp group. The molecular length and molecular weight are identical in both **1a** and **1b**, however, the overall molecular length and/or shape

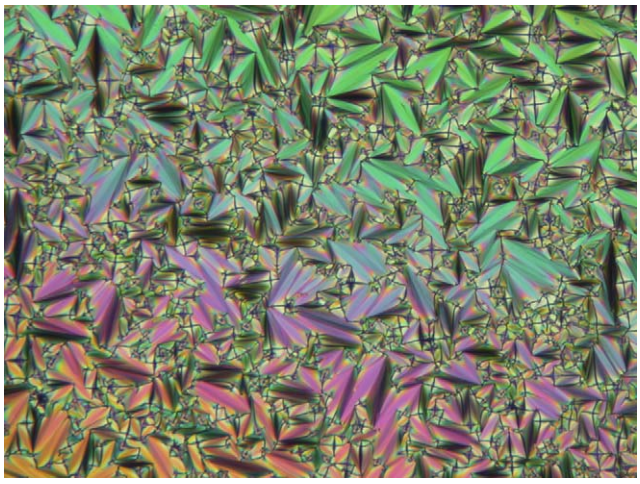


**Figure 5**. Optical texture of SmA phase at 167 °C observed by **2** ($n$=12).

formed by compounds **1a** and **1b** are slightly different due to their conformers. The thermal behavior of compounds **1b** is listed in Table 2. All mesogenic phases except for the SmC phase with $n$=6 were kinetically enantiotropic. Besides the N or SmA phase observed in compounds **1a**, an extra smectic C phase was observed in the entire series. Compounds with a shorter terminal carbon chain ($n$=6, 8, 10, 12) formed N and SmC phases, however, compounds with a longer carbon chain ($n$=14, 16) formed SmA and SmC phases. The clearing temperatures slightly decreased with carbon chain length. Some of transition temperatures were directly obtained by optical microscopy (see Fig. 7) due to their relatively small enthalpies of phase transitions. They were all ranged from 197.0 ($n$=6) to 184.0 °C ($n$=16). However, the temperature ranges of mesophases measured at ca. 60.2–79.0 °C on cooling cycle were much wider (i.e., 14.0–33.8 °C) than those in compounds **1a**. In addition, the observation of SmC phases in compounds **1b** was probably attributed to the better molecular attraction between the layers than in compounds **1a**. On the other hand, their precursors, β-diketones **4**, were also non-mesogenic, and only transitions of crystal-to-isotropic at 140.5 °C

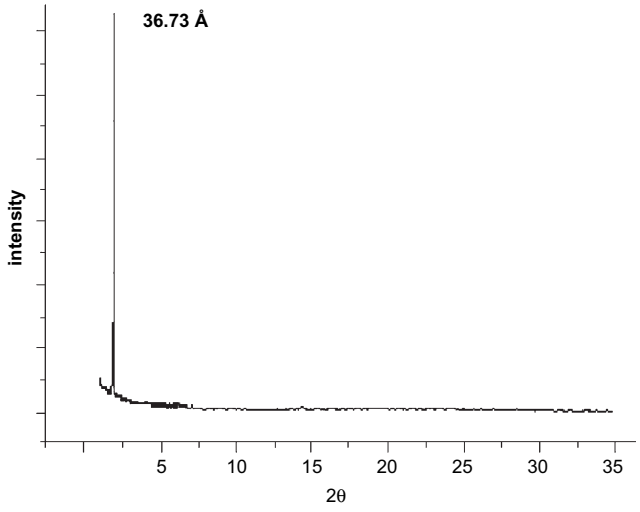



**Figure 6**. X-ray diffraction pattern of compound **1a** ($n$=16) at 178.0 °C.

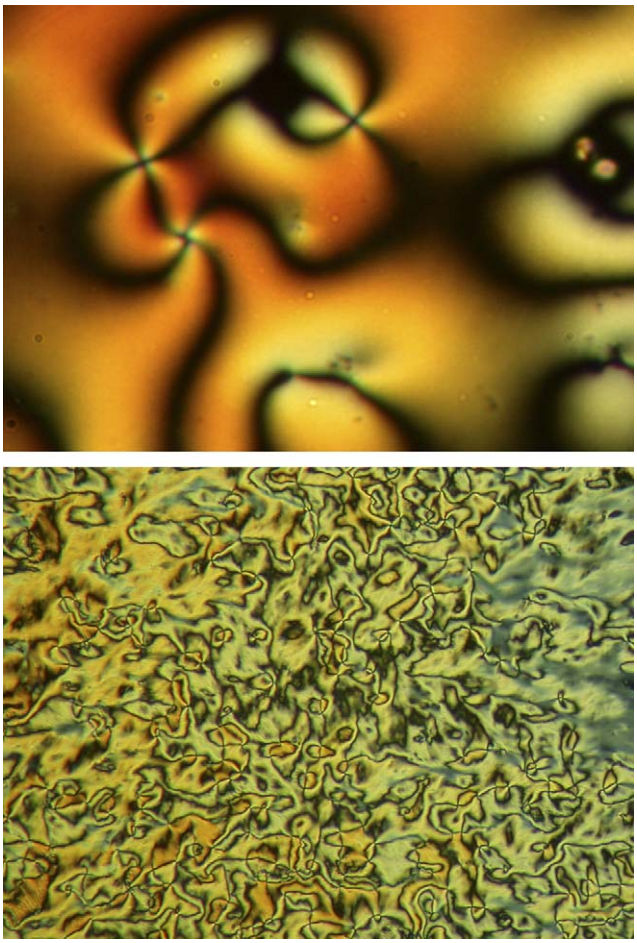


**Figure 7**. Optical textures of N phase at 179 °C (top) and SmC phase at 159 °C observed by **1b** ($n$=12).

($n$=10), 120.1 °C ($n$=12), and 122.4 °C ($n$=14) were observed (Table 2).

The electrochemical behavior of two compounds **1** ($n$=16) and **2** ($n$=16) was also investigated by cyclic voltammetry measured in $CH_2Cl_2$. The $E_{ox}$ data measured with a scan rate of 100 mV/s are reported relative to ferrocene, which has an $E_{ox}$ at 135 mV relative to $Ag/Ag^+$, and the anodic peak–cathodic peak separation ($\Delta E_p$) is 80 mV. Compound **1** ($n$=16) has an $E_{ox}$ at 15 mV and compound **2** ($n$=16) has an $E_{ox}$ at 25 mV. The data indicate that both compounds **1** ($\Delta E_p$=85) and **2** ($\Delta E_p$=70) have one reversible redox process, which is similar to unsubstituted ferrocene.

## 3. Conclusion

Though the ferrocenyl moiety could be considered as a relatively bulky group, the mesomorphic behavior of two series of newly prepared monosubstituted ferrocenomesogens was improved by structural modification. A small mesogenic domain due to the unfavorable packing caused by the relatively large ferrocenyl group can be reduced or minimized by increasing the overall molecular length. However, a less bent structure deviated significantly from better linearity compared with their precursors, diketonates, was used to explain the lack of mesogenic behavior.

## 4. Experimental

### 4.1. General procedures

All chemicals and solvents were reagent grade from Lancaster or Aldrich. Solvents were dried by standard techniques. $^1H$ and $^{13}C$ NMR spectra were measured on a Bruker AM-300. FTIR spectra were performed on Nicolet Magna-IR 550 spectrometer. DSC thermographs were carried out on a Mettler DSC 821 and calibrated with a pure indium sample (mp 156.60 °C, 28.45 J/K), and all phase transitions were determined using a scan rate of 10.0 °C/min. Optical polarized microscopy was carried out on an Zeiss AxiaPlan equipped with a hot stage system of Mettler FP90/FP82HT. Elemental analysis for carbon, hydrogen, and nitrogen was conducted on a Heraeus Vario EL-III elemental analyzer at National Taiwan University. Methyl-4-alkoxylbenzoates,[15a] 4-alkoxybenzyl alcohols,[15b] 4-alkoxybenzyl chlorides,[15c] 4-alkoxyacetophenones,[15d] and 4-(4-alkoxybenzyloxy)-phenyl methyl ketone[15d] were prepared by literature procedures. Synthetic procedures and characterization data of selected compounds are presented in the following sections.

**4.1.1. 4-(4-Hexadecyloxybenzyloxy)phenyl methyl ketone[15d] ($n$=16).** White solid, yield 86%. $^1H$ NMR ($CDCl_3$): $\delta$ 0.86 (t, $J$=6.1 Hz, $-CH_3$, 3H), 1.25–1.81 (m, $-CH_2$, 28H), 2.53 (s, $-OCH_3$, 3H), 3.93 (t, $J$=6.5 Hz, $-OCH_2$, 2H), 5.03 (s, $-CH_2$, 2H), 6.90 (d, $J$=5.8 Hz, $-C_6H_4$, 2H), 6.98 (d, $J$=6.9 Hz, $-C_6H_4$, 2H), 7.32 (d, $J$=8.6 Hz, $-C_6H_4$, 2H), 7.91 (d, $J$=6.9 Hz, $-C_6H_4$, 2H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.09, 22.68, 26.02, 29.21, 29.37, 29.59, 29.69, 31.92, 67.92, 69.86, 114.37, 114.41, 127.70, 129.15, 130.21, 130.42, 159.08, 162.58, 196.69.

**4.1.2. Ethyl 4-ferrocenylbenzoate.** Ethyl 4-ferrocenylbenzoate was similarly prepared by the diazonium methods.[5b,6c] The mixture of ethyl 4-aminobenzoate (2.00 g, 12 mmol) and powdered $NaNO_2$ (0.92 g, 13 mmol) was dissolved in 10 mL of distilled water, and the solution was stirred for 10 min. To the solution, dilute $H_2SO_4$ (10%, 10.0 mL) was dropwise added at ice bath temperature, and the mixture was stirred for 20 min. The solution was then filtered to remove insoluble solids, and the solution was kept at 0 °C. The solution of ferrocene (2.25 g, 12 mmol) dissolved in 10.0 mL of $CH_2Cl_2$ and the aqueous solution of $CH_3COONa$ (0.78 g, in 10.0 mL $H_2O$) were simultaneously added dropwise in a two-neck flask, and the solution was stirred for 2 h. The deep blue solution was extracted three times with methylene chloride. The deep red organic layers were collected and dried with anhydrous $MgSO_4$. The product was purified by flash chromatography with eluting hexane/$CH_2Cl_2$ (5:1). Red crystals were isolated after recrystallization from hexane. Yield 38%. $^1H$ NMR ($CDCl_3$): $\delta$ 1.41 (t, $J$=2.4 Hz, $-CH_3$, 3H), 4.02 (s, $-C_5H_5$, 5H), 4.35 (m, $-C_5H_4$, $-OCH_2$, 4H), 4.69 (t, $J$=1.9 Hz, $-C_5H_4$, 2H), 7.48 (d, $J$=8.5 Hz, $-C_6H_4$, 2H), 7.97 (d, $J$=8.5 Hz, $-C_6H_2$, 2H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 14.26, 60.65, 66.72, 69.61, 69.67, 83.22, 125.42, 127.49, 129.52, 144.83, 166.52.

**4.1.3. 1-[4-(4-Hexadecyloxybenzyloxy)phenyl]-3-(4-ferrocenylphenyl)propane-1,3-dione (3a; $n$=16).** A similar compound[16] has been prepared. A mixture of powder

NaH (1.08 g, 0.045 mol) and 4-hexadecyloxybenzylacetophenone (4.2 g, 0.009 mol) was dissolved in 50 mL of dried THF under nitrogen atmosphere. The solution was then added to the solution of ethyl 4-ferrocenylbenzoate (3.0 g, 0.009 mol) in 20 mL of THF, and the solution was refluxed for 24 h. The solution was carefully neutralized with 150 mL of dilute hydrochloric acid (1.0 M, 1.0 mL), and then extracted twice with 100 mL of $CH_2CH_2/H_2O$ (1:1). The organic layers were combined and dried over anhydrous $MgSO_4$. The product, isolated as deep red solids, was obtained after recrystallization from $CH_2Cl_2$/MeOH. Yield 68%. $^1$H NMR ($CDCl_3$): $\delta$ 0.84 (t, $J$=6.6 Hz, –$CH_3$, 3H), 1.24–1.80 (m, –$CH_2$, 28H), 3.97 (t, $J$=6.5 Hz, –$OCH_2$, 2H), 4.05 (s, $C_5H_5$, 5H), 4.38 (t, $J$=1.7 Hz, $C_5H_4$, 2H), 4.71 (t, $J$=1.8 Hz, $C_5H_4$, 2H), 5.05 (s, –$CH_2$, 2H), 6.78 (s, –CCHCO, 1H), 6.91 (d, $J$=8.6 Hz, $C_6H_4$, 2H), 7.03 (d, $J$=8.8 Hz, $C_6H_4$, 2H), 7.33 (d, $J$=8.5 Hz, $C_6H_4$, 2H), 7.53 (d, $J$=8.4 Hz, $C_6H_4$, 2H), 7.88 (d, $J$=8.4 Hz, $C_6H_4$, 2H), 7.96 (d, $J$=8.8 Hz, $C_6H_4$, 2H), 17.11 (s, –OH, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.99, 22.55, 25.88, 29.09, 29.22, 29.45, 29.54, 31.78, 66.69, 67.92, 69.69, 69.89, 83.27, 91.86, 114.50, 114.66, 125.74, 127.03, 127.78, 128.24, 129.06, 129.16, 132.59, 144.47, 159.09, 162.64, 183.86, 185.44. FABMS ($m/z$), calcd for $M^+$ 754.82, found 754.64. FTIR (KBr): 3099, 2921, 2852, 1605, 1518, 1252, 1229, 1173, 1038, 1011, 849, 813, 790 cm$^{-1}$. Anal. Calcd for $C_{48}H_{58}O_4Fe$: C, 76.38; H, 7.74. Found: C, 76.77; H, 7.93.

**4.1.4. 5-[4-(4-Hexadecyloxybenzyloxy)phenyl]-3-(4-ferrocenylphenyl)-1*H*-pyrazole (1a; *n*=16).** A hot solution of 1-[4-(4-hexadecyloxybenzyloxy)phenyl]-3-(4-ferrocenylphenyl)propane-1,3-dione (5.0 g, 6.7 mmol) dissolved in THF/EtOH (1:1) was slowly added to the solution of hydrazine monohydrate (1.06 mL, 22.0 mmol) under nitrogen atmosphere. The solution was gently refluxed for 2 h and then stirred at room temperature for 12 h. The solution was concentrated, and the product isolated as yellow solids was obtained after recrystallization from THF/hexane. Yield 80%. $^1$H NMR ($CDCl_3$): $\delta$ 0.87 (t, $J$=6.2 Hz, –$CH_3$, 3H), 1.24–1.76 (m, –$CH_2$, 28H), 3.96 (t, $J$=6.5 Hz, –$OCH_2$, 2H), 4.04 (s, $C_5H_5$, 5H), 4.32 (t, $J$=1.7 Hz, $C_5H_4$, 2H), 4.67 (t, $J$=1.9 Hz, $C_5H_4$, 2H), 5.01 (s, –$CH_2$, 2H), 6.74 (s, –CCHCO, 1H), 6.88 (d, $J$=8.6 Hz, $C_6H_4$, 2H), 6.96 (d, $J$=8.8 Hz, $C_6H_4$, 2H), 7.33 (d, $J$=8.5 Hz, $C_6H_4$, 2H), 7.50 (d, $J$=8.3 Hz, $C_6H_4$, 2H), 7.62 (d, $J$=8.6 Hz, $C_6H_4$, 4H). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.95, 22.53, 25.86, 29.05, 29.22, 29.43, 29.52, 31.75, 66.40, 67.91, 68.82, 69.85, 84.81, 98.87, 114.44, 115.00, 126.15, 126.77, 127.59, 128.35, 129.11, 134.04, 139.10, 158.79, 158.93. FABMS ($m/z$), calcd for $M^+$ 750.83, found 750.79. FTIR (KBr): 3297, 3232, 3143, 3099, 3035, 2952, 2928, 2867, 2859, 1619, 1518, 1454, 1443, 1257, 1178, 840, 797 cm$^{-1}$. Anal. Calcd for $C_{48}H_{58}N_2O_2Fe$: C, 76.78; H, 7.79; N, 3.73. Found: C, 76.55; H, 7.91; N, 3.71.

**4.1.5. 1-[4-(4-Dodecyloxybenzyloxy)phenyl]-3-phenylpropane-1,3-dione (4; *n*=12).** White solid, yield 78%. $^1$H NMR ($CDCl_3$): $\delta$ 0.88 (t, $J$=6.7 Hz, –$CH_3$, 3H), 1.24–1.80 (m, –$CH_2$, 20H), 3.95 (t, $J$=6.5 Hz, –$OCH_2$, 2H), 5.03 (s, –$CH_2$, 2H), 6.79 (s, –CCHCO, 1H), 6.91 (d, $J$=8.6 Hz, –$C_6H_4$, 2H), 7.03 (d, $J$=8.7 Hz, –$C_6H_4$, 2H), 7.33 (d, $J$=8.5 Hz, –$C_6H_4$, 2H), 7.44 (d, $J$=6.2 Hz, –$C_6H_4$, 2H), 7.52 (d, $J$=6.8 Hz, –$C_6H_5$, 2H), 7.57 (s, –$C_6H_5$, 1H), 7.96 (d, $J$=8.8 Hz, –$C_6H_5$, 2H), 17.10 (s, –OH, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.00, 22.57, 25.91, 29.11, 29.23, 29.45, 29.54, 31.79, 67.92, 69.89, 92.22, 114.52, 114.68, 126.88, 127.59, 127.78, 128.58, 128.74, 132.02, 135.41, 159.11, 162.37, 183.89, 185.98. FABMS ($m/z$), calcd for $M^+$ 514.69, found 514.90. Anal. Calcd for $C_{34}H_{42}N_2O_4$: C, 79.34; H, 8.22. Found: C, 79.75; H, 8.34.

**4.1.6. 5-[4-(4-Dodecyloxybenzyloxy)phenyl]-3-phenyl-1*H*-pyrazole (2; *n*=12).** The synthetic procedures were similarly followed as above for the compound **1a** ($n$=16). White solid, yield 82%. $^1$H NMR ($CDCl_3$): $\delta$ 0.88 (t, $J$=8.4 Hz, –$CH_3$, 3H), 1.24–1.80 (m, –$CH_2$, 20H), 3.94 (t, $J$=6.5 Hz, –$OCH_2$, 2H), 4.94 (s, –$CH_2$, 2H), 6.71 (s, –CNCH, 1H), 6.90 (dd, $J$=3.0, 8.7 Hz, –$C_6H_4$, 2H), 7.28 (d, $J$=6.1 Hz, –$C_6H_4$, 2H), 7.33 (s, –$C_6H_5$, 1H), 7.35 (d, $J$=6.1 Hz, –$C_6H_4$, 2H), 7.58 (d, $J$=8.7 Hz, –$C_6H_4$, 2H), 7.68 (dd, $J$=2.1 Hz, 7.7 Hz, –$C_6H_5$, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.92, 22.59, 26.03, 29.25, 29.30, 29.34, 29.59, 31.86, 68.26, 70.11, 99.55, 114.82, 115.45, 124.32, 125.66, 126.94, 128.02, 128.74, 128.85, 129.03, 131.79, 159.16, 159.23. FTIR (KBr): 3240, 2917, 2849, 1558, 1540, 1519, 1473, 1457, 1252, 1176, 1051, 1027, 1011, 968, 826, 796, 761 cm$^{-1}$. Anal. Calcd for $C_{34}H_{42}N_2O_2$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.88; H, 8.40; N, 5.54.

**4.1.7. 4-Hexadecyloxyacetophenone[15d] (*n*=16).** White solid, yield 93%. $^1$H NMR ($CDCl_3$): $\delta$ 0.84 (t, $J$=6.1 Hz, –$CH_3$, 3H), 1.25–1.79 (m, –$CH_2$, 28H), 2.45 (s, –$COCH_3$, 3H), 3.94 (t, $J$=6.5 Hz, –$OCH_2$, 2H), 6.85 (d, $J$=6.8 Hz, –$C_6H_4$, 2H), 7.84 (d, $J$=6.8 Hz, –$C_6H_4$, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.96, 22.25, 25.74, 26.13, 27.80, 29.06, 29.18, 29.56, 31.66, 68.13, 113.78, 129.87, 130.47, 162.93, 196.54. FABMS ($m/z$), calcd for $M^+$ 560.57, found $(M+1)^+$ 561.40.

**4.1.8. (4-Ferrocenylphenyl)methanol.** This compound has been reported previously in the literatures.[5] A THF solution of ethyl 4-ferrocenylbenzoate (10.0 g, 0.027 mol) was added dropwise to a solution of $LiAlH_4$ (2.61 g, 0.07 mol) dissolved in 30 mL of THF. The mixture was stirred for 24 h at room temperature. The solution was carefully quenched with dilute hydrochloric acid (0.5 M) at 0 °C, and the solution was extracted with 100 mL of $CH_2Cl_2$. The deep red organic solutions were collected and dried over anhydrous $MgSO_4$. The solution was concentrated to give crude red solids. The product isolated as red crystals was obtained by recrystallization from $CH_2Cl_2$/MeOH. Yield 80%. $^1$H NMR ($CDCl_3$): $\delta$ 4.02 (s, –$C_5H_5$, 5H), 4.31 (t, –$C_5H_4$, 2H), 4.63 (m, –$CH_2$, –$C_5H_4$, 4H), 7.26 (d, $J$=8.0 Hz, –$C_6H_4$, 2H), 7.45 (d, $J$=7.9 Hz, –$C_6H_4$, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 65.12, 66.35, 68.79, 69.45, 84.90, 126.01, 127.0, 138.22, 138.62.

**4.1.9. 1-Chloromethyl-4-ferrocenylbenzene.** (4-Ferrocenylphenyl)methanol (10.0 g, 0.003 mol) was completely dissolved in 200 mL of dried THF, and the solution was then carefully added to thionyl chloride (23.5 mL, 0.34 mol) at ice bath temperature. The solution was stirred for 4 h at room temperature. The excess of $SOCl_2$ was removed by vacuum in the hood. The viscous residue was washed with dried THF, and the solution was then concentrated by vacuum again. The process of wash-and-pump was repeatedly followed three times, and the product

isolated as powder was directly used for the next step without any other purification.

**4.1.10. 4-(4-Ferrocenylbenzyloxy)benzoic acid methyl ester.**[5] A mixture of methyl-4-hydroxyacetophenone (5.0 g, 0.035 mol), anhydrous $K_2CO_3$ (5.66 g, 0.039 mol), KI (catalytic amount), and 1-chloromethyl-4-ferrocenylbenzene (21.74 g, 0.07 mol) was dissolved in 250 mL of dried acetone under nitrogen atmosphere. The solution was refluxed for 48 h. The solution was cooled to room temperature and then filtered to remove solids by suction. The solution was first washed with aqueous brine solution and then extracted twice with $CH_2Cl_2$. The organic solution was combined and dried over anhydrous $Na_2SO_4$. The product was purified by flash chromatography with hexane/$CH_2Cl_2$ (2:1). Yellow crystals were isolated after recrystallization from $CH_2Cl_2$/$CH_3OH$. Yield 42%. $^1$H NMR ($CDCl_3$): $\delta$ 3.87 (s, –$OCH_3$, 3H), 4.05 (s, –$C_5H_5$, 5H), 4.30 (t, $J$=1.8 Hz, –$C_5H_4$, 2H), 4.62 (t, $J$=1.8 Hz, –$C_5H_4$, 2H), 5.06 (s, –$CH_2$, 2H), 6.99 (d, $J$=6.9 Hz, –$C_6H_4$, 2H), 7.32 (d, $J$=8.2 Hz, –$C_6H_4$, 2H), 7.46 (d, $J$=6.5 Hz, –$C_6H_4$, 2H), 8.00 (d, $J$=6.8 Hz, –$C_6H_4$, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 51.75, 66.42, 69.00, 69.48, 69.93, 84.68, 114.30, 122.62, 126.19, 127.59, 131.47, 133.46, 139.35, 162.41, 166.71. Anal. Calcd for $C_{25}H_{22}O_3Fe$: C, 70.44; H, 5.20. Found: C, 70.58; H, 5.39.

**4.1.11. 1-[4-(4-Ferrocenylbenzyloxy)phenyl]-3-(4-decyloxyphenyl)propane-1,3-dione (3b; *n*=10).** The synthetic procedures were similarly followed as above for the compound. Deep red solid, yield 68%. $^1$H NMR ($CDCl_3$): $\delta$ 0.88 (t, $J$=6.1 Hz, –$CH_3$, 3H), 1.33–1.85 (m, –$CH_2$, 16H), 4.00 (t, $J$=3.1 Hz, –$OCH_2$, 2H), 4.03 (s, –$C_5H_5$, 5H), 4.31 (t, $J$=1.8 Hz, –$C_5H_4$, 2H), 4.63 (t, $J$=1.9 Hz, –$C_5H_4$, 2H), 5.05 (s, –$CH_2$, 2H), 6.68 (s, –CCHCO, 1H), 6.93 (d, $J$=8.9 Hz, –$C_6H_4$, 2H), 7.04 (d, $J$=8.9 Hz, –$C_6H_4$, 2H), 7.35 (d, $J$=8.3 Hz, –$C_6H_4$, 2H), 7.48 (d, $J$=8.3 Hz, –$C_6H_4$, 2H), 7.64 (d, $J$=5.4 Hz, –$C_6H_4$, 4H), 17.12 (s, –OH, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.00, 22.55, 25.84, 29.00, 29.21, 29.42, 29.45, 31.78, 66.42, 68.12, 68.90, 69.48, 69.70, 84.67, 91.33, 114.25, 114.52, 126.61, 127.61, 127.71, 128.23, 128.93, 133.49, 139.37, 162.06, 162.53, 183.26, 184.61. FTIR (KBr): 3097, 2918, 2850, 1603, 1508, 1498, 1471, 1259, 1228, 1173, 1120, 1002, 841, 818, 784 cm$^{-1}$. FABMS (*m*/*z*), calcd for $M^+$ 670.27, found 670.47. Anal. Calcd for $C_{42}H_{46}O_4Fe$: C, 75.22; H, 6.91. Found: C, 75.54; H, 7.02.

**4.1.12. 3-[4-(4-Ferrocenylbenzyloxy)phenyl]-5-(4-decyloxyphenyl)-1*H*-pyrazole (1b, *n*=10).** The synthetic procedures were similarly followed as above for the compound. Yellow-orange solid, yield 84%. $^1$H NMR ($CDCl_3$): $\delta$ 0.93 (t, $J$=6.3 Hz, –$CH_3$, 3H), 1.33–1.85 (m, –$CH_2$, 16H), 4.03 (t, $J$=2.6 Hz, –$OCH_2$, 2H), 4.08 (s, –$C_5H_5$, 5H), 4.35 (t, $J$=2.0 Hz, –$C_5H_4$, 2H), 4.68 (t, $J$=1.9 Hz, –$C_5H_4$, 2H), 5.10 (s, –$CH_2$, 2H), 6.71 (s, –CCHCO, 1H), 6.98 (d, $J$=8.2 Hz, –$C_6H_4$, 2H), 7.06 (d, $J$=8.2 Hz, –$C_6H_4$, 2H), 7.39 (d, $J$=7.9 Hz, –$C_6H_4$, 2H), 7.53 (d, –$C_6H_4$, 2H), 7.67 (dd, $J$=2.1, 7.2 Hz, –$C_6H_4$, 4H). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.99, 22.62, 25.06, 29.27, 29.32, 29.40, 29.53, 31.87, 66.56, 68.23, 68.95, 69.59, 70.18, 85.08, 99.02, 114.94, 115.31, 124.07, 124.70, 126.29, 126.92, 126.98, 127.63, 134.42, 139.24, 159.02, 159.35. FABMS (*m*/*z*), calcd for $M^+$ 666.67, found 666.85. FTIR (KBr): 3244, 3072, 3034, 2934, 2862, 1616, 1505, 1457, 1448, 1246, 1173, 1105, 1038, 968, 834, 822, 791 cm$^{-1}$. Anal. Calcd for $C_{42}H_{46}N_2O_2Fe$: C, 75.67; H, 6.95; N, 4.20. Found: C, 75.74; H, 6.85; N, 3.90.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.028.

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# Synthesis and some transformations of new 9-furylnaphtho[2,3-*b*]furan derivatives

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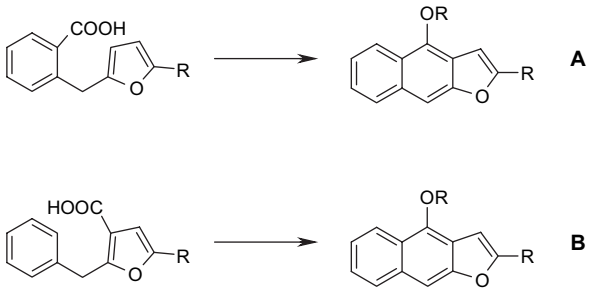
**Abstract**—The synthesis of a number of naphtho[2,3-*b*]furan derivatives, containing a furyl substituent in position 9 by intramolecular cyclization of 2-carboxy and 2-formylbis(5-alkylfur-2-yl)methanes is described. The reactivity of the title compounds in formylation, acetylation, nitration, and oxidation reactions has been investigated. It was shown that nitration of 2-methyl-9-(5-methyl-2-furyl)naphtho-[2,3-*b*]furan-4-yl acetate leads to oxidative furan ring opening rather than to electrophilic substitution.


## 1. Introduction

Among natural compounds, representatives incorporating the naphthofuran framework are quite common. Thus, maturin and maturinin were isolated from the roots of *Cacalia decomposita*.[1a] Later, another group of authors[1b] isolated the natural analogs of the naphthofurans from the roots of *Senecio Canescens*, namely 13-hydroxydehydroxycacalohastine, 13-acetoxydehydrocacalohastine along with the sesquiterpenoid naphthofuran derivative. In their recent communication, some Japanese authors have reported[1c] that a number of the above-mentioned naturally occurring naphthofuran derivatives like maturin and 14-methoxydehydrocacalohastine were also isolated from *Trichilia cuneata*. The synthesis of naphthofuran derivatives attracts our attention because of a fairly wide spectrum of biological activity.[2] For example, nitro derivatives of naphthofurans possess pronounced mutagenic activity,[2b,c,f,g,m–o] that is of interest for medicinal chemistry. It should also be noted that furonaphthoquinones, a class of naturally occurring biologically active compounds,[3] can be synthesized directly from naphthofuran derivatives.[4]

A number of methods for construction of the naphthofuran framework are known. Thus, authors[5] have demonstrated some pathways to annulate furan ring directly onto the naphthalene nucleus. For example, Narasimhan and Mali[5a] have proposed a convenient method based on cyclization of 2-methoxy-3-(2-methoxyvinyl)naphthalene, synthesized from 2-methoxy-3-naphthaldehyde. It is also reported that under the action of lithium iodide cyclobuta[*a*]naphthalene derivatives undergo a transformation into naphthofurans.[5b] The reaction of α-chloro-α-phenylthioketones with 2-naphthol, catalyzed by Lewis acids, also leads to the formation of naphthofurans.[5c] Photolysis or thermolysis of cyclopropa[*b*]naphthalene derivatives give naphthofurans with low yields.[5d] In the paper of Royer et al.,[5e] a route to naphthofuran derivatives starting from methyl 3-hydroxy-2-naphthoate is disclosed.

However, the two most widespread and popular synthetic approaches for the synthesis of the naphthofuran nucleus are based on intramolecular cyclization of the corresponding carboxy 2-benzylfurans (Scheme 1). Cyclization of the




**Scheme 1**.

*Keywords*: Furan; Cyclization; 9-Furylnaphtho[2,3-*b*]furan.
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*ortho*-carboxy group in the benzene part of the molecule onto the β-position of the furan ring[4] (path A) and β-carboxyfuran cyclization onto the *ortho*-position of the aromatic ring[3b,6] (path B) eventually leads to the formation of the naphthofuran framework. For our synthesis of new naphthofuran derivatives with potential biological activity, the reaction in pathway A (Scheme 1) was employed.

## 2. Results and discussion

### 2.1. Synthesis of derivatives of 9-furylnaphtho-[2,3-*b*]furan

In this article, we disclose our results on the synthesis and transformations of the 9-furylsubstituted naphthofurans **4** and **7**. Preliminary results were reported earlier.[7] It is known that the furan cycle can easily undergo different kinds of transformations[8] and therefore it is a very attractive substituent for the introduction into naphthofuran ring system.

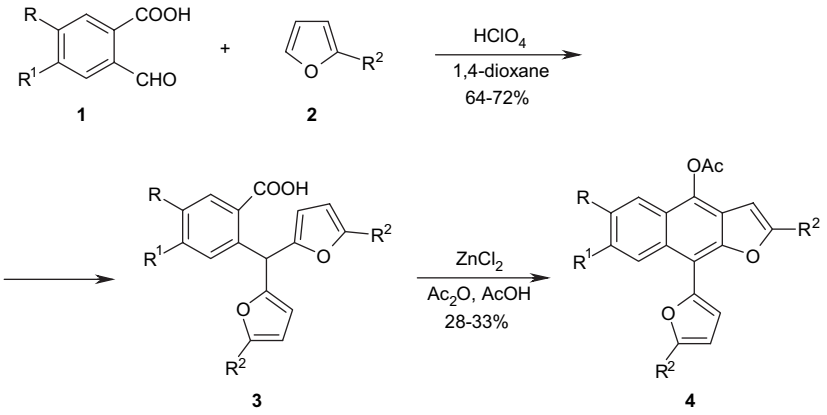
The synthesis of 4-acetoxy-9-furylnaphthofurans **4** was accomplished according to the known procedure.[4a,b] As key starting compounds, we used *ortho*-carboxybenzylfurans **3**, that are readily available via the reported condensation of derivatives of 2-formylbenzoic acid **1** and 2-alkylfuran **2** in the presence of catalytic amounts of 70% perchloric acid in dry 1,4-dioxane at 65–70 °C (Scheme 2).[9]

Benzaldehydes **6**, which served as precursors for the 4-unsubstituted 9-furylnaphthofurans **7**, were obtained by reduction of benzoic acids **3** into alcohols **4** with subsequent mild oxidation (Scheme 3). The last cyclization catalyzed by hydrogen chloride in ethanol furnished the desired naphthofurans (Table 1).

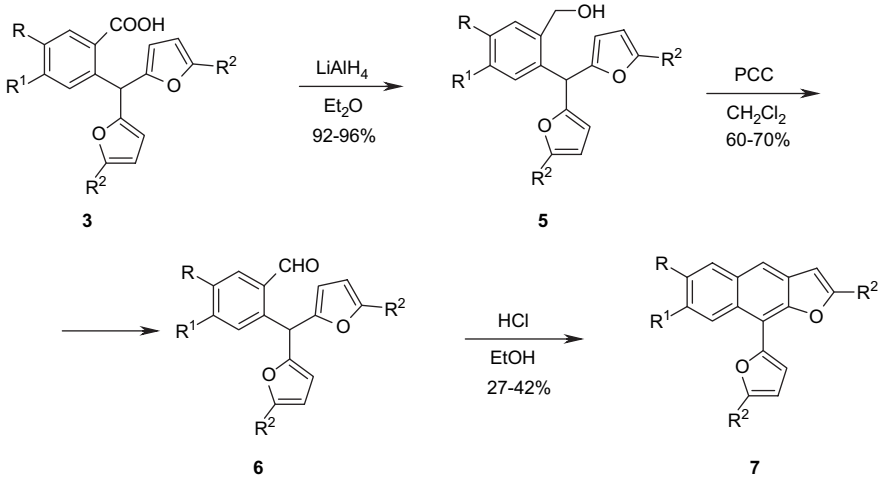
The structure and spatial orientation of compound **7a** was unambiguously proved by X-ray crystallography (Fig. 1). In a monocrystal of compound **7a**, two independent mole-

**Table 1**. Naphthofuran synthesis via cyclization of compounds **3** and **6**

| **4–7** | R | $R^1$ | $R^2$ | Yield, % | | | |
|---|---|---|---|---|---|---|---|
| | | | | **4** | **5** | **6** | **7** |
| **a** | H | H | Me | 31 | 92 | 70 | 37 |
| **b** | Cl | H | Me | 30.5 | 96 | 61 | 42 |
| **c** | Br | H | Me | 33 | 93 | 60 | 39 |
| **d** | Br | H | Et | 28 | 93 | 67 | 27 |
| **e** | Br | H | *t*-Bu | 32 | — | — | — |
| **f** | H | Cl | Me | 31 | — | — | — |




**Scheme 2**.




**Scheme 3**.

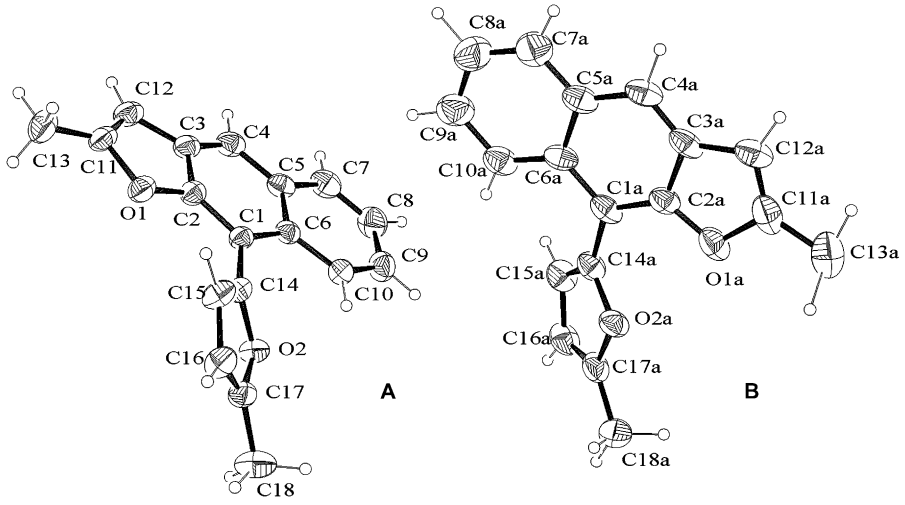



**Figure 1**. The X-ray crystal structure of two conformationally independent molecules of naphthofuran **7a**.

cules were detected with different orientation of the furan ring with regard to the naphthofuran framework.

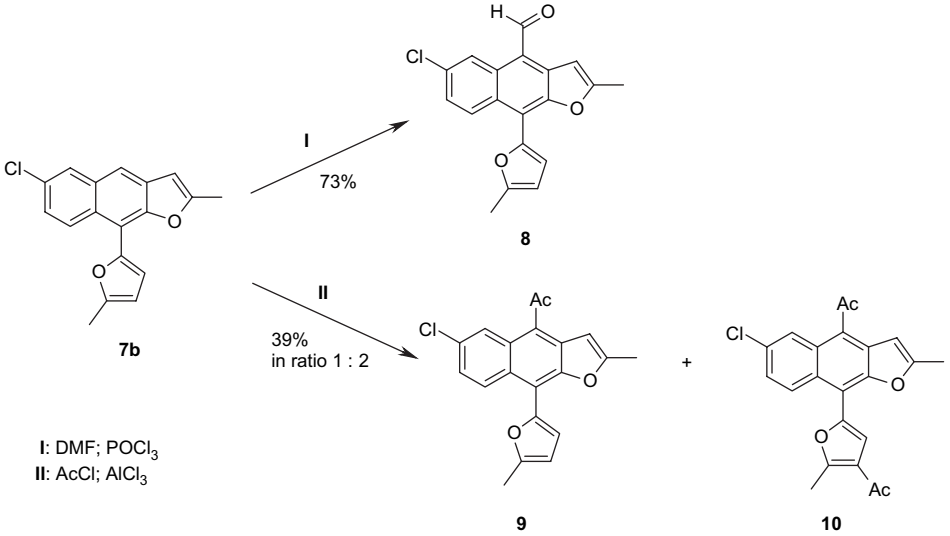
In both molecules, the naphthofuran fragment is planar (plane 1). In molecule **B**, the furan cycle O2a–C14a–C15a–C16a–C17a is rotated to 40.7° relative to the plane 1 with oxygen atoms faced as 'one toward the other'. In molecule **A**, furan O2–C14–C15–C16–C17 is rotated to 41.3° relative to the plane 1 with oxygen atoms 'one against the other'.

### 2.2. Reactions of 9-furylnaphtho[2,3-*b*]furans

Literature reports on the reactivity of naphthofuran derivatives are scarce. As mentioned above, naphthofuran derivatives are rather widespread in nature and some natural and synthetic naphthofurans possess biological activity. Therefore, the search for new transformations of naphthofurans and screening of the obtained compounds for biological activity evaluation is of great importance. Aiming at further functionalization of the naphthofuran nucleus, we attempted an introduction of different reactive groups into compounds **4** and **7**.

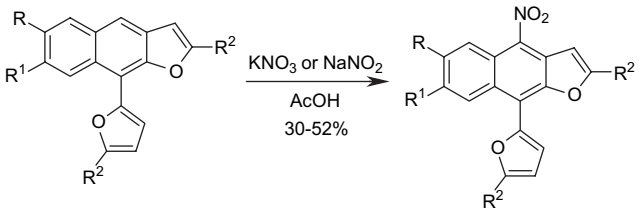
Having taken into account the free activated position 4 in naphthofurans **7**, we investigated some electrophilic reactions of the title compounds. Formylation of compound **7b** using Vilsmeier reaction conditions selectively gave rise to aldehyde **8** (73% yield). In turn, acylation of the same compound with acetyl chloride in the presence of $AlCl_3$ gave monoacetylated **9** and bisacetylated products **10** in the ratio of 1:2 and 39% overall yield (Scheme 4). The disappearance of the signal at 6.3 ppm in $^1$H NMR spectrum of compound **10** was attributed to the presence of the acetyl group in the 4-position of the furan substituent.

Nitration of 9-furylnaphthofurans **7a**,**b** with potassium nitrate in glacial acetic acid gave rise to new nitro derivatives of naphthofurans **11a**,**b**. As expected, nitration took place at position 4 of the naphthofuran framework (Scheme 5). Unexpectedly, the same nitro compound **11b** was obtained in the attempted nitrosation of compound **7b** with sodium




**Scheme 4**.

nitrite and acetic acid. To the best of our knowledge, the nitration of the electron-rich aromatic and heterocyclic systems under similar conditions is well documented.[10] It was shown that this reaction starts with single electron transfer from the substrate to the nitrogen oxides or nitrosonium cation with formation of the radical cation of the substrate. The intermediate radical cation can react further with nitrite-anion or nitrogen dioxide with the formation of the radical or cationic complex with subsequent aromatization into the nitro compound. The distinct reaction pathway depends on the spin density distribution in the initially formed radical cation and this study is under investigation.

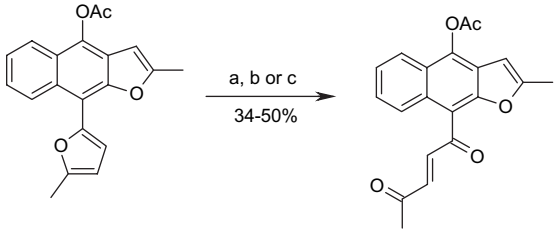



**7a,b** **11a,b**

a: R = H, $R^1$ = H, $R^2$ = Me
b: R = Cl, $R^1$ = H, $R^2$ = Me

**Scheme 5**.

Nitration of 4-acetoxynaphthofuran **4a**, in which the 4-position susceptible to the electrophilic attack is already occupied, with potassium nitrate in glacial acetic acid gave compound **12** rather than any nitro compound (Scheme 6). The structure of the compound was confirmed by the existence of 1H doublets at $\delta$ 7.02 and 7.70 ppm in the NMR spectrum with spin–spin splitting constant of $J$=15.9 Hz, which is typical for vicinal olefinic protons in trans orientation. Compound **12** resulting from the oxidative ring opening of the furan ring in the 9-position of the naphthofuran was also obtained from an alternative synthesis (Scheme 6). For this purpose, the PCC or MMPP, common oxidants for the synthesis of 1,4-unsaturated diketones from the furan derivatives, were used.[11]

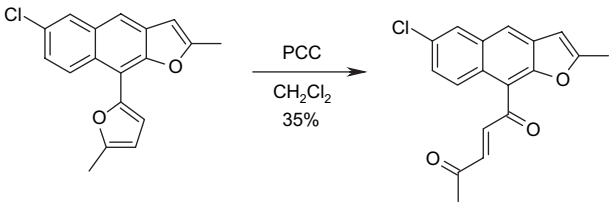



**4a** **12**

a: $KNO_3$ / AcOH
b: MMPP / benzene
c: PCC / $CH_2Cl_2$

**Scheme 6**.

The furan ring opening was also observed in the case of the 4-unsubstituted naphthofurans **7**. It was shown that treatment of compound **7b** with pyridinium chlorochromate in methylene chloride gave corresponding unsaturated diketone **13** with 36% yield (Scheme 7).




**7b** **13**

**Scheme 7**.

## 3. Conclusion

The elaborated synthetic pathways allow broadening the range of available naphthofuran derivatives. The structure and spatial orientation of the molecules in the single crystal of 2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan (**7a**) were studied by X-ray crystallography. Electrophilic substitution reactions onto the 4-position of the naphthofuran framework were studied as well as oxidative furan ring-opening reactions. Further research on reactivity of the obtained compounds is in progress.

## 4. Experimental

### 4.1. General

Melting points are uncorrected. $^1$H NMR spectra were recorded in $CDCl_3$ on a Bruker AC 200 spectrometer at 200 MHz. Chemical shifts are reported in parts per million relatively to the tetramethylsilane as an internal standard and coupling constants ($J$) are given in absolute values in Hertz to the nearest 0.1 Hz. $^{13}$C NMR spectra were recorded on a Bruker AM300 (50.32 MHz) at ambient temperature in $CDC1_3$. Mass spectra were recorded on a Kratos MS-30 instrument with 70 eV electron impact ionization at 200 °C. IR spectra were recorded on InfraLUM FT-02. Column chromatography was carried out using silica gel KSK (50–160 mkm) manufactured by LTD Sorbpolymer. Single crystal suitable for X-ray crystallography was grown from hexane.

**4.1.1. General procedure for the preparation of naphthofurans 4.** A mixture of **3** (1.0 mmol), acetic acid (2 mL), acetic anhydride (2 mL), and $ZnCl_2$ (2–4 mg) as catalyst was refluxed until completion of the reaction (monitored with TLC). The reaction mixture was poured into water (10 mL), neutralized with $NaHCO_3$, and extracted with $CH_2Cl_2$ (3×10 mL). The organic layer was separated, dried over $Na_2SO_4$, treated with active charcoal, and filtered off. The solvent was removed in rotatory evaporator, and the residue was purified on silica gel column with hexane–$CH_2Cl_2$ (4:1) as an eluent. The solvent was removed in rotatory evaporator and the residue was recrystallized from $CH_2Cl_2$–hexane.

**4.1.1.1. 2-Methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]-furan-4-yl acetate (4a).** Yield 100 mg, 31% as colorless crystals; mp 145–147 °C; IR (KBr): 1753, 1366, 1224, 1195, 1159, 1068, 1008, 948, 780, 753, 726 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.50 (s, 3H, C$H_3$), 2.52 (s, 3H, C$H_3$), 2.54 (s, 3H, C$H_3$), 6.27 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.40 (s,

1H, 3-H), 6.88 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.47–7.54 (m, 2H, 6-H, 7-H), 7.95–8.00 (m, 1H, 5-H), 8.54–8.59 (m, 1H, 8-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 14.5, 20.8, 99.9, 107.5, 108.3, 113.0, 120.8, 122.5, 123.6, 124.5, 125.5, 126.3, 128.9, 136.5, 146.3, 151.5, 152.5, 158.5, 168.9. MS: *m/z* (%) 320 ($M^+$, 10), 278 (100), 235 (19), 189 (14), 178 (20). Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.05; H, 5.10.

**4.1.1.2. 6-Chloro-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan-4-yl acetate (4b).** Yield 110 mg, 30.5% as colorless crystals; mp 140–143 °C; IR (KBr): 1751, 1195, 1008, 905, 860, 795, 775, 730, 563 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.50 (s, 3H, C$H_3$), 2.52 (s, 3H, C$H_3$), 2.55 (s, 3H, C$H_3$), 6.27 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.38 (s, 1H, 3-H), 6.89 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.42 (dd, $J$=2.1, 9.3 Hz, 1H, 7-H), 7.94 (d, $J$=2.1 Hz, 1H, 5-H), 8.54 (d, $J$=9.3 Hz, 1H, 8-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 14.5, 20.8, 100.1, 107.6, 108.6, 113.5, 119.7, 123.5, 124.4, 126.2, 126.9, 128.3, 130.6, 135.5, 145.9, 151.3, 152.8, 159.1, 168.6. MS: *m/z* (%) 354/356 ($M^+$, 10/3), 312/314 (100/33), 277 (44), 269 (15), 189 (10), 178 (14), 149 (13). Anal. Calcd for $C_{20}H_{15}ClO_4$: C, 67.71; H, 4.26. Found: C, 67.78; H, 4.20.

**4.1.1.3. 6-Bromo-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan-4-yl acetate (4c).** Yield 130 mg, 33% as colorless crystals; mp 148–150 °C; IR (KBr): 1755, 1597, 1555, 1395, 1350, 1334, 1220, 1194, 1081, 1004, 902, 792, 778, 563 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.49 (s, 3H, C$H_3$), 2.52 (s, 3H, C$H_3$), 2.55 (s, 3H, C$H_3$), 6.27 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.38 (s, 1H, 3-H), 6.89 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.54 (dd, $J$=2.1, 9.3 Hz, 1H, 7-H), 8.11 (d, $J$=2.1 Hz, 1H, 5-H), 8.47 (d, $J$=9.3 Hz, 1H, 8-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.0, 14.5, 20.9, 100.1, 107.7, 108.7, 113.5, 118.9, 123.0, 123.5, 124.9, 127.1, 128.4, 128.7, 135.4, 145.9, 151.3, 152.8, 159.2, 168.7. MS: *m/z* (%) 398/400 ($M^+$, 17/17), 356/358 (100/98), 277 (42), 234 (18), 219 (12), 178 (13), 149 (11). Anal. Calcd for $C_{19}H_{15}BrO_4$: C, 60.17; H, 3.79. Found: C, 60.20; H, 3.72.

**4.1.1.4. 6-Bromo-2-ethyl-9-(5-ethyl-2-furyl)naphtho-[2,3-*b*]furan-4-yl acetate (4d).** Yield 120 mg, 28%; mp 84–86 °C; IR (KBr): 1756, 1587, 1545, 1389, 1344, 1354, 1193, 1100, 1035, 903, 758 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.34–1.50 (m, 6H, $CH_2CH_3$), 2.56 (s, 3H, COC$H_3$), 2.79–2.92 (m, 4H, C$H_2$CH$_3$), 6.27 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.38 (s, 1H, 3-H), 6.92 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.54 (dd, $J$=2.1, 9.3 Hz, 1H, 7-H), 8.11 (d, $J$=2.1 Hz, 1H, 5-H), 8.51 (d, $J$=9.3 Hz, 1H, 8-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 11.5, 12.35, 20.9, 21.7, 22.1, 98.4, 106.1, 108.8, 113.2, 118.8, 123.0, 123.3, 124.9, 127.0, 128.4, 128.6, 135.6, 145.9, 151.2, 158.3, 164.5, 168.6. MS: *m/z* (%) 426/428 ($M^+$, 14/14), 384/386 (100/93), 370/372 (56/53), 290 (10), 233 (14), 189 (16), 149 (15). Anal. Calcd for $C_{22}H_{19}BrO_4$: C, 61.84; H, 4.48. Found: C, 61.89; H, 4.42.

**4.1.1.5. 6-Bromo-2-(*tert*-butyl)-9-[5-(*tert*-butyl)-2-furyl]naphtho[2,3-*b*]furan-4-yl acetate (4e).** Yield 155 mg, 32% as colorless crystals; mp 101–103 °C; IR (KBr): 1759, 1586, 1365, 1194, 1161, 1117, 1025, 906, 810, 793 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.43 (s, 18H, C$H_3$), 2.57 (s, 3H, COC$H_3$), 6.25 (d, $J$=3.2 Hz, 1H, 4-$H_{Fur}$), 6.35 (s, 1H, 3-H), 6.91 (d, $J$=3.2 Hz, 1H, 3-$H_{Fur}$), 7.53 (dd, $J$=1.9, 9.3 Hz, 1H, 7-H), 8.09 (d, $J$=1.9 Hz, 1H, 5-H), 8.60 (d, $J$=9.3 Hz, 1H, 8-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.9, 28.8 (3C), 29.3 (3C), 33.0, 33.4, 96.3, 104.0, 109.0, 112.8, 118.7, 123.0, 123.4, 124.9, 126.7, 128.3, 128.5, 129.7, 135.6, 146.0, 151.0, 164.6, 168.7. MS: *m/z* (%) 482/484 ($M^+$, 11/10), 440/442 (67/62), 425/427 (100/98). Anal. Calcd for $C_{26}H_{27}BrO_4$: C, 64.93; H, 6.26. Found: C, 65.01; H, 6.20.

**4.1.1.6. 7-Chloro-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan-4-yl acetate (4f).** Yield 110 mg, 31% as colorless crystals; mp 166–168 °C; IR (KBr): 1751, 1616, 1541, 1396, 1356, 1342, 1220, 1186, 1118, 1067, 1008, 949, 977, 884, 813, 783, 739 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.51 (s, 3H, C$H_3$), 2.52 (s, 3H, C$H_3$), 2.54 (s, 3H, C$H_3$), 6.29 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.38 (s, 1H, 3-H), 6.91 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.41 (dd, $J$=1.9, 9.0 Hz, 1H, 6-H), 7.90 (d, $J$=9.0 Hz, 1H, 5-H), 8.62 (d, $J$=1.9 Hz, 1H, 8-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 14.5, 20.8, 100.0, 107.6, 107.9, 113.4, 122.1, 122.6, 122.8, 125.2, 125.4, 129.3, 131.5, 136.6, 145.7, 152.0, 152.8, 158.8, 168.5. MS: *m/z* (%) 354/356 ($M^+$, 8/3), 312/314 (100/31), 277 (15), 269 (18), 178 (19), 149 (11). Anal. Calcd for $C_{20}H_{15}ClO_4$: C, 67.71; H, 4.26. Found: C, 67.75; H, 4.22.

**4.1.2. General procedure for the preparation of alcohols 5.** To a stirred suspension of benzoic acid **3** (50.0 mmol) in anhydrous $Et_2O$ (150 mL), $LiAlH_4$ (100.0 mmol) was added portionwise under cooling (−3 to 0 °C). The reaction was monitored by TLC analysis, and after 5 h the mixture was carefully poured into ice water and neutralized with 6 M hydrochloric acid. The product was extracted with $Et_2O$ (3×100 mL), dried with $Na_2SO_4$, treated with active charcoal, and filtered off. The solvent was removed in rotatory evaporator and the residue was recrystallized from hexane.

**4.1.2.1. 2-Di(5-methyl-2-furyl)methylphenylmethanol (5a).** Yield 13 g, 92% as colorless crystals; mp 65–67 °C; IR (KBr): 3296, 1612, 1562, 1450, 1218, 1022, 1002, 951, 778 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.61 (br s, 1H, O*H*), 2.26 (s, 6H, C$H_3$), 4.75 (s, 2H, C$H_2$), 5.74 (s, 1H, C*H*), 5.85 (d, $J$=3.2 Hz, 2H, 3-$H_{Fur}$), 5.89 (d, $J$=3.2 Hz, 2H, 4-$H_{Fur}$), 7.19–7.31 (m, 3H, $H_{Ar}$), 7.40–7.45 (m, 1H, $H_{Ar}$). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.50; H, 6.49.

**4.1.2.2. 5-Chloro-2-di(5-methyl-2-furyl)methylphenylmethanol (5b).** Yield 15.5 g, 98% as colorless crystals; mp 71–72 °C; IR (KBr): 3252, 1616, 1561, 1477, 1407, 1216, 1087, 1049, 1020, 880, 778 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.70 (br s, 1H, O*H*), 2.25 (s, 6H, $CH_3$), 4.72 (s, 2H, C$H_2$), 5.62 (s, 1H, C*H*), 5.84 (d, $J$=3.2 Hz, 2H, 3-$H_{Fur}$), 5.89 (d, $J$=3.2 Hz, 2H, 4-$H_{Fur}$), 7.10 (d, $J$=8.3 Hz, 1H, $H_{Ar}$), 7.25 (dd, $J$=1.8, 8.3 Hz, 1H, $H_{Ar}$), 7.46 (d, $J$=1.8 Hz, 1H, $H_{Ar}$). Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41. Found: C, 68.31; H, 5.39.

**4.1.2.3. 5-Bromo-2-di(5-methyl-2-furyl)methylphenylmethanol (5c).** Yield 16.8 g, 93% as colorless crystals; mp 75–76 °C; IR (KBr): 3252, 1717, 1589, 1558, 1473, 1451, 1047, 1020, 864, 777 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.66 (br s, 1H, O*H*), 2.25 (s, 6H, C$H_3$), 4.72 (s, 2H, C$H_2$), 5.61 (s, 1H, C*H*), 5.85 (d, $J$=3.2 Hz, 2H, 3-$H_{Fur}$), 5.88 (d, $J$=3.2 Hz, 2H, 4-$H_{Fur}$), 7.05 (d, $J$=8.3 Hz, 1H, $H_{Ar}$), 7.39

(dd, $J$=2.1, 8.3 Hz, 1H, $H_{Ar}$), 7.60 (d, $J$=2.1 Hz, 1H, $H_{Ar}$). Anal. Calcd for $C_{18}H_{17}BrO_3$: C, 59.85; H, 4.74. Found: C, 59.91; H, 4.69.

**4.1.2.4. 5-Bromo-2-di(5-ethyl-2-furyl)methylphenylmethanol (5d).** Yield 18 g, 93% as colorless crystals; mp 85–87 °C; IR (KBr): 3266, 1556, 1473, 1401, 1365, 1181, 1047, 1011, 863, 775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.19 (t, $J$=7.6 Hz, 6H, $CH_2CH_3$), 1.68 (br s, 1H, O*H*), 2.58 (q, $J$=7.6 Hz, 2H, $CH_2CH_3$), 4.71 (s, 2H, $CH_2$), 5.61 (s, 1H, CH), 5.85 (d, $J$=3.1 Hz, 2H, 3-$H_{Fur}$), 5.89 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 7.00 (d, $J$=8.3 Hz, 1H, $H_{Ar}$), 7.38 (dd, $J$=1.9, 8.3 Hz, 1H, $H_{Ar}$), 7.60 (d, $J$=1.9 Hz, 1H, $H_{Ar}$). Anal. Calcd for $C_{20}H_{21}BrO_3$: C, 61.71; H, 5.44. Found: C, 61.78; H, 5.39.

**4.1.3. General procedure for the preparation of benzaldehydes 6.** A solution of alcohol **5** (35.5 mmol) in dry $CH_2Cl_2$ (100 mL) was added dropwise to the suspension of pyridinium chlorochromate (70.0 mmol) in dry $CH_2Cl_2$ (100 mL). The mixture was stirred for 6 h at rt. At the end of the reaction (TLC monitoring), the precipitate was filtered off and washed with hot $CH_2Cl_2$ (3×100 mL). The filtrate was concentrated in rotatory evaporator, and the oily residue was purified chromatographically on silica gel column with hexane–$CH_2Cl_2$ (10:1) mixture as eluent. The fraction containing desired benzaldehyde was concentrated to the volume of 20 mL and left to crystallize overnight.

**4.1.3.1. 2-Di(5-methyl-2-furyl)methylbenzaldehyde (6a).** Yield 7 g, 70% as colorless crystals; mp 63–65 °C; IR (KBr): 1695, 1572, 1213, 1019, 949, 871, 780, 753, 717, 678 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.25 (s, 6H, $CH_3$), 5.87 (s, 4H, $H_{Fur}$), 6.46 (s, 1H, C*H*), 7.31–7.33 (m, 1H, $H_{Ar}$), 7.42–7.54 (m, 1H, $H_{Ar}$), 7.85–7.88 (m, 1H, $H_{Ar}$), 10.27 (s, 1H, C*H*O). Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.20; H, 5.58.

**4.1.3.2. 5-Chloro-2-di(5-methyl-2-furyl)methylbenzaldehyde (6b).** Yield 6.8 g, 61% as colorless crystals; mp 75–77 °C; IR (KBr): 1693, 1563, 1475, 1404, 1227, 1191, 1109, 1022, 967, 900, 785, 721 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.25 (s, 6H, $CH_3$), 5.89 (s, 4H, $H_{Fur}$), 6.34 (s, 1H, C*H*), 7.26 (d, $J$=8.3 Hz, 1H, $H_{Ar}$), 7.49 (dd, $J$=2.1, 8.3 Hz, 1H, $H_{Ar}$), 7.84 (d, $J$=2.1 Hz, 1H, $H_{Ar}$), 10.23 (s, 1H, C*H*O). Anal. Calcd for $C_{18}H_{15}ClO_3$: C, 68.69; H, 4.80. Found: C, 68.73; H, 4.85.

**4.1.3.3. 5-Bromo-2-di(5-methyl-2-furyl)methylbenzaldehyde (6c).** Yield 7.6 g, 60% as colorless crystals; mp 85–87 °C; IR (KBr): 1699, 1562, 1476, 1278, 1232, 1187, 1020, 881, 782, 713 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.25 (s, 6H, $CH_3$), 5.89 (s, 4H, $H_{Fur}$), 6.32 (s, 1H, C*H*), 7.19 (d, $J$=8.3 Hz, 1H, $H_{Ar}$), 7.64 (dd, $J$=2.1, 8.3 Hz, 1H, $H_{Ar}$), 7.98 (d, $J$=2.1 Hz, 1H, $H_{Ar}$), 10.22 (s, 1H, C*H*O). Anal. Calcd for $C_{18}H_{15}BrO_3$: C, 60.19; H, 4.21. Found: C, 60.25; H, 4.18.

**4.1.3.4. 5-Bromo-2-di(5-ethyl-2-furyl)methylbenzaldehyde (6d).** Yield 9.2 g, 67% as colorless oil; IR (KBr): 1693, 1605, 1560, 1462, 1377, 1183, 1014, 883, 789 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17–1.22 (m, 6H, $CH_2CH_3$), 2.56–2.63 (m, 4H, $CH_2CH_3$), 5.90 (s, 4H, $H_{Fur}$), 6.32 (s, 1H, C*H*), 7.16 (d, $J$=8.3 Hz, 1H, $H_{Ar}$), 7.63 (dd, $J$=2.1, 8.3 Hz, 1H, $H_{Ar}$), 7.99 (d, $J$=2.1 Hz, 1H, $H_{Ar}$), 10.22 (s, 1H, C*H*O). Anal. Calcd for $C_{18}H_{15}BrO_3$: C, 62.03; H, 4.94. Found: C, 62.08; H, 4.89.

**4.1.4. General procedure for the preparation of naphthofurans 7.** A solution of **6** (1 g) in EtOH (12 mL) was treated with ethanolic HCl solution (2 mL) prepared by saturation of 200 g of ethanol with 100 g of gaseous HCl. The mixture was kept at 50 °C for 1 h (TLC monitoring). The reaction mixture was poured into water (100 mL), neutralized with $NaHCO_3$, and extracted with $CH_2Cl_2$ (3×50 mL). The organic layer was separated, dried with $Na_2SO_4$, treated with active charcoal, and filtered off. The solvent was removed under reduced pressure, and the oily residue was purified on silica gel column eluting with hexane–benzene (3:1). The residue was recrystallized from hexane–benzene.

WARNING: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.

**4.1.4.1. 2-Methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan (7a).** Yield 350 mg, 37% as colorless crystals; mp 59–61 °C; IR (KBr): 1619, 1604, 1540, 1399, 1331, 1250, 1216, 1152, 1094, 1022, 943, 894, 879, 793, 752 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.52 (s, 3H, $CH_3$), 2.54 (s, 3H, $CH_3$), 6.28 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.50 (s, 1H, 3-H), 6.93 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.39–7.52 (m, 2H, 6-H, 7-H), 7.89 (s, 1H, 4-H), 7.90–7.95 (m, 1H, 5-H), 8.57–8.61 (m, 1H, 8-H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.0, 14.5, 102.4, 107.5, 109.4, 113.0, 118.0, 123.9, 125.0, 126.1, 128.4 (2C), 130.1, 131.0, 146.9, 151.3, 152.4, 158.3. MS: $m/z$ (%) 262 ($M^+$, 100), 219 (66), 191 (12), 190 (23), 189 (33), 149 (19). Anal. Calcd for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.49; H, 5.43.

**4.1.4.2. Crystal data of compound 7a.** $C_{18}H_{14}O_2$, monoclinic, space group $P2(1)/c$; $a$=9.569(2) Å, $b$=34.400(7) Å, $c$=8.457(2) Å, $\alpha$=90° $\beta$=95.90(3)° $\gamma$=90°, $V$=2769.1(10) $Å^3$, $Z$=8, $D_{calcd}$=1.258 $mg/m^3$, $F(000)$=1104; 5138 reflections collected, 4842 unique ($R_{int}$=0.0325); final $R$ indices (4842 observed collections $I>2\sigma I$): $R_1$=0.0366, $wR_2$=0.0976; final $R$ indices (all data): $R_1$=0.1419, $wR_2$=0.1132. Crystallographic data (excluding structure factors) for the structure in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 295796. 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.uc]. Each request should be accompanied by the complete citation of this paper.

**4.1.4.3. 6-Chloro-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan (7b).** Yield 400 mg, 42% as colorless crystals; mp 94–96 °C; IR (KBr): 1600, 1539, 1396, 1241, 1153, 1024, 943, 919, 880, 784 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.51 (s, 3H, $CH_3$), 2.54 (s, 3H, $CH_3$), 6.29 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.50 (s, 1H, 3-H), 6.95 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.40 (dd, $J$=2.1, 9.3 Hz, 1H, 7-H), 7.78 (s, 1H, 4-H), 7.89 (d, $J$=2.1 Hz, 1H, 5-H), 8.55 (d, $J$=9.3 Hz, 1H, 8-H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.1, 14.5, 102.4, 107.6, 109.7, 113.3, 116.9, 125.6, 126.3, 126.6, 127.9, 129.6, 131.0, 131.7, 146.5, 151.0, 152.6, 158.9. MS: $m/z$ (%) 296/298 ($M^+$, 100/35), 253/255 (49/19), 219 (21), 218 (38), 190 (28),

189 (61), 149 (10). Anal. Calcd for $C_{18}H_{13}ClO_2$: C, 72.85; H, 4.42. Found: C, 72.80; H, 4.48.

**4.1.4.4. 6-Bromo-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan (7c).** Yield 370 mg, 39% as colorless crystals; mp 119–121 °C; IR (KBr): 1622, 1593, 1396, 1241, 1150, 1018, 960, 909, 868, 806, 775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.50 (s, 3H, C$H_3$), 2.54 (s, 3H, C$H_3$), 6.28 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.50 (s, 1H, 3-H), 6.95 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.50 (dd, $J$=2.1, 9.3 Hz, 1H, 7-H), 7.77 (s, 1H, 4-H), 8.06 (d, $J$=2.1 Hz, 1H, 5-H), 8.48 (d, $J$=9.3 Hz, 1H, 8-H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.0, 14.6, 102.5, 107.7, 109.7, 113.4, 116.9, 117.8, 126.5, 128.1 (2C), 130.0, 131.0, 132.2, 146.5, 150.0, 152.6, 158.9. MS: *m*/*z* (%) 340/342 ($M^+$, 94/100), 297/299 (45/28), 262 (14), 233 (14), 219 (27), 218 (35), 190 (32), 189 (56), 149 (28). Anal. Calcd for $C_{18}H_{13}BrO_2$: C, 63.36; H, 3.84. Found: C, 63.42; H, 3.80.

**4.1.4.5. 6-Bromo-2-methyl-9-(5-ethyl-2-furyl)naphtho[2,3-*b*]furan (7d).** Yield 260 mg, 27% as colorless crystals; mp 58–60 °C; IR (KBr): 1613, 1592, 1526, 1442, 1396, 1212, 1139, 1037, 915, 894, 808, 775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35–1.42 (m, 6H, $CH_2CH_3$), 2.81–2.92 (m, 4H, $CH_2CH_3$), 6.28 (d, $J$=3.2 Hz, 1H, 4-$H_{Fur}$), 6.50 (s, 1H, 3-H), 6.98 (d, $J$=3.2 Hz, 1H, 3-$H_{Fur}$), 7.52 (dd, $J$=1.9, 9.3 Hz, 1H, 7-H), 7.77 (s, 1H, 4-H), 8.06 (d, $J$=1.9 Hz, 1H, 5-H), 8.54 (d, $J$=9.3 Hz, 1H, 8-H);$^{13}C$ NMR $\delta$ 11.6, 12.4, 21.8, 22.1, 100.8, 106.1, 109.9, 113.2, 116.9, 117.8, 126.4, 128.0, 128.1, 130.0, 130.8, 132.2, 146.5, 150.9, 158.1, 164.3. MS: *m*/*z* (%) 368/370 ($M^+$, 67/69), 353/355 (100/96), 297/299 (15/18), 290 (13), 262 (13), 246 (17), 231 (25), 218 (31), 203 (17), 202 (23), 190 (14), 189 (39), 176 (12), 170 (16). Anal. Calcd for $C_{20}H_{17}BrO_2$: C, 65.06; H, 4.64. Found: C, 65.02; H, 4.68.

**4.1.5. Formylation and acylation of naphthofuran 7b.**

**4.1.5.1. 6-Chloro-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan-4-carbaldehyde (8).** To a cooled (−1 to 0 °C) solution of **7b** (500 mg, 1.7 mmol) in DMF (8 mL), $POCl_3$ (8 mL) was added dropwise. The mixture was stirred for 5 h at rt. At the end of the reaction (TLC monitoring), the mixture was carefully poured into crash ice. The precipitate obtained was filtered off, washed with water, and air-dried. The recrystallization from diethyl ether with charcoal afforded compound **8** as yellow crystals (400 mg, 73%). Mp=179–181 °C; IR (KBr): 1668, 1572, 1513, 1429, 1242, 1048, 1032, 893, 809, 785 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.51 (s, 3H, C$H_3$), 2.52 (s, 3H, C$H_3$), 6.28 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 7.04 (s, 1H, 3-H), 7.07 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.36 (dd, $J$=1.6, 9.2 Hz, 1H, 7-H), 8.57 (d, $J$=9.2 Hz, 1H, 8-H), 8.98 (d, $J$=1.6 Hz, 1H, 5-H), 10.68 (s, 1H, C*H*O); $^{13}C$ NMR $\delta$ 14.0, 14.6, 101.8, 108.3, 115.9, 116.7, 117.8, 122.2, 125.5, 125.9, 128.5, 130.7, 133.2, 135.5, 145.6, 149.7, 154.1, 162.6, 188.6. MS: *m*/*z* (%) 324/326 ($M^+$, 100/33), 295/297 (17/7), 253/255 (22/10), 218 (10), 202 (11), 189 (27). Anal. Calcd for $C_{19}H_{13}ClO_3$: C, 70.27; H, 4.03. Found: C, 70.32; H, 4.08.

**4.1.5.2. 1-[6-Chloro-2-methyl-9-(5-methyl-2-furyl)naphtho[2,3-*b*]furan-4-yl]-1-ethanone (9), 1-[5-(4-acetyl-6-chloro-2-methylnaphtho[2,3-*b*]furan-9-yl)-2-methyl-3-furyl]-1-ethanone (10).** To the cooled (−7 to 0 °C) stirred suspension of $AlCl_3$ (670 mg, 50.5 mmol) in dry $CH_2Cl_2$ the solution of acetyl chloride (400 mg, 50.5 mmol) in dry $CH_2Cl_2$ was added and kept for 20 min. Then solution of **7b** (500 mg, 1.7 mmol) in dry $CH_2Cl_2$ was added. The mixture was stirred for 2 h at rt. At the end of the reaction (TLC monitoring), the mixture was poured into water and neutralized with $NaHCO_3$. The emulsion was extracted with $CH_2Cl_2$, combined organic layers were treated with $Na_2SO_4$ and charcoal. The solvent was evaporated under reduced pressure. The residue was separated by column chromatography using silica gel (5–40 mkm) and benzene–hexane=2:1 as eluent to give products **9** (75 mg) and **10** (170 mg) in ratio 1:2 in total 39% yield.

WARNING: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.

Compound **9** was isolated as yellow crystals with mp 122–124 °C; IR (KBr): 1668, 1596, 1529, 1424, 1384, 1357, 1248, 1143, 1034, 933, 791 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.51 (s, 3H, C$H_3$), 2.55 (s, 3H, C$H_3$), 2.78 (s, 3H, C$H_3$), 6.29 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 6.63 (s, 1H, 3-H), 7.00 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.43 (dd, $J$=1.8, 9.2 Hz, 1H, 7-H), 8.28 (d, $J$=1.8 Hz, 1H, 5-H), 8.60 (d, $J$=9.2 Hz, 1H, 8-H); $^{13}C$ NMR ($CDCl_3$) 14.0, 14.6, 32.3, 102.5, 107.9, 112.9, 115.0, 124.0, 126.0, 126.5, 126.9, 128.3, 128.4, 130.0, 131.8, 145.6, 150.1, 153.5, 160.7, 202.1. MS: *m*/*z* (%) 338/340 ($M^+$, 52/27), 323/325 (100/42), 296/298 (39/19), 261 (23), 205 (13), 203 (10), 190 (26). Anal. Calcd for $C_{20}H_{15}ClO_3$: C, 70.91; H, 4.46. Found: C, 70.95; H, 4.41.

Compound **10** was isolated as colorless crystals with mp 188–190 °C; IR (KBr): 1672, 1573, 1556, 1406, 1374, 1154, 943, 926, 811, 687, 640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.97 (s, 3H, C$H_3$), 2.44 (s, 3H, C$H_3$), 2.70 (s, 3H, C$H_3$), 6.64 (s, 1H, 3-H), 7.42 (dd, $J$=2.0, 9.0 Hz, 1H, 7-H), 7.70 (d, $J$=9.2 Hz, 1H, 5-H), 8.01 (d, $J$=2.0 Hz, 1H, 8-H), 8.50 (s, 1H, $H_{Fur}$); $^{13}C$ NMR $\delta$ 13.7, 15.9, 28.4, 31.2, 106.9, 109.3, 117.3, 121.7, 121.7, 126.7, 127.4, 127.5, 128.4, 130.8, 131.8, 148.0, 151.1, 153.8, 166.2, 193.2, 193.4. MS: *m*/*z* (%) 380/382 ($M^+$, 98/33), 365/367 (100/35), 337/339 (14/3), 320 (10). Anal. Calcd for $C_{22}H_{17}ClO_4$: C, 69.39; H, 4.50. Found: C, 69.45; H, 4.42.

**4.1.6. Nitrosation and nitration of naphthofurans 7.**

**4.1.6.1. 2-Methyl-9-(5-methyl-2-furyl)-4-nitronaphtho[2,3-*b*]furan (11a).** To a stirred suspension of $KNO_3$ (580 mg, 5.7 mmol) in glacial acetic acid (10 mL), a solution of **7a** (1 g, 3.8 mmol) in 20 mL acetic acid was added. The mixture was kept at 50 °C for 0.5 h (TLC monitoring). The mixture was poured into water (100 mL), neutralized with $NaHCO_3$ and precipitate filtered off and recrystallized from ethanol. Compound **11a** (350 mg, 30%) was obtained as yellow crystals with mp 157–159 °C; IR (KBr): 1539, 1508, 891, 786, 760, 687, 575 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.53 (s, 3H, C$H_3$), 2.61 (s, 3H, C$H_3$), 6.33 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 7.05 (s, 1H, 3-H), 7.10 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.56–7.60 (m, 1H, $H_{Ar}$), 7.66–7.70 (m, 1H, $H_{Ar}$), 8.71–8.79 (m, 2H, $H_{Ar}$); $^{13}C$ NMR $\delta$ 14.1, 14.7, 103.3, 108.3, 116.2, 116.5, 123.1, 124.2, 126.0 (2C), 127.0 (2C), 127.8, 127.9, 128.3, 145.1, 154.4, 162.8. MS: *m*/*z* (%) 307 ($M^+$, 54), 278 (27), 277 (100), 235 (14), 234 (56), 203 (15), 189 (35), 178 (16), 149 (30). Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26. Found: C, 70.40; H, 4.21.

**4.1.6.2. 6-Chloro-2-methyl-9-(5-methyl-2-furyl)-4-nitronaphtho[2,3-*b*]furan (11b).** Nitronaphthofuran **11b** was synthesized similar to **11a** starting from naphthofuran **7b** (yield: 430 mg, 33%) as yellow crystals with mp 211–213 °C; IR (KBr): 1596, 1539, 1494, 1319, 1233, 898, 791 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.53 (s, 3H, C$H_3$), 2.59 (s, 3H, C$H_3$), 6.33 (d, $J$=3.1 Hz, 1H, 4-$H_{Fur}$), 7.04 (s, 1H, 3-H), 7.11 (d, $J$=3.1 Hz, 1H, 3-$H_{Fur}$), 7.47 (dd, $J$=2.1, 9.2 Hz, 1H, 7-$H_{Ar}$), 8.66 (d, $J$=9.2 Hz, 1H, 5-$H_{Ar}$), 8.82 (d, $J$=2.1 Hz, 1H, 8-$H_{Ar}$); $^{13}C$ NMR $\delta$ 14.0, 14.7, 103.6, 108.5, 116.5, 117.1, 122.2, 125.1, 126.1, 126.8, 128.7 (2C), 129.3 (2C), 134.6, 144.9, 154.8, 163.5. MS: *m*/*z* (%) 341/343 ($M^+$, 100/36), 311/313 (75/36), 295/297 (25/11), 189 (14). Anal. Calcd for $C_{18}H_{12}ClNO_4$: C, 63.26; H, 3.54. Found: C, 63.31; H, 3.50.

**4.1.6.3. 6-Chloro-2-methyl-9-(5-methyl-2-furyl)-4-nitronaphtho[2,3-*b*]furan (11b) by nitration with $NaNO_2$.** To a stirred solution of **7b** (500 mg, 1.7 mmol) in glacial acetic acid (10 mL), $NaNO_2$ (160 mg, 2.3 mmol) was added. The mixture was kept at rt for 0.5 h (TLC monitoring). The reaction mixture was poured into water (100 mL), neutralized with $NaHCO_3$, and filtered off. The residue was recrystallized from acetone. Compound **11b** (300 mg, 52%) was obtained as yellow crystals with mp 211–213 °C.

**4.1.7. Oxidation of naphthofurans.**

**4.1.7.1. 2-Methyl-9-[(*E*)-4-oxo-2-pentenoyl]naphtho[2,3-*b*]furan-4-yl acetate (12) (oxidation with nitric acid).** To a stirred suspension of $KNO_3$ (470 mg, 4.7 mmol) in glacial acetic acid (10 mL), the solution of **4a** (1 g, 3.1 mmol) in 20 mL acetic acid was added. The mixture was kept at 50 °C for 1 h (TLC monitoring). The mixture was poured into water (100 mL), neutralized with $NaHCO_3$, and the precipitate was filtered off. The residue was recrystallized from ethanol. Compound **12** (520 mg, 50%) was obtained as yellow crystals with mp 188–190 °C; IR (KBr): 1764, 1683, 1659, 1582, 1508, 1375, 1247, 1170, 1122, 1006, 971, 868, 807, 769, 728, 563 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.43 (s, 3H, C$H_3$), 2.52 (s, 3H, C$H_3$), 2.56 (s, 3H, C$H_3$), 6.43 (s, 1H, 3-H), 7.02 (d, $J$=15.9 Hz, 1H, *H*C=CH), 7.50–7.61 (m, 2H, 6-H, 7-H), 7.70 (d, $J$=15.9 Hz, 1H, HC=C*H*), 8.00–8.03 (m, 1H, 5-H), 8.46–8.49 (m, 1H, 8-H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.4, 20.8, 28.4, 100.1, 114.6, 121.2, 122.5, 123.7, 125.2, 125.3, 127.5, 129.1, 137.9, 139.1, 140.5, 153.9, 158.8, 168.2, 191.0, 198.4. MS: *m*/*z* (%) 336 ($M^+$, 26), 295 (38), 294 (100), 252 (17), 251 (85), 225 (72), 197 (20), 169 (27). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.48; H, 4.83.

**4.1.7.2. 2-Methyl-9-[(*E*)-4-oxo-2-pentenoyl]naphtho[2,3-*b*]furan-4-yl acetate (12) (oxidation with PCC).** A solution of naphthofuran **4a** (1 g, 3.1 mmol) in dry $CH_2Cl_2$ (20 mL) was added dropwise to the suspension of pyridinium chlorochromate (4 g, 18.8 mmol) in dry $CH_2Cl_2$ (20 mL). The mixture was stirred for 60 h at rt. At the end of the reaction (TLC monitoring), the precipitate was filtered off and washed with hot $CH_2Cl_2$ (3×50 mL). The filtrate was concentrated in rotatory evaporator, and the oily residue was purified chromatographically on silica gel eluting with hexane–benzene (3:1). The eluate was concentrated to the volume of 10 mL and left to crystallize overnight. Compound **12** (520 mg, 50%) was obtained as yellow crystals.

WARNING: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.

**4.1.7.3. 2-Methyl-9-[(*E*)-4-oxo-2-pentenoyl]naphtho[2,3-*b*]furan-4-yl acetate (12) oxidation by MMPP.** To a solution of naphthofuran **4a** (1 g, 3.1 mmol) in dry benzene (50 mL), MMPP (15.3 g, 31.0 mmol) was added. The mixture refluxed for 5 h. At the end of the reaction (TLC monitoring), the phthalic acid was filtered off and washed with hot benzene. The benzene extracts were combined and washed with hot water. Then benzene solution concentrated in vacuum. The product was recrystallized from the hexane–benzene mixture. Compound **12** (360 mg, 34%) was obtained as yellow crystals.

WARNING: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.

**4.1.7.4. (*E*)-1-(6-Chloro-2-methylnaphtho[2,3-*b*]-furan-9-yl)-2-pentene-1,4-dione (13).** A solution of naphthofuran **7b** (1 g, 3.4 mmol) in dry $CH_2Cl_2$ (20 mL) was added dropwise to the suspension of pyridinium chlorochromate (3.6 g, 16.8 mmol) in dry $CH_2Cl_2$ (20 mL). The mixture was stirred for 60 h at rt. At the end of the reaction (TLC monitoring), the precipitate was filtered off and washed with hot $CH_2Cl_2$ (3×50 mL). The filtrate was concentrated in vacuum, and the oily residue was purified chromatographically on silica gel eluting with hexane–benzene (3:1). The eluate was concentrated to the volume of 10 mL and left to crystallize overnight. Compound **13** (370 mg, 35%) was obtained as yellow crystals with mp 124–126 °C; IR (KBr): 1694, 1661, 1492, 1400, 1337, 1285, 1241, 1094, 918, 886, 791 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.44 (s, 3H, C$H_3$), 2.54 (s, 3H, C$H_3$), 6.54 (s, 1H, 3-H), 6.98 (d, $J$=15.9 Hz, 1H, *H*C=CH), 7.45 (dd, $J$=2.0, 9.2 Hz, 1H, 7-H), 7.69 (d, $J$=15.9 Hz, 1H, HC=C*H*), 7.90 (d, $J$=2.0 Hz, 1H, 5-H), 7.97 (s, 1H, 4-H), 9.37 (d, $J$=9.2 Hz, 1H, 8-H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.5, 28.5, 102.4, 115.8, 122.1, 126.4, 126.8, 126.9, 127.7, 130.5, 131.2, 131.3, 138.0, 139.0, 153.2, 159.5, 191.5, 198.5. MS: *m*/*z* (%) 312/314 ($M^+$, 67/25), 269/271 (76/25), 243/245 (100/27), 187/189 (40/13), 152 (74). Anal. Calcd for $C_{18}H_{13}ClO_3$: C, 69.13; H, 4.19. Found: C, 69.20; H, 4.15.

WARNING: Care should be taken when handling benzene as a solvent due to its carcinogenic properties.

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# Asymmetric total synthesis of enantiopure (−)-methyl jasmonate via catalytic asymmetric intramolecular cyclopropanation of α-diazo-β-keto sulfone

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**Abstract**—A new asymmetric total synthesis of enantiopure (–)-methyl jasmonate is described. This synthesis was accomplished starting from the new enantiopure building block prepared via the catalytic asymmetric intramolecular cyclopropanation (IMCP) of the α-diazo-β-keto 1-naphthyl sulfone, which was devised to give good selectivity both in the IMCP reaction and in the C-alkynylation of the intermediate required for the total synthesis of enantiopure (–)-methyl jasmonate.

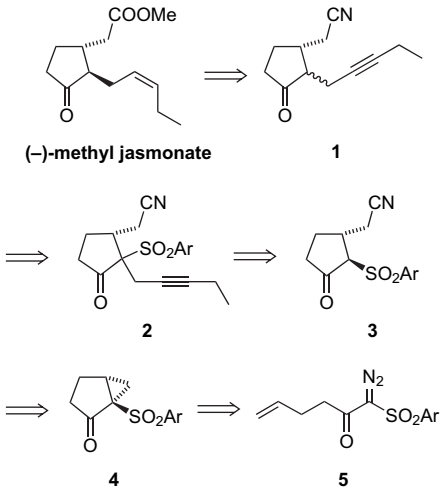

## 1. Introduction

(–)-Methyl jasmonate[1] is a key natural product occurring in *Jasminium grandiflorum* L. and in the blossoms of many flowers, and is used widely in the formulation of many perfumes. Although its structure is not complicated, key biological roles for (–)-methyl jasmonate have been noted[2] including roles in gene expression,[3] odor production,[4] and growth inhibition.[5] (–)-Methyl jasmonate possesses two stereogenic centers on a cyclopentanone ring substituted by a *cis*-2-pentenyl group and a methoxycarbonylmethyl group at its α- and β-positions of the carbonyl group, respectively. Its biological activities and structural features have motivated numerous attempts for total synthesis.[6] The asymmetric synthesis of enantiopure (–)-methyl jasmonate via enantioselective reaction has been limited[6] because an enantiopure cyclopentanone derivative suitable for the starting material is not commercially available, indicating one of the synthetic problems in the asymmetric total synthesis of this compound.

We report herein an asymmetric total synthesis of enantiopure (–)-methyl jasmonate starting from a new enantiopure chiral building block prepared via the originally developed catalytic asymmetric intramolecular cyclopropanation (IMCP) reaction of the α-diazo-β-keto sulfone.

## 2. Results and discussion

As outlined in Scheme 1, we expected that hydrogenation of the alkyne **1** with Lindlar's catalyst, following hydrolysis of the nitrile, and methylation of the resulting carboxylic acid would afford (–)-methyl jasmonate. The alkyne **1** could be produced as a mixture of diastereomers at the stereogenic center adjacent to the carbonyl group because it would be converged to the thermodynamically more stable *trans*-2,3-disubstituted isomer during the hydrolysis of the nitrile group under basic conditions. Alkyne **1** was difficult to obtain by direct alkynylation of the corresponding cyclopentanone derivative because the alkynylation would proceed at




**Scheme 1**. Retrosynthetic analysis of (–)-methyl jasmonate.

*Keywords*: Catalytic asymmetric synthesis; Chiral building blocks; Intramolecular cyclopropanation; Total synthesis.
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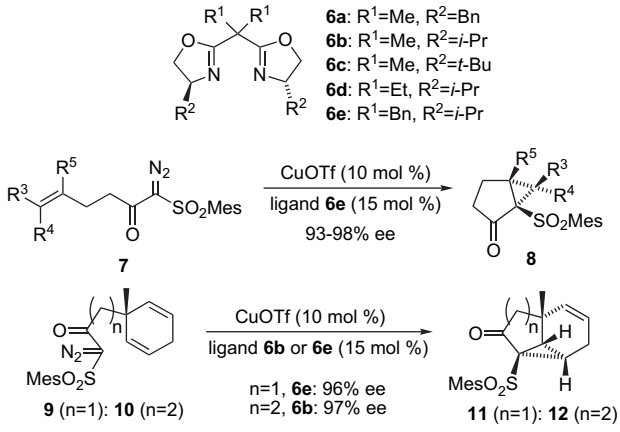
the less hindered α-position of the carbonyl group. Rather alkynylation of β-keto sulfone **3** was expected to produce **2** regioselectively because the aryl sulfonyl group stabilizes the anion generated at its α-position. Although O-alkynylation of **3** was also expected to occur as a side reaction, the *O*-alkynylated product would be hydrolyzed to regenerate **3** under acidic conditions. Since the bicyclo[3.1.0]hexan-2-one derivative **4** reacts with soft nucleophiles (such as sodium thiophenoxide)[7,8] to open the cyclopropane ring, and reaction of a cyanide ion with the cyclopropane derivative possessing an ester group in place of the sulfonyl group in **4** has been reported,[6bb] reaction of a cyanide ion with **4** was expected to afford β-keto sulfone **3**. Consequently, the bicyclo[3.1.0]hexan-2-one derivative **4** was envisioned to be a key intermediate for the asymmetric total synthesis of (−)-methyl jasmonate.

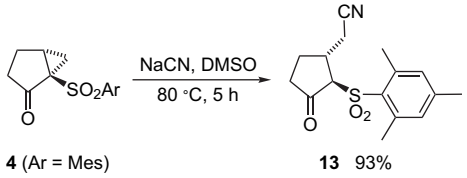
The asymmetric synthesis of natural products starting from the bicyclo[3.1.0]hexan-2-one derivatives prepared by the IMCP reaction of α-diazo-β-keto ester has been reported,[7,9] however, the reported preparation has been limited to the diastereoselective cyclopropanation reaction by use of a chiral auxiliary.[9]

We have studied the asymmetric catalysis of the IMCP reaction of α-diazo-β-keto ester, but found it to be difficult.[10a] Hence, we have developed the catalytic asymmetric IMCP reactions of α-diazo-β-keto sulfones **7**, **9**, and **10** (Scheme 2) by use of ligand **6** to afford the corresponding cyclopropanes **8**, **11**, and **12** with 93–98% ee, respectively.[10] Since cyclopropanes thus prepared from α-diazo-β-keto sulfones are highly crystalline and easily purified by recrystallization as enantiomerically pure compounds, this catalytic asymmetric IMCP reaction is useful for preparing new enantiopure chiral building blocks toward natural products' syntheses. Our recent reports regarding the asymmetric total synthesis of enantiopure (−)-malyngolide[8a] and the first asymmetric total synthesis of (−)-allocyathin $B_2$[8b] via the catalytic asymmetric IMCP reaction prove its wide applicability.




**Scheme 2**. Asymmetric catalysis of α-diazo-β-keto sulfones **7**, **9**, and **10**.

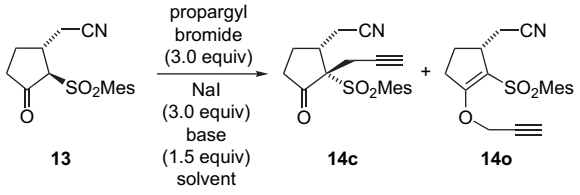
Initial synthetic studies on (−)-methyl jasmonate began with the previously reported enantiopure cyclopropane **4** (Ar=Mes) (Scheme 3).[10] Reaction of cyclopropane **4** (Ar=Mes) with sodium cyanide in DMSO at 80 °C smoothly produced β-keto sulfone **13**[11] in 93% yield. Since the alkylation reaction of β-keto phenyl sulfone under basic conditions was known to afford the *C*-alkylated product exclusively,[12] propargylation of **13** was studied as the model reaction for the conversion of **3** to **2** (Scheme 1) toward the total synthesis of (−)-methyl jasmonate.




**Scheme 3**. Reaction of **4** (Ar=Mes) with sodium cyanide.

The propargylation of **13** afforded the *O*-propargylated product, designated as **14o**, as the major product under various conditions (Table 1), while the best yield of the *C*-propargylated product, **14c**, was 27% (entry 2). We examined alkylation of **13** with less bulky methyl iodide (Table 2), too; however, all the reactions under several conditions afforded the *O*-methylated product **15o** as the major product.

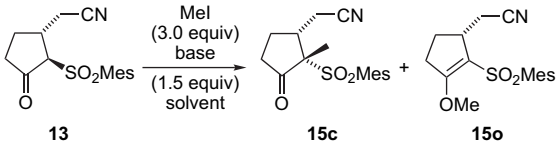
**Table 1**. Propargylation of **13**




| Entry | Base | Solvent | Temperature (°C) | Time (h) | Yield (%)[a] | |
|---|---|---|---|---|---|---|
| | | | | | **14c**[b] | **14o** |
| 1 | $K_2CO_3$ | Acetone | Reflux | 8 | 10 | 81 |
| 2 | $K_2CO_3$ | DMF | rt | 2 | 27 | 63 |
| 3 | $K_2CO_3$ | DMSO | rt | 2 | 23 | 68 |
| 4 | $K_2CO_3$ | $CH_3CN$ | rt | 4 | 16 | 82 |
| 5 | NaH | THF | 0→rt | 36 | 7 | 92 |
| 6 | TBAF | THF | Reflux | 12 | 16 | 80 |
| 7 | $Cs_2CO_3$ | DMF | rt | 2 | 22 | 70 |

The relative stereochemistry was determined by NOESY.
[a] Isolated yields.
[b] A single isomer.

**Table 2**. Methylation of **13**



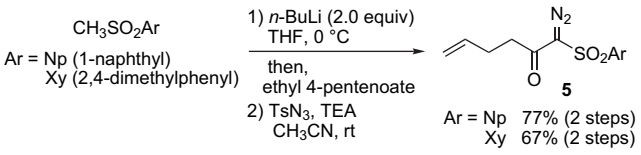

| Entry | Base | Solvent | Temperature (°C) | Time (h) | Yield (%)[a] | |
|---|---|---|---|---|---|---|
| | | | | | **15c**[b] | **15o** |
| 1 | $K_2CO_3$ | Acetone | Reflux | 5 | 5 | 92 |
| 2 | $K_2CO_3$ | $CH_3CN$ | Reflux | 12 | 27 | 71 |
| 3 | $K_2CO_3$ | DMF | rt | 5 | 38 | 60 |
| 4 | NaH | DMF | rt | 3 | 15 | 78 |
| 5 | TBAF | DMF | rt | 3 | 12 | 81 |

The relative stereochemistry was determined by NOESY.
[a] Isolated yields.
[b] A single isomer.

The preferred formation of the *O*-alkylated products in the reaction of **13** could be attributed to the bulky mesityl group. The β-keto sulfone possessing a less bulky phenyl group in place of the mesityl group was expected to increase the ratio of *C*-alkylated product, however, the cyclopropane **4** (Ar=Ph) was generated with a relatively low ee (75% ee[10a]), not useful for the asymmetric synthesis of natural products. Consequently, we decided to find other α-diazo-β-keto sulfones, which afforded the products with high ee by the catalytic asymmetric IMCP reaction.

The enantioselectivity in the catalytic asymmetric IMCP reaction of **7** ($R^3$=$R^4$=$R^5$=H) was higher than that of the corresponding phenyl sulfone.[10a] This result suggested that the *ortho* methyl groups of 2,4,6-trimethylphenyl sulfone in **7** played a crucial role for the high enantioselectivity. Consequently, we examined the catalytic asymmetric IMCP reactions of α-diazo-β-keto sulfones **5** (Ar=Np, Xy) because a 1-naphthyl group and a 2,4-dimethylphenyl group are smaller than the mesityl group but retain sufficient bulkiness to give good selectivity both in the IMCP reaction and in the C-alkylation of the intermediates corresponding to **13**. In addition, commercial availability of the starting materials for the preparation of methyl 1-naphthyl sulfone[13] and 2,4-dimethylphenyl methyl sulfone[14] was also the point in employing these aryl groups.

α-Diazo-β-keto sulfones **5** (Ar=Np, Xy) were successfully prepared according to the previously reported procedure for **7**[10a] (Scheme 4). Dianions of either methyl 1-naphthyl sulfone or 2,4-dimethylphenyl methyl sulfone were reacted with ethyl 4-pentenoate to produce the corresponding β-keto sulfones, which were converted to α-diazo-β-keto sulfones **5** (Ar=Np, Xy), respectively.[15]

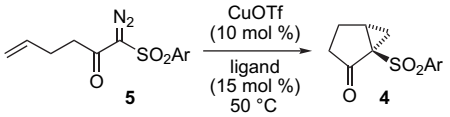



**Scheme 4**. Preparation of **5**.

The relationships between the ligand and the enantioselectivity in the IMCP reaction of **5** (Ar=Np) differed from those of **7**, which were reported previously.[10a] As indicated in Table 3, ligand **6e**, which had endowed the highest ee in the IMCP reaction of **7** (Scheme 2), was not so effective in the IMCP reaction of **5** (Ar=Np), affording **4** with 79% ee (entry 5). The best result (83% ee) was obtained with ligand **6d** in the case of **5** (Ar=Np). On the other hand, the IMCP reaction of **5** (Ar=Xy) showed the same trend in the relationships between the ligand and the enantioselectivity as that of **7** because ligand **6e** gave the best result (81% ee).

Since **4** (Ar=Np, Xy) and their crystalline derivatives were unsuitable for X-ray crystallographic analysis, we converted **4** (Ar=Np, Xy) to **16** to determine their absolute configuration by comparing their sign of the specific rotations with that of **16**, which was derived from the known **4** (Ar=Mes)[10a] via **13** (Scheme 5). As shown in Scheme 5, reactions of **4** (Ar=Np, Xy) with sodium cyanide in DMSO at 80 °C for 5 h opened the cyclopropane ring to generate **3**

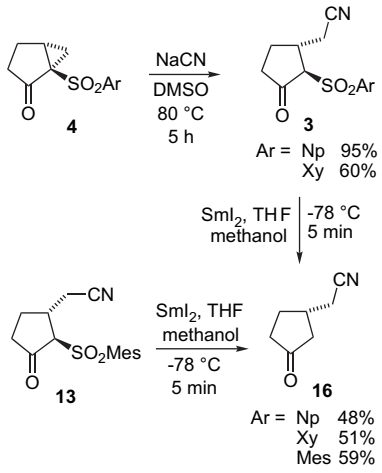
**Table 3**. Enantioselective IMCP reaction of α-diazo-β-keto sulfone **5**




| Entry | Ligand | Ar[a] | Time (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **6a** | Np | 4 | 91 | 71 (1*R*) |
| 2 | **6b** | Np | 3 | 95 | 72 (1*R*) |
| 3 | **6c** | Np | 14 | 59 | 45 (1*R*) |
| 4 | **6d** | Np | 5 | 93 | *83* (1*R*) |
| 5 | **6e** | Np | 2 | 82 | 79 (1*R*) |
| 6 | **6a** | Xy | 4 | 75 | 72 (1*R*) |
| 7 | **6b** | Xy | 2 | 83 | 62 (1*R*) |
| 8 | **6c** | Xy | 12 | 89 | 37 (1*R*) |
| 9 | **6d** | Xy | 5 | 99 | 74 (1*R*) |
| 10 | **6e** | Xy | 5 | 97 | *81* (1*R*) |

[a] Np=1-naphthyl; Xy=2,4-dimethylphenyl.
[b] Isolated yields.
[c] Enantiomeric excess (ee) determined by HPLC. For HPLC conditions, see Section 4.

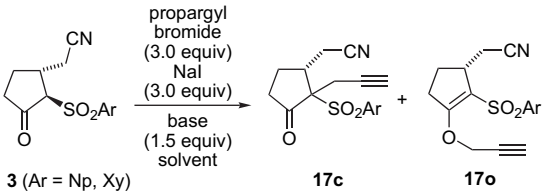
(Ar=Np, Xy)[11] in 95% and 60% yields, respectively. Desulfonylation of **3** (Ar=Np, Xy) and **13** with $SmI_2$ in the presence of methanol successfully afforded **16** in 48%, 51%, and 59% yields, respectively. Their specific rotations had a minus sign, elucidating that **4** possesses 1*R* configuration because the absolute configuration of **13**, which was derived from **4** (Ar=Mes),[10a] is known. These results indicate that enantioselectivity of the IMCP reaction of **5** (Ar=Np, Xy) with ligand **6e** is well explained by our previously reported model,[10a] which had been proposed to explain the enantioselectivity of the IMCP reaction of **7** ($R^3$=$R^4$=$R^5$=H).




**Scheme 5**. Conversion of **4** to **16** and **13** to **16**.

Since the catalytic asymmetric IMCP reactions of α-diazo-β-keto sulfone **5** (Ar=Np, Xy) afforded the products with high ee, which were isolated in enantiopure form by recrystallization, we next examined the propargylation of **3** (Ar=Np, Xy). Among various solvents examined, polar aprotic solvents were effective for the C-propargylation in both substrates **3** (Ar=Np, Xy) (Table 4). DMF and DMSO gave comparable yields in the reactions of both substrates **3** (Ar=Np, Xy) (entries 2 and 3, 9 and 10), but the ratio of **17c/17o** was slightly higher when the solvent was DMF. In DMF, the use of potassium carbonate as the base

**Table 4**. Propargylation of **3** (Ar=Np, Xy)



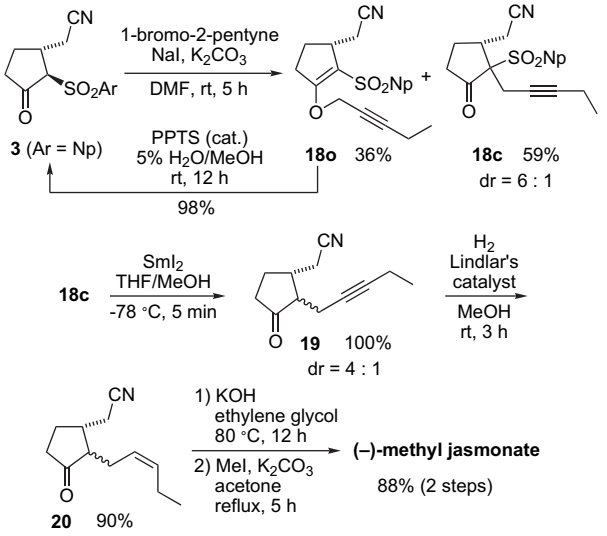

| Entry | Ar | Base | Solvent | Temperature (°C) | Time (h) | Yield (%)[a] | |
|---|---|---|---|---|---|---|---|
| | | | | | | **17c**[b] | **17o** |
| 1 | Np | $K_2CO_3$ | Acetone | Reflux | 10 | 15 | 80 |
| 2 | Np | $K_2CO_3$ | DMF | rt | 2 | *75* | 21 |
| 3 | Np | $K_2CO_3$ | DMSO | rt | 2 | 72 | 26 |
| 4 | Np | $K_2CO_3$ | $CH_3CN$ | rt | 3 | 58 | 41 |
| 5 | Np | NaH | THF | 0→rt | 12 | 11 | 81 |
| 6 | Np | TBAF | THF | Reflux | 10 | 55 | 40 |
| 7 | Np | $Cs_2CO_3$ | DMF | rt | 2.5 | 72 | 24 |
| 8 | Xy | $K_2CO_3$ | Acetone | Reflux | 5 | 21 | 72 |
| 9 | Xy | $K_2CO_3$ | DMF | rt | 2 | 44 | 52 |
| 10 | Xy | $K_2CO_3$ | DMSO | rt | 2 | 41 | 58 |
| 11 | Xy | $K_2CO_3$ | $CH_3CN$ | rt | 3 | 31 | 67 |
| 12 | Xy | NaH | THF | 0→rt | 24 | 15 | 81 |
| 13 | Xy | TBAF | THF | Reflux | 6 | 27 | 64 |
| 14 | Xy | $Cs_2CO_3$ | DMF | rt | 2 | 40 | 54 |

[a] Isolated yields.
[b] A mixture of diastereomers; dr=11/1 for entries 1–7; dr=7/1 for entries 8–14.[16]

gave a higher ratio of **17c/17o** than did cesium carbonate (entries 2 and 7, 9 and 14). A crucial factor in the ratio of **17c/17o** was attributed to the nature of the aryl sulfonyl group. Thus, Table 4 clearly shows that the ratio of **17c/17o** in the reaction is improved if the naphthyl substituent of **5** is used rather than the 2,4-dimethylphenyl substituent. Consequently, although both versions of **5** (Ar=Np, Xy) showed comparable enantioselectivities in the IMCP reaction, **3** (Ar=Np) was adopted for the synthesis of (−)-methyl jasmonate.

The reaction of **3** (Ar=Np) with 1-bromo-2-pentyne under the same conditions as those employed in entry 2 of Table 4 afforded *C*-alkylated product **18c** as a mixture of diastereomers (6/1)[16] in 59% yield and *O*-alkylated product **18o** in 36% yield (Scheme 6). The *C*- and *O*-alkylated products were separated by flash chromatography, and **18o** was successfully hydrolyzed under acidic conditions to regenerate **3** (Ar=Np) in 98% yield.

Desulfonylation of **18c** was successfully carried out by $SmI_2$ in 100% yield, but affording **19** as a mixture of diastereomers (dr=4/1).[16] This mixture was used for the next step without separation because the hydrolysis of nitrile **20** was anticipated to proceed with epimerization at its C-2 position. Hydrogenation of **19** with Lindlar's catalyst gave *cis*-alkene **20** in 90% yield, and successive treatment of **20** with KOH in ethylene glycol produced the corresponding carboxylic acid with concomitant epimerization at its C-2 position to afford the carboxylic acid expectedly as the single product. Finally, methylation of the obtained carboxylic acid with methyl iodide furnished methyl jasmonate (88%, two steps). Synthetic methyl jasmonate proved to be identical in all respects to the reported spectral data ($^1$H NMR, IR, MS, and $^{13}$C NMR; >99% de[16])[1a] of methyl jasmonate. The specific rotation




**Scheme 6**. Total synthesis of (−)-methyl jasmonate.

of the synthetic methyl jasmonate ($[\alpha]_D^{23}$) showed −90.2 (*c* 1.03, MeOH) (lit.[1a] $[\alpha]_D^{23}$ −90.3 (*c* 1.03, MeOH)), revealing that (−)-methyl jasmonate has been synthesized.

## 3. Conclusion

In summary, we found that catalytic asymmetric IMCP reactions of the 1-naphthyl sulfone **5** (Ar=Np) and 2,4-dimethylphenyl sulfone **5** (Ar=Xy) produced new cyclopropanes **4** (Ar=Np, Xy) in 83% and 81% ee, respectively, and **4** (Ar=Np) was successfully purified by recrystallization in optically pure form. Reaction of **4** (Ar=Np) with sodium cyanide gave **3** (Ar=Np), which was alkylated with 1-bromo-2-pentyne to produce *C*-alkylated product **18c** as the major product. *O*-Alkylated product **18o** was hydrolyzed under acidic conditions to regenerate **3** (Ar=Np), and *C*-alkylated product **18c** was successfully converted to enantiopure (−)-methyl jasmonate. Optically pure new chiral building blocks **4** (Ar=Np, Xy) developed in this study would be useful for the asymmetric total synthesis of enantiopure natural products, especially those containing a 2,3-disubstituted cyclopentanone ring in their molecules.

## 4. Experimental

### 4.1. General procedures

$^1$H and $^{13}$C NMR spectra were recorded on a JEOL AL-400 spectrometer. $^1$H and $^{13}$C chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS, $\delta$ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Melting points (mp) are uncorrected, recorded on a Yamato capillary melting point apparatus equipped with a digital thermometer. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP-1000. Chiral HPLC analysis

was performed on JASCO PU-980 and UV-970. Mass spectrometric analyses and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). THF was distilled from sodium/benzophenone ketyl, and methylene chloride ($CH_2Cl_2$), benzene were distilled from calcium hydride. Toluene was distilled from sodium. Acetonitrile was distilled from $CaH_2$ under reduced pressure. $(CuOTf)_2C_6H_6$ and all other reagents were purchased from Aldrich, TCI, or Kanto Chemical Co. Ltd.

**4.1.1. (1*R*,2*R*)-[3-Oxo-2-(2,4,6-trimethylphenylsulfonyl)-cyclopentyl]acetonitrile (13).** To a solution of **4** (Ar=Mes)[10a] (1.00 g, 3.59 mmol) in DMSO (30 mL) was added sodium cyanide (194.0 mg, 3.95 mmol) and the reaction mixture was stirred at 80 °C for 5 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with ethyl acetate (30 mL×2). The combined organic layer was washed with brine (30 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **13** (1.02 g, 93%) as a white solid.

Mp=117–118 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{24}$ −78.2 (*c* 1.00, $CHCl_3$); IR (KBr) $\nu_{max}$: 2247, 1654, 1449, 1143, 932, 741 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.01 (s, 2H), 3.73 (d, *J*=9.8 Hz, 1H), 3.34–3.24 (m, 1H), 3.08 (dd, *J*=5.9, 17.1 Hz, 1H), 2.84 (dd, *J*=3.9, 17.1 Hz, 1H), 2.60 (s, 6H), 2.56–2.36 (m, 3H), 2.33 (s, 3H), 1.82 (dddd, *J*=1.7, 7.8, 9.3, 9.8 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=204.4, 144.3, 140.5, 132.4, 131.7, 116.9, 71.3, 38.9, 33.8, 25.9, 22.9, 22.5, 21.2; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{19}NO_3S$+H 306.1164, found 306.1169. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; S, 10.50. Found: C, 62.89; H, 6.24; N, 4.61; S, 10.53.

**4.1.2. (1*R*,2*S*)-[3-Oxo-2-(2-propynyl)-2-(2,4,6-trimethylphenylsulfonyl)cyclopentyl]acetonitrile (14c) and (*R*)-[3-(2-propynyloxy)-2-(2,4,6-trimethylphenylsulfonyl)-2-cyclopentenyl]acetonitrile (14o).** To a solution of **13** (41.5 mg, 0.137 mmol) in DMF (2 mL) were added potassium carbonate (28.4 mg, 0.205 mmol), sodium iodide (61.6 mg, 0.411 mmol), and propargyl bromide (0.031 mL, 0.411 mmol) successively, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (3 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **14c** (12.7 mg, 27%, a single isomer) and **14o** (29.6 mg, 63%) as white solids.

Compound **14c**: mp=112–113 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{25}$ +67.4 (*c* 1.25, $CHCl_3$); IR (KBr) $\nu_{max}$: 2260, 2132, 1666, 854, 734 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.02 (s, 2H), 3.75–3.58 (m, 1H), 3.06 (dd, *J*=4.3, 16.8 Hz, 1H), 2.97 (dd, *J*=11.5, 16.8 Hz, 1H), 2.87 (dd, *J*=2.7, 16.0 Hz, 1H), 2.80–2.25 (m, 13H, including $\delta$=2.33, s, 3H), 2.06 (dd, *J*=2.7, 2.7 Hz, 1H), 2.01–1.80 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=206.8, 144.9, 133.1, 127.2, 117.5, 76.7, 75.9, 73.4, 39.0, 36.7, 26.0, 23.9, 21.1, 19.2, 18.7; HRMS (FAB): *m*/*z* calcd for $C_{19}H_{21}NO_3S$+H 344.1320, found 344.1389.

Compound **14o**: mp=94–96 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{24}$ −42.8 (*c* 1.40, $CHCl_3$); IR (KBr) $\nu_{max}$: 2252, 854, 734 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=6.91 (s, 2H), 4.42 (dd, *J*=2.4, 16.3 Hz, 1H), 4.37 (dd, *J*=2.4, 16.3 Hz, 1H), 3.50–3.32 (m, 1H), 3.00–2.85 (m, 2H), 2.75–2.57 (m, 8H, including $\delta$=2.62, s, 6H), 2.47 (dd, *J*=2.4, 2.4 Hz, 1H), 2.38–2.25 (m, 4H, including $\delta$=2.30, s, 3H), 1.94 (dddd, *J*=3.2, 7.8, 9.0, 10.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=163.9, 142.6, 140.1, 135.1, 131.7, 118.3, 117.5, 76.6, 57.9, 39.9, 28.9, 25.7, 23.4, 22.5, 20.9; HRMS (FAB): *m*/*z* calcd for $C_{19}H_{21}NO_3S$+H 344.1320, found 344.1307.

**4.1.3. (1*R*,2*S*)-[2-Methyl-3-oxo-2-(2,4,6-trimethylphenylsulfonyl)cyclopentyl]acetonitrile (15c) and (*R*)-[3-methoxy-2-(2,4,6-trimethylphenylsulfonyl)-2-cyclopentenyl]-acetonitrile (15o).** To a solution of **13** (1.00 g, 3.27 mmol) in DMF (30 mL) were added potassium carbonate (452.0 mg, 4.91 mmol) and methyl iodide (0.61 mL, 9.81 mmol) successively, and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (30 mL) and extracted with ether (30 mL×2). The combined organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **15c** (397 mg, 38%, a single isomer) and **15o** (626 mg, 60%) as white solids.

Compound **15c**: mp=108–109 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{26}$ −60.6 (*c* 1.01, $CHCl_3$); IR (KBr) $\nu_{max}$: 2240, 1657, 1452, 1126, 857, 719 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=6.94 (s, 2H), 3.65–3.40 (m, 1H), 2.88 (dd, *J*=4.6, 16.8 Hz, 1H), 2.70–2.05 (m, 9H, including $\delta$=2.53, s, 3H; $\delta$=2.51, s, 3H), 2.26 (s, 3H), 1.75–1.45 (m, 2H), 1.26 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=208.3, 144.4, 132.9, 128.1, 117.7, 75.0, 38.5, 36.5, 24.7, 23.9, 21.0, 19.7, 13.5; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{21}NO_3S$+H 320.1320, found 320.1343.

Compound **15o**: mp=139–140 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{26}$ −34.5 (*c* 1.00, $CHCl_3$); IR (KBr) $\nu_{max}$: 2241, 1445, 1136, 877, 723 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=6.91 (s, 2H), 3.63 (s, 3H), 3.42–3.32 (m, 1H), 2.89 (dd, *J*=3.7, 16.8 Hz, 2H), 2.75–2.50 (m, 8H, including $\delta$=2.60, s, 6H), 2.45–2.20 (m, 4H, including $\delta$=2.30, s, 3H), 2.00–1.85 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=166.6, 142.5, 140.0, 135.4, 131.7, 118.5, 114.7, 57.9, 40.2, 28.8, 25.6, 23.5, 22.4, 20.9; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{21}NO_3S$+H 320.1320, found 320.1335.

**4.1.4. 1-(1-Naphthalenesulfonyl)-5-hexen-2-one.** To a solution of methyl 1-naphthyl sulfone (347.0 mg,

1.68 mmol) in THF (10 mL) was added *n*-butyllithium in hexane (2.12 mL, 3.36 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 15 min. Then to the reaction mixture was added ethyl 4-pentenoate (227 mg, 1.77 mmol) at 0 °C, and the stirring was continued for 30 min. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (30 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford 1-(1-naphthalenesulfonyl)-5-hexen-2-one (461 mg, 95%) as a white solid.

Mp=37.5–37.6 °C ($CH_2Cl_2$/hexane); IR (KBr) $\nu_{max}$: 1660, 1507, 1316, 1157, 1127, 768 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=8.62 (d, $J$=8.7 Hz, 1H), 8.20 (d, $J$=7.3 Hz, 1H), 8.10 (d, $J$=8.3 Hz, 1H), 7.93 (d, $J$=8.3 Hz, 1H), 7.66 (dd, $J$=8.7, 8.3 Hz, 1H), 7.58 (dd, $J$=7.3, 8.3 Hz, 1H), 7.54 (dd, $J$=8.3, 8.3 Hz, 1H), 5.67 (ddt, $J$=10.4, 17.0, 6.6 Hz, 1H), 4.94 (dd, $J$=1.5, 17.0 Hz, 1H), 4.91 (dd, $J$=1.5, 10.4 Hz, 1H), 4.26 (s, 2H), 2.75 (t, $J$=7.1 Hz, 2H), 2.32 (dt, $J$=6.6, 7.1 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=196.9, 136.0, 135.8, 134.1, 133.7, 131.0, 129.4, 129.0, 128.5, 127.1, 124.3, 123.5, 115.7, 66.4, 43.7, 27.2; HRMS (FAB): *m/z* calcd for $C_{16}H_{16}O_3S$+H 289.0898, found 289.0901. Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59; S, 11.12. Found: C, 66.71; H, 5.65; S, 11.36.

**4.1.5. 1-Diazo-1-(1-naphthalenesulfonyl)-5-hexen-2-one (5 (Ar=Np)).** To a solution of 1-(1-naphthalenesulfonyl)-5-hexen-2-one (417.0 mg, 1.44 mmol) in $CH_3CN$ (10 mL) was added triethylamine (0.482 mL, 3.47 mmol) at 0 °C, and then a solution of *p*-toluenesulfonyl azide (456.0 mg, 2.31 mmol) in $CH_3CN$ (1.5 mL×2) via a canula. The reaction mixture was stirred at room temperature for 6 h. The light yellow reaction mixture was concentrated under reduced pressure and diluted with ether (100 mL). To the ether solution was added 1 M KOH aqueous solution (10 mL), and the separated aqueous solution was extracted with ether (10 mL×2). The combined organic layer was washed with brine (10 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=15/1) to afford **5** (Ar=Np) (366.0 mg, 81%) as a yellow-green solid.

Mp=84–86 °C; IR (KBr) $\nu_{max}$: 1666, 1334, 1127, 768 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=8.36 (d, $J$=7.6 Hz, 1H), 8.35 (d, $J$=7.6 Hz, 1H), 8.09 (d, $J$=8.3 Hz, 1H), 7.93 (d, $J$=8.1 Hz, 1H), 7.67 (dd, $J$=7.6, 8.1 Hz, 1H), 7.59 (dd, $J$=7.6, 8.1 Hz, 1H), 7.57 (dd, $J$=8.1, 8.3 Hz, 1H), 5.47 (ddt, $J$=11.2, 15.6, 6.6 Hz, 1H), 4.78 (dd, $J$=1.3, 11.2 Hz, 1H), 4.76 (dd, $J$=1.3, 15.6 Hz, 1H), 2.48 (t, $J$=7.3 Hz, 2H), 2.11 (dt, $J$=6.6, 7.3 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=187.6, 136.2, 135.8, 135.7, 134.3, 131.3, 129.1, 127.6, 127.2, 124.1, 123.2, 115.6, 38.1, 27.4; HRMS (FAB): *m/z* calcd for $C_{16}H_{14}N_2O_3S$+H 315.0803, found 315.0808.

**4.1.6. 1-(2,4-Dimethylphenylsulfonyl)-5-hexen-2-one.** To a solution of 2,4-dimethylphenyl methyl sulfone (3.05 g, 16.6 mmol) in THF (160 mL) was added *n*-butyllithium (21.5 mL, 33.1 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. After cooling the reaction mixture to 0 °C again, ethyl 4-pentenoate (2.34 g, 18.2 mmol) was added to the reaction mixture at the same temperature. After 1 h, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (60 mL) and extracted with ether (10 mL×2). The combined organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford 1-(2,4-dimethylphenylsulfonyl)-5-hexen-2-one (3.56 g, 80%) as a white solid.

Mp=33–34 °C ($CH_2Cl_2$/hexane); IR (KBr) $\nu_{max}$: 1684, 1462, 884, 770 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.79 (d, $J$=8.5 Hz, 1H), 7.15 (d, $J$=8.5 Hz, 1H), 7.14 (s, 1H), 5.74 (ddt, $J$=10.5, 17.1, 6.6 Hz, 1H), 5.02 (dd, $J$=1.5, 17.1 Hz, 1H), 4.97 (dd, $J$=1.5, 10.5 Hz, 1H), 4.16 (s, 2H), 2.80 (t, $J$=7.1 Hz, 2H), 2.63 (s, 3H), 2.37 (s, 3H), 2.28 (dt, $J$=6.6, 7.1 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=197.2, 145.0, 137.7, 136.0, 133.8, 133.4, 130.1, 127.1, 115.5, 66.2, 43.3, 27.0, 21.3, 20.2; HRMS (FAB): *m/z* calcd for $C_{14}H_{18}O_3S$+H 267.1055, found 267.1057.

**4.1.7. 1-Diazo-1-(2,4-dimethylphenylsulfonyl)-5-hexen-2-one (5 (Ar=Xy)).** To a solution of 1-(2,4-dimethylphenylsulfonyl)-5-hexen-2-one (3.56 g, 13.4 mmol) in $CH_3CN$ (150 mL) was added triethylamine (4.47 mL, 32.1 mmol) at 0 °C, and then a solution of *p*-toluenesulfonyl azide (3.16 g, 16.0 mmol) in $CH_3CN$ (15 mL×2) was added via a canula. The reaction mixture was stirred at room temperature for 8 h. The light yellow reaction mixture was concentrated under reduced pressure and diluted with ether (300 mL). To the ether solution was added 1 M KOH aqueous solution (50 mL), and the separated aqueous layer was extracted with ether (20 mL×2). The combined organic layer was washed with brine (10 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=15/1) to afford **5** (Ar=Xy) (3.27 g, 84%) as a yellow-green solid.

Mp=78–79 °C; IR (KBr) $\nu_{max}$: 2139, 1653, 1330, 923, 831, 749 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=8.00 (d, $J$=8.5 Hz, 1H), 7.21 (d, $J$=8.5 Hz, 1H), 7.18 (s, 1H), 5.67 (ddt, $J$=10.0, 17.2, 6.9 Hz, 1H), 4.94 (dd, $J$=1.5, 17.2 Hz, 1H), 4.89 (dd, $J$=1.5, 10.0 Hz, 1H), 2.56 (s, 3H), 2.55 (t, $J$=7.9 Hz, 2H), 2.41 (s, 3H), 2.24 (dt, $J$=6.9, 7.9 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=188.1, 145.3, 137.2, 136.6, 136.0, 133.7, 130.3, 127.3, 115.6, 38.0, 27.4, 21.3, 19.9; HRMS (FAB): *m/z* calcd for $C_{14}H_{16}N_2O_3S$+H 293.0960, found 293.0986.

**4.1.8. (1*R*,5*R*)-1-(1-Naphthalenesulfonyl)bicyclo[3.1.0]-hexan-2-one (4 (Ar=Np)).** A toluene azeotroped $(CuOTf)_2 \cdot C_6H_6$ (50.0 mg, 0.110 mmol, 10 mol % as CuOTf (90% purity)) was placed in a dried flask (100 mL) under Ar atmosphere. To this flask was added a solution of toluene azeotroped ligand **6d** (98.0 mg, 0.331 mmol, 15 mol %) in toluene (5 mL×3) via a canula. The mixture was stirred at room temperature for 0.5 h and then to the light blue solution was added a solution of toluene azeotroped **5** (Ar=Np) (624.0 mg, 1.99 mmol) in toluene (5 mL×3) via a canula. The reaction mixture was stirred at 50 °C for 5 h, quenched with aqueous $NH_4OH$ solution (10 mL), and the separated aqueous layer was extracted with ether (10 mL). The aqueous layer was further extracted with $CH_2Cl_2$ (5 mL×2). The combined organic layer was washed with brine

(10 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford **4** (Ar=Np) (528.0 mg, 93%, 83% ee) as a white solid.

Enantiomeric excess (ee) was determined by HPLC (254 nm); DAICEL CHIRALCEL OD-H (0.46 cm ϕ× 25 cm; hexane/2-propanol=4/1; flow rate=5 mL $min^{-1}$); retention time: 42 min for **4** (Ar=Np), 38 min for ***ent*-4** (Ar=Np).

Mp=111–112 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{23}$ −60.3 (*c* 1.00, $CHCl_3$, >99% ee); IR (KBr) $\nu_{max}$: 1737, 1302, 1124, 763 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=8.75 (d, *J*=8.8 Hz, 1H), 8.51 (d, *J*=7.5 Hz, 1H), 8.12 (d, *J*=8.1 Hz, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.67–7.55 (m, 3H), 3.15–3.10 (m, 1H), 2.47 (dd, *J*=3.9, 17.1 Hz, 1H), 2.18–1.94 (m, 4H), 1.58 (dd, *J*=5.6, 5.6 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=202.9, 135.2, 132.8, 129.6, 129.1, 128.1, 126.6, 126.4, 124.4, 124.3, 53.5, 33.5, 31.3, 20.2, 20.0; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{14}O_3S$+H 287.0742, found 287.0773. Anal. Calcd for $C_{16}H_{14}NO_3S$: C, 67.11; H, 4.93; S, 11.20. Found: C, 66.13; H, 4.88; S, 11.87.

**4.1.9. (1*R*,5*R*)-1-(2,4-Dimethylphenylsulfonyl)bicyclo[3.1.0]hexan-2-one (4 (Ar=Xy)).** A toluene azeotroped $(CuOTf)_2 \cdot C_6H_6$ (6.0 mg, 0.0132 mmol, 10 mol % as CuOTf (90% purity)) was placed in a dried flask (20 mL) under Ar atmosphere and to this flask was added a solution of toluene azeotroped ligand **6e** (17.0 mg, 0.397 mmol, 15 mol %) in toluene (2 mL×2) via a canula. The mixture was stirred at 50 °C for 5 h and then to the blue-green solution was added a solution of toluene azeotroped **5** (Ar=Xy) (77.0 mg, 0.264 mmol) in toluene (2 mL×2) via a canula. The reaction mixture was stirred at 50 °C for 5 h, quenched with a mixture of saturated aqueous $NH_4Cl$ solution (2 mL) and aqueous $NH_4OH$ solution (10 mL), and the separated aqueous layer was extracted with ether (10 mL). The aqueous layer was further extracted with $CH_2Cl_2$ (5 mL×2). The combined organic layer was washed with brine (10 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=3/1) to afford (1*R*,5*R*)-1-(2,4-dimethylphenylsulfonyl)bicyclo[3.1.0]hexan-2-one **4** (Ar=Xy) (98.0 mg, 97%, 81% ee) as a white solid.

Enantiomeric excess (ee) was determined by HPLC (254 nm); DAICEL CHIRALPAK AS-H (0.46 cm ϕ×25 cm; hexane/2-propanol=4/1; flow rate=5 mL $min^{-1}$); retention time: 89 min for **4** (Ar=Xy), 86 min for ***ent*-4** (Ar=Xy).

Mp=98–99 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{27}$ −48.5 (*c* 1.00, $CHCl_3$, >99% ee); IR (KBr) $\nu_{max}$: 1686, 1035, 967, 810 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.88 (d, *J*=8.1 Hz, 1H), 7.09 (d, *J*=8.1 Hz, 1H), 7.03 (s, 1H), 2.96–2.90 (m, 1H), 2.58 (s, 3H), 2.34–2.23 (m, 4H, including $\delta$=2.30, s, 3H), 2.21–2.09 (m, 3H), 2.02–1.90 (m, 1H), 1.52 (dd, *J*=5.5, 5.5 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=203.4, 144.3, 138.1, 133.2, 131.5, 126.9, 53.5, 33.6, 30.7, 21.4, 20.8, 20.4, 20.2; HRMS (FAB): *m*/*z* calcd for $C_{14}H_{16}O_3S$+H 265.0898, found 265.0890.

**4.1.10. (1*R*,2*R*)-[2-(1-Naphthalenesulfonyl)-3-oxocyclopentyl]acetonitrile (3 (Ar=Np)).** To a solution of **4** (Ar=Np) (1.36 g, 4.76 mmol) in DMSO (40 mL) was added sodium cyanide (257.0 mg, 5.24 mmol) and the reaction mixture was stirred at 80 °C for 5 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 mL), and extracted with ethyl acetate (40 mL×2). The combined organic layer was washed with brine (8 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **3** (Ar=Np) (1.41 g, 95%) as a white solid.

Mp=137–138 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{23}$ +20.0 (*c* 1.00, $CHCl_3$); IR (KBr) $\nu_{max}$: 1737, 1302, 1124, 763 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=8.62 (d, *J*=8.6 Hz, 1H), 8.27 (d, *J*=7.3 Hz, 1H), 8.25 (d, *J*=7.3 Hz, 1H), 8.01 (d, *J*=8.3 Hz, 1H), 7.80–7.58 (m, 3H), 3.92 (d, *J*=9.8 Hz, 1H), 3.50–3.32 (m, 1H), 3.08 (dd, *J*=4.9, 17.1 Hz, 1H), 2.88 (dd, *J*=3.9, 17.1 Hz, 1H), 2.60–2.30 (m, 3H), 1.90–1.72 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=202.4, 136.2, 134.2, 134.1, 132.4, 131.8, 129.3, 127.2, 124.3, 123.0, 116.7, 70.9, 38.6, 34.4, 25.7, 22.5, 21.9; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{15}NO_3S$+H 314.0851, found 314.0857.

**4.1.11. (1*R*,2*R*)-[2-(2,4-Dimethylphenylsulfonyl)-3-oxocyclopentyl]acetonitrile (3 (Ar=Xy)).** To a solution of **4** (Ar=Xy) (1.12 g, 4.24 mmol) in DMSO (40 mL) was added sodium cyanide (229.0 mg, 4.66 mmol) and the reaction mixture was stirred at 80 °C for 5 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with ethyl acetate (40 mL×2). The combined organic layer was washed with brine (6 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **3** (Ar=Xy) (740.0 mg, 60%) as a white solid.

Mp=89–90 °C ($CH_2Cl_2$/hexane); $[\alpha]_D^{23}$ −23.5 (*c* 1.14, $CHCl_3$); IR (KBr) $\nu_{max}$: 1758, 1407, 827, 742, 607 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.79 (d, *J*=8.1 Hz, 1H), 7.18 (d, *J*=8.1 Hz, 1H), 7.13 (s, 1H), 3.69 (d, *J*=9.8 Hz, 1H), 3.40–3.18 (m, 1H), 2.97 (dd, *J*=3.7, 17.1 Hz, 1H), 2.81 (dd, *J*=1.2, 17.1 Hz, 1H), 2.62 (s, 3H), 3.02–2.30 (m, 6H, including $\delta$=2.41, s, 3H), 1.85–1.75 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=203.9, 145.5, 138.2, 133.5, 132.7, 131.4, 127.2, 116.8, 70.8, 38.6, 34.1, 25.6, 22.2, 21.4, 20.3; HRMS (FAB): *m*/*z* calcd for $C_{15}H_{17}NO_3S$+H 292.1007, found 292.1009.

**4.1.12. (*R*)-(3-Oxocyclopentyl)acetonitrile (16).** To a $SmI_2$ solution in THF, which was prepared from samarium (1.33 g, 8.87 mmol) and 1,2-diiodoethane (1.24 g, 4.43 mmol) in THF (10 mL), was added methanol (1 mL), and the solution was cooled to −78 °C. To this cooled solution was added a solution of **13** (536.0 mg, 1.77 mmol) in THF (3 mL) via a canula, and the reaction mixture was stirred at the same temperature for 5 min. The reaction was quenched by introducing air into the solution, and to the resultant solution was added saturated aqueous $NH_4Cl$ solution (10 mL) and extracted with ether (4 mL×2). The combined organic layer was washed with brine (6 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography

(hexane/ethyl acetate=2/1) to afford **16** (135.0 mg, 59%) as a colorless oil.

$[\alpha]_D^{22}$ −70.1 (*c* 1.20, $CHCl_3$); IR (neat) $\nu_{max}$: 1744, 1462, 1164 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=2.56–2.10 (m, 7H), 1.98–1.92 (m, 1H), 1.73–1.66 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=215.9, 117.6, 43.4, 37.9, 33.1, 28.3, 22.2; HRMS (FAB): *m/z* calcd for $C_7H_9NO$+Na 146.0582, found 146.0582.

According to the above procedure, **16** was also obtained from **3** (Ar=Np, Xy) in 48% and 51% yields, respectively.

$[\alpha]_D^{22}$ −70.1 (*c* 1.20, $CHCl_3$) (from **3** (Ar=Np)).

$[\alpha]_D^{23}$ −70.0 (*c* 1.20, $CHCl_3$) (from **3** (Ar=Xy)).

**4.1.13. (1*R*,2*RS*)-[2-(1-Naphthalenesulfonyl)-3-oxo-2-(2-propynyl)cyclopentyl]acetonitrile (17c (Ar=Np)) and (*R*)-[2-(1-naphthalenesulfonyl)-3-(2-propynyloxy)-2-cyclopentenyl]acetonitrile (17o (Ar=Np)).** To a solution of **3** (Ar=Np) (200.0 mg, 0.638 mmol) in DMF (6 mL) were added potassium carbonate (132.0 mg, 0.957 mmol), sodium iodide (286.0 mg, 1.91 mmol), and propargyl bromide (0.170 mL, 1.91 mmol) successively, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (10 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (1 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **17c** (Ar=Np) (161.0 mg, 75%, a mixture of diastereomers, dr=11/1) as a white solid and **17o** (Ar=Np) as a yellow oil (45.0 mg, 21%).

Compound **17c** (Ar=Np): IR (KBr) $\nu_{max}$: 2250, 1681, 809, 771 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): major product: $\delta$=8.78 (d, *J*=8.5 Hz, 1H), 8.22 (d, *J*=7.8 Hz, 1H), 8.14 (d, *J*=7.6 Hz, 1H), 7.96 (d, *J*=7.8 Hz, 1H), 7.69 (dd, *J*=7.6, 8.5 Hz, 1H), 7.62 (dd, *J*=7.8, 8.5 Hz, 1H), 7.59 (dd, *J*=7.8, 8.5 Hz, 1H), 3.70–3.58 (m, 1H), 3.10–2.90 (m, 2H), 2.83 (dd, *J*=1.5, 16.3 Hz, 1H), 2.69 (dd, *J*=1.5, 16.3 Hz, 1H), 2.60–2.40 (m, 3H), 2.10–1.90 (m, 2H); minor product: $\delta$=8.78 (d, *J*=8.5 Hz, 1H), 8.22 (d, *J*=7.8 Hz, 1H), 8.14 (d, *J*=7.6 Hz, 1H), 8.00 (d, *J*=7.8 Hz, 1H), 7.69 (dd, *J*=7.6, 8.5 Hz, 1H), 7.62 (dd, *J*=7.8, 8.5 Hz, 1H), 7.59 (dd, *J*=7.8, 8.5 Hz, 1H), 3.70–3.58 (m, 1H), 3.10–2.90 (m, 2H), 2.83 (dd, *J*=1.5, 16.3 Hz, 1H), 2.69 (dd, *J*=1.5, 16.3 Hz, 1H), 2.60–2.40 (m, 3H), 2.10–1.90 (m, 2H); HRMS (FAB): *m/z* calcd for $C_{20}H_{17}NO_3S$+H 352.1007, found 352.0970.

Compound **17o** (Ar=Np): $[\alpha]_D^{27}$ +10.1 (*c* 1.30, $CHCl_3$); IR (neat) $\nu_{max}$: 2248, 866, 736 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=8.69 (d, *J*=8.5 Hz, 1H), 8.34 (d, *J*=7.3 Hz, 1H), 8.09 (d, *J*=8.0 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 1H), 7.67 (dd, *J*=8.0, 8.5 Hz, 1H), 7.62 (dd, *J*=7.3, 7.8 Hz, 1H), 7.59 (dd, *J*=7.8, 8.0 Hz, 1H), 4.52 (dd, *J*=2.2, 16.3 Hz, 1H), 4.46 (dd, *J*=2.2, 16.3 Hz, 1H), 3.32–3.22 (m, 1H), 2.93 (dd, *J*=3.7, 16.8 Hz, 2H), 2.75–2.62 (m, 2H), 2.43 (dd, *J*=2.2, 2.2 Hz, 1H), 2.29–2.18 (m, 1H), 1.94–1.82 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=166.6, 136.3, 134.5, 134.0, 129.7, 128.9, 128.8, 128.1, 126.7, 124.3, 124.1, 118.2, 114.3, 76.8, 76.6, 58.1, 39.9, 29.0, 25.5, 23.4; HRMS (FAB): *m/z* calcd for $C_{20}H_{17}NO_3S$+H 352.1007, found 352.1008.

**4.1.14. (1*R*,2*RS*)-[2-(2,4-Dimethylphenylsulfonyl)-3-oxo-2-(2-propynyl)cyclopentyl]acetonitrile (17c (Ar=Xy)) and (*R*)-[2-(2,4-dimethylphenylsulfonyl)-3-(2-propynyloxy)-2-cyclopentenyl]acetonitrile (17o (Ar=Xy)).** To a solution of **3** (Ar=Xy) (200.0 mg, 0.686 mmol) in DMF (6 mL) were added potassium carbonate (142.0 mg, 1.02 mmol), sodium iodide (307.0 mg, 2.05 mmol), and propargyl bromide (0.182 mL, 2.05 mmol) successively, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (10 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (1 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **17c** (Ar=Xy) (95.0 mg, 44%, a mixture of diastereomers, dr=7/1) as a white solid and **17o** (Ar=Xy) (112.0 mg, 52%) as a yellow oil.

Compound **17c** (Ar=Xy): IR (KBr) $\nu_{max}$: 2263, 1661, 822, 767 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): major product: $\delta$=7.63 (d, *J*=8.0 Hz, 1H), 7.17 (d, *J*=8.0 Hz, 1H), 7.13 (s, 1H), 3.66–3.52 (m, 1H), 3.10–2.75 (m, 3H, including $\delta$=2.83, dd, *J*=2.7, 16.5 Hz, 1H), 2.64–2.45 (m, 8H, including $\delta$=2.50, s, 3H), 2.41 (s, 3H), 2.10–1.90 (m, 1H); minor product: $\delta$=7.56 (d, *J*=8.3 Hz, 1H), 7.16 (d, *J*=8.3 Hz, 1H), 7.13 (s, 1H), 3.66–3.52 (m, 1H), 3.10–2.75 (m, 3H, including $\delta$=2.76, dd, *J*=2.4, 16.5 Hz, 1H), 2.66–2.45 (m, 8H, including $\delta$=2.53, s, 3H), 2.41 (s, 3H), 2.10–1.90 (m, 1H); HRMS (FAB): *m/z* calcd for $C_{18}H_{19}NO_3S$+H 330.1164, found 330.1177.

Compound **17o** (Ar=Xy): $[\alpha]_D^{23}$ −9.82 (*c* 1.15, $CHCl_3$); IR (neat) $\nu_{max}$: 2240, 854, 740 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=7.89 (d, *J*=8.0 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 1H), 7.08 (s, 1H), 4.53 (dd, *J*=2.4, 16.0 Hz, 1H), 4.48 (dd, *J*=2.4, 16.0 Hz, 1H), 3.30–3.20 (m, 1H), 3.02–2.85 (m, 1H), 2.80 (dd, *J*=3.7, 14.6 Hz, 2H), 2.72 (dddd, *J*=3.7, 3.7, 7.1, 10.0 Hz, 1H), 2.67–2.55 (m, 4H, including $\delta$=2.58, s, 3H), 2.52 (dd, *J*=2.4, 2.4 Hz, 1H), 2.37 (s, 3H), 1.90 (dddd, *J*=3.7, 7.8, 9.0, 10.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=165.8, 143.8, 137.9, 136.5, 133.0, 129.5, 126.6, 118.2, 114.4, 76.8 (6), 76.8 (2), 58.0, 39.8, 29.0, 25.6, 23.3, 21.2, 19.9; HRMS (FAB): *m/z* calcd for $C_{18}H_{19}NO_3S$+H 330.1164, found 330.1171.

**4.1.15. (1*R*,2*RS*)-[2-(1-Naphthalenesulfonyl)-3-oxo-2-(2-pentynyl)cyclopentyl]acetonitrile (18c) and (*R*)-[2-(1-naphthalenesulfonyl)-3-(2-pentynyloxy)-2-cyclopentenyl]-acetonitrile (18o).** To a solution of **3** (Ar=Np) (564.0 mg, 1.80 mmol) in DMF (20 mL) were added potassium carbonate (373.0 mg, 2.70 mmol), sodium iodide (809.0 mg, 5.40 mmol), and 1-bromo-2-pentyne (0.533 mL, 5.40 mmol) successively, and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (30 mL) and extracted with ether (30 mL×2). The combined organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford **18c** (399.0 mg, 59%, a mixture of diastereomers,

dr=6/1) as a white solid and **18o** (243.0 mg, 36%) as a yellow oil.

Compound **18c**: IR (KBr) $\nu_{max}$: 2921, 1662, 1508, 1309, 1123, 808, 770 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): major product: $\delta$=8.79 (d, $J$=8.8 Hz, 1H), 8.20 (d, $J$=8.1 Hz, 1H), 8.13 (d, $J$=7.6 Hz, 1H), 7.95 (d, $J$=7.8 Hz, 1H), 7.66 (dd, $J$=7.6, 8.8 Hz, 1H), 7.62 (dd, $J$=7.6, 8.1 Hz, 1H), 7.60 (dd, $J$=7.6, 7.8 Hz, 1H), 3.67–3.56 (m, 1H), 3.08–2.85 (m, 2H), 2.81 (dd, $J$=2.4, 16.1 Hz, 1H), 2.65 (dd, $J$=2.2, 16.1 Hz, 1H), 2.58–2.40 (m, 3H), 2.10–1.70 (m, 3H), 1.01 (t, $J$=7.3 Hz, 3H); minor product: $\delta$=8.79 (d, $J$=8.8 Hz, 1H), 8.20 (d, $J$=8.1 Hz, 1H), 8.13 (d, $J$=7.6 Hz, 1H), 8.00 (d, $J$=7.8 Hz, 1H), 7.66 (dd, $J$=7.6, 8.8 Hz, 1H), 7.62 (dd, $J$=7.6, 8.1 Hz, 1H), 7.60 (dd, $J$=7.6, 7.8 Hz, 1H), 3.67–3.56 (m, 1H), 3.08–2.85 (m, 2H), 2.81 (dd, $J$=2.4, 16.1 Hz, 1H), 2.65 (dd, $J$=2.2, 16.1 Hz, 1H), 2.58–2.40 (m, 3H), 2.10–1.70 (m, 3H), 1.00 (t, $J$=7.3 Hz, 3H); HRMS (FAB): $m/z$ calcd for $C_{22}H_{21}NO_3S$+H 380.1320, found 380.1316.

Compound **18o**: $[\alpha]_D^{26}$ −17.6 ($c$ 1.00, $CHCl_3$); IR (neat) $\nu_{max}$: 2934, 1507, 1349, 1122, 1021, 928, 776 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=8.73 (d, $J$=8.3 Hz, 1H), 8.33 (d, $J$=7.3 Hz, 1H), 8.07 (d, $J$=8.3 Hz, 1H), 7.91 (d, $J$=7.9 Hz, 1H), 7.65 (dd, $J$=7.3, 8.6 Hz, 1H), 7.57 (dd, $J$=8.3, 8.6 Hz, 1H), 7.55 (dd, $J$=7.9, 8.3 Hz, 1H), 4.48 (dt, $J$=15.6, 2.0 Hz, 1H), 4.43 (dt, $J$=15.6, 2.1 Hz, 1H), 3.70–3.20 (m, 1H), 2.95–2.80 (m, 2H, including $\delta$=2.82, dd, $J$=3.7, 16.1 Hz, 1H), 2.75–2.60 (m, 2H), 2.30–2.20 (m, 3H), 1.95–1.80 (m, 1H), 1.02 (t, $J$=7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$=167.5, 136.7, 134.5, 134.1, 129.8, 129.0, 128.9, 128.1, 126.7, 124.6, 124.2, 118.4, 113.6, 91.0, 72.7, 59.1, 40.0, 29.2, 25.7, 23.5, 13.3, 12.3; HRMS (FAB): $m/z$ calcd for $C_{22}H_{21}NO_3S$+H 380.1320, found 380.1346.

**4.1.16. (1*R*,2*R*)-[2-(1-Naphthalenesulfonyl)-3-oxocyclopentyl]acetonitrile (3 (Ar=Np)).** To a solution of **18o** (100.0 mg, 0.264 mmol) in 5% $H_2O$/MeOH (methanol including 5% $H_2O$, 3.0 mL) was added PPTS (10.0 mg, 0.026 mmol) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (5 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **3** (Ar=Np) (81.0 mg, 98%) as a white solid.

**4.1.17. (1*R*,2*RS*)-[3-Oxo-2-(2-pentynyl)cyclopentyl]acetonitrile (19).** To a suspension of samarium chip (402.0 mg, 2.68 mmol) in THF (3.0 mL) was added a solution of 1,2-diiodoethane (377 mg, 1.34 mmol) in THF (2 mL) via a canula at room temperature, and the reaction mixture was stirred at this temperature for 2 h. To the resultant $SmI_2$ solution in THF was added methanol (0.4 mL) at −78 °C, and then a solution of **18c** (203.0 mg, 0.535 mmol) in THF (2 mL). The reaction mixture was stirred at this temperature for 5 min. After air was bubbled into the solution, the reaction was quenched with saturated aqueous $NH_4Cl$ solution (5 mL) and extracted with ether (5 mL×2). The combined organic layer was washed with brine (5 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **19** (101.0 mg, 100%, a mixture of diastereomers, dr=4/1) as a colorless oil.

IR (neat) $\nu_{max}$: 1748, 1560, 1462, 1324, 1154 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): major product: $\delta$=2.83 (dd, $J$=4.4, 17.1 Hz, 1H), 2.70 (dd, $J$=6.8, 17.1 Hz, 1H), 2.61 (ddt, $J$=4.4, 17.1, 2.4 Hz, 1H), 2.57–1.99 (m, 8H), 1.78–1.68 (m, 1H), 1.09 (t, $J$=7.6 Hz, 3H); minor product: $\delta$=2.83 (dd, $J$=4.4, 17.1 Hz, 1H), 2.66 (dd, $J$=7.1, 17.1 Hz, 1H), 2.61 (ddt, $J$=4.4, 17.1, 2.4 Hz, 1H), 2.57–1.99 (m, 8H), 1.78–1.68 (m, 1H), 1.10 (t, $J$=7.6 Hz, 3H); HRMS (FAB): $m/z$ calcd for $C_{12}H_{15}NO$+H 190.1232, found 190.1236.

**4.1.18. (1*R*,2*RS*,*Z*)-[3-Oxo-2-(2-pentenyl)cyclopentyl]acetonitrile (20).** A mixture of **19** (57.0 mg, 0.301 mmol, a mixture of diastereomers) and a catalytic amount of Lindlar's catalyst in MeOH (3 mL) was stirred under an atmosphere of hydrogen. After 3 h, the mixture was filtered through Celite, and the residue was washed with ether. The combined filtrate was concentrated under reduced pressure, and the resulting oil was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **20** (52.0 mg, 90%, a mixture of diastereomers at the C-2 position) as a colorless oil.

IR (neat) $\nu_{max}$: 1742, 1652, 1464, 1288, 1154 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): major product: $\delta$=5.60–5.47 (m, 1H), 5.31–5.21 (m, 1H), 2.70 (dd, $J$=4.4, 17.1 Hz, 1H), 2.51–1.97 (m, 10H), 1.75–1.61 (m, 1H), 0.96 (t, $J$=7.6 Hz, 3H); minor product: $\delta$=5.60–5.47 (m, 1H), 5.31–5.21 (m, 1H), 2.66 (dd, $J$=4.4, 17.1 Hz, 1H), 2.51–1.97 (m, 10H), 1.75–1.61 (m, 1H), 0.97 (t, $J$=7.5 Hz, 3H); HRMS (FAB): $m/z$ calcd for $C_{12}H_{17}NO$+H 192.1388, found 192.1397.

**4.1.19. (−)-Methyl jasmonate.** To a solution of **20** (30.0 mg, 0.157 mmol, a mixture of diastereomers at C-2 position) in ethylene glycol (2 mL) was added KOH (35.0 mg, 0.627 mmol), and the mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the reaction mixture was quenched with water (2 mL) and extracted with $CH_2Cl_2$ (2 mL×3). The aqueous layer was acidified with 2 M HCl (1 mL) and was extracted with $CH_2Cl_2$ (2 mL×3). The combined organic layer was washed with brine (1 mL), dried over $Na_2SO_4$, and evaporated. The residue was dissolved in acetone (3 mL), and to this solution were added potassium carbonate (32.0 mg, 0.235 mmol) and methyl iodide (0.029 mL, 0.471 mmol). The reaction mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution (2 mL) and extracted with ether (3 mL×2). The combined organic layer was washed with brine (1 mL), dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford (−)-methyl jasmonate (35.0 mg, 88%, two steps) as a colorless oil.

$[\alpha]_D^{23}$ −90.2 ($c$ 1.03, MeOH); IR (neat) $\nu_{max}$: 1738, 1438, 1198, 1164 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$=5.48–5.41 (m, 1H), 5.29–5.22 (m, 1H), 3.69 (s, 3H), 2.74–2.67 (m, 1H), 2.42–2.01 (m, 9H), 1.89–1.87 (m, 1H), 1.51–1.43 (m, 1H), 0.95 (t, $J$=7.3 Hz, 3H); $^{13}C$ NMR (100 MHz,

$CDCl_3$): $\delta$=219.0, 172.6, 134.1, 124.9, 54.1, 51.6, 38.8, 38.1, 37.8, 27.2, 25.6, 20.6, 14.1; HRMS (FAB): *m/z* calcd for $C_{13}H_{20}O_3$+H 225.1491, found 225.1465.

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# A practical synthesis of *N*-aryl-substituted oxazolidinone-containing ketone catalysts for asymmetric epoxidation

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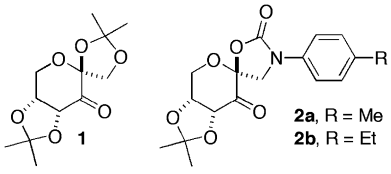
**Abstract**—*N*-Aryl-substituted oxazolidinone-containing ketone catalysts for the asymmetric epoxidation of olefins can be efficiently prepared from D-glucose and anilines.

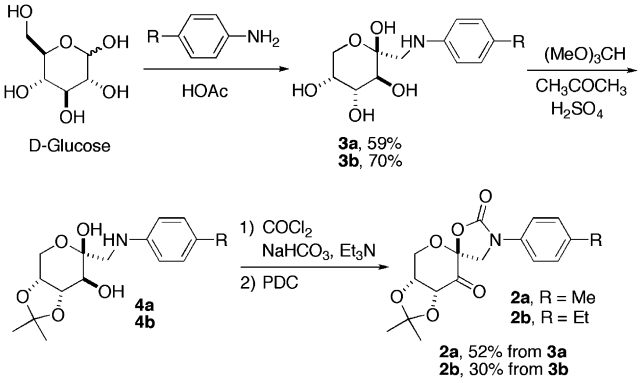

## 1. Introduction

Dioxiranes generated in situ from chiral ketones are effective for the asymmetric epoxidation of olefins.[1] In our earlier studies, we have shown that fructose-derived ketone **1** gives high ee's for trans- and trisubstituted olefins (Scheme 1).[2] Subsequently, we have found that *N*-aryl substituted oxazolidinone-containing ketones **2a** and **2b**, readily prepared from D-glucose and *p*-toluidine or 4-ethylaniline, provide high ee's for substrates such as cis-olefins,[3] styrenes,[4] and certain trisubstituted and tetrasubstituted olefins,[5] which are not effective with ketone **1**. While our original procedure for the synthesis of ketone **2** is suitable for small scale, operational drawbacks such as column chromatography purification make large-scale ketone synthesis less convenient (Scheme 2). Considering that these ketone catalysts could potentially be useful, efforts have been made to further improve their synthesis so that large quantities of ketone catalysts can be readily obtained.




**Scheme 1**.

The original and improved syntheses of ketones **2a**[3a] and **2b**[4] are outlined in Schemes 2 and 3, respectively. In the original procedure, the ketalization of aminoalcohol **3** was achieved with $(MeO)_3CH$ and $H_2SO_4$ in acetone. Aminodiol **4** was isolated as an oil after neutralization with $NH_4OH$. Extensive vacuum pumping of compound **4** is required to remove all of the water contained in ammonium hydroxide, which is harmful to the phosgene cyclization. In addition, the isolated compound (**4**) is contaminated with small amounts of impurities from the ketalization reaction (amounts of impurities are highly dependent on how well the reaction is monitored). Consequently, column chromatography is required after phosgene cyclization to ensure product purity, which is highly undesirable for a large-scale operation. However, it was observed that a large amount of white solid precipitated during the ketalization, and the white solid was found to be hydrogen sulfate salt **5**, which could be obtained in good yield by simple filtration. The impurity previously encountered could easily be removed by washing with ether. It was also found that using the less expensive dimethoxypropane (DMP) in place of $HC(OMe)_3$ further improved the ketalization and caused **5** to efficiently crystallize in the




**Scheme 2**. Original syntheses of ketones **2a** and **2b**.

*Keywords*: Asymmetric epoxidation; Chiral dioxirane; Chiral ketone.
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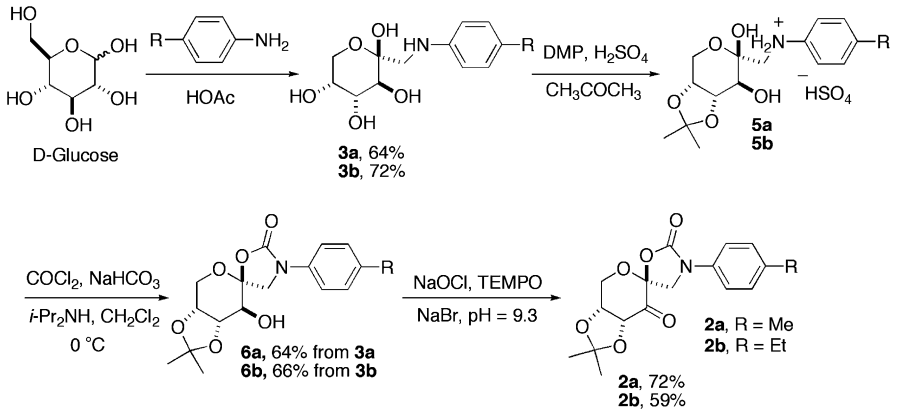
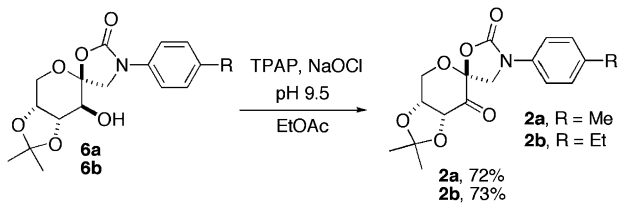



**Scheme 3**. Improved syntheses of ketones **2a** and **2b**.

reaction mixture. Therefore, the isolation of salt **5** instead of oil **4** is highly beneficial.

Salt **5** was then directly used for neutralization and phosgene cyclization. Subjecting salt **5** to the previous reaction conditions ($NaHCO_3$, phosgene, followed by $Et_3N$)[4] resulted in low yield. However, the reaction was much cleaner if additional base such as diisopropylamine was added.[6] Diisopropylamine could possibly act as a proton shuttle between the insoluble salt **5** and solid $NaHCO_3$. The formed oxazolidinone **6** can be isolated by recrystallization or can be used directly in the oxidation step without isolation.

In the previous procedure, the oxidation was accomplished using PDC as oxidizing agent. To further improve this step, various other oxidation methods, such as $RuCl_3 \cdot xH_2O$–$NaIO_4$,[7a] $Py \cdot SO_3$–DMSO,[7b] $Ac_2O$–DMSO,[7c] TEMPO–Oxone,[7d] and TEMPO–bleach[7e] were briefly investigated. Among these oxidation methods, TEMPO–bleach system was found to be the best choice overall. After much experimentation, it was found that a catalytic amount of TEMPO (1.5%) with bleach as the primary oxidant yielded ketone **2** in good yield after recrystallization of the final product. It was found that the choice of solvent and reaction pH are very important for this transformation.[8] The oxidation proceeded efficiently at pH 9.3 in a mixture of $CH_2Cl_2$ and toluene (5:1). Finally, a similar TPAP–bleach oxidation procedure was also found to yield ketone **2** in good yield and purity (Scheme 4).[9] Catalysts prepared by the improved synthetic pathway were found to give comparable epoxidation results to ketones prepared by the original sequence using Oxone as oxidant.




**Scheme 4**.

In summary, we report a practical synthesis of *N*-aryl-substituted oxazolidinone-containing ketone catalysts for asymmetric epoxidation of olefins from D-glucose and anilines in four steps. The process described is operationally simpler when compared to the original procedure and can easily produce the desired ketone catalysts in large quantities.

## 2. Experimental

### 2.1. Synthesis of ketone 2a

To a mixture of D-glucose (270.0 g, 1.5 mol), *p*-toluidine (192.9 g, 1.8 mol), and water (51.4 mL) was added HOAc (1.62 g, 0.027 mol). The mixture was rotated on a rotary evaporator (sealed without vacuum) at 90–93 °C for 2 h (during this time the product precipitated from the reaction mixture). After cooling to room temperature, ether–ethanol (3:1, 1600 mL) was added. Upon stirring at room temperature for an additional 2 h, the mixture was filtered, washed with ether (2×400 mL), ether–ethanol (5:1, 420 mL), ether (2×400 mL), and dried under vacuum to give aminoalcohol **3a** as a white solid (259.4 g, 64%).[10]

To a mixture of aminoalcohol **3a** (161.4 g, 0.6 mol) and 2,2-dimethoxypropane (222.0 mL, 1.8 mol) in acetone (1400 mL) with stirring (using mechanical stirrer) under Ar at 0 °C was added concd $H_2SO_4$ (48.0 mL, 0.86 mol) via addition funnel over 45 min. After stirring at 0 °C for an additional 1.5 h (the white solid product precipitated in the reaction mixture over the course of the reaction), ether (150 mL) was added. The mixture was filtered, washed with acetone–ether (1:4, 3×350 mL), ether (350 mL), and dried under vacuum for 2–3 h to give salt **5a** as a white solid (220.2 g, 90%) (Compound **5a** should be used immediately for the next step. Exhaustive vacuum drying and/or prolonged storage could lead to decomposition). IR (NaCl, film): 3364 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO) $\delta$ 7.15–7.07 (m, 5H), 6.40 (br s, 3H), 4.22 (d, $J$=5.7 Hz, 1H), 4.12–4.02 (m, 2H), 3.87 (d, $J$=13.5 Hz, 1H), 3.47 (d, $J$=7.5 Hz, 1H), 3.44–3.35 (m, 1H), 3.30–3.16 (m, 1H), 2.25 (s, 3H), 1.40 (s, 3H), 1.28 (s, 3H); $^{13}C$ NMR (75 MHz, DMSO) $\delta$ 137.0, 135.9, 130.1, 121.9, 107.9, 95.1, 76.1, 73.0, 70.6, 59.4, 56.5, 28.1, 26.4, 20.7. Anal. Calcd for $C_{16}H_{25}NO_9S$: C, 47.17; H, 6.18; N, 3.44; S, 7.87. Found: C, 47.05; H, 6.04; N, 3.60; S, 8.11.

A mixture of salt **5a** (220.2 g, 0.54 mol) and $NaHCO_3$ (403.2 g, 4.8 mol) in $CH_2Cl_2$ (1000 mL) was stirred (using

mechanical stirrer) under Ar at 0 °C for 1 h. Diisopropylamine (30.3 g, 0.3 mol) was then added. Upon stirring at 0 °C for 30 min, phosgene (20% solution in toluene, 377 mL, 0.71 mol) was added via addition funnel over 5.3 h. After stirring at 0 °C for an additional 1.5 h, the cold bath was removed. The reaction mixture was stirred overnight, filtered, and washed with satd $NaHCO_3$ (200 mL), water (2×200 mL), brine (200 mL), dried ($Na_2SO_4$), filtered, concentrated to about 300 mL, and filtered to give **6a** as white solid (104.5 g). The filtrate was concentrated and recrystallized from hexane–$CH_2Cl_2$ (3:1, 200 mL) to give an additional 24.9 g of **6a** (combined yields, 72%). IR (NaCl, film): 3400, 1761 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.37 (d, $J$=8.4 Hz, 2H), 7.15 (d, $J$=8.4 Hz, 2H), 4.37–4.26 (m, 4H), 4.14 (d, $J$=13.5 Hz, 1H), 3.81–3.78 (m, 2H), 2.91 (s, 1H), 2.32 (s, 3H), 1.57 (s, 3H), 1.40 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 153.1, 135.0, 134.3, 129.7, 118.8, 110.0, 100.9, 76.7, 73.3, 71.7, 62.0, 53.3, 28.4, 26.3, 21.1. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.61; H, 6.16; N, 4.35.

To a mixture of alcohol **6a** (30.2 g, 0.09 mol) and NaBr (9.26 g, 0.09 mol) in $CH_2Cl_2$–toluene (5:1, 360 mL) at 0 °C was added TEMPO (0.215 g, 0.0014 mol). Recently purchased 5% NaOCl (270 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] was added with vigorous stirring (using mechanical stirrer) over 2.5 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C, and the reaction was monitored by GC). The layers of the reaction mixture were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2×100 mL). The combined organic layers were washed with satd $Na_2S_2O_3$ (2×200 mL), water (6×100 mL), dried ($Na_2SO_4$), filtered through a pad of silica gel (40 g), and washed with EtOAc (200 mL). The filtrate was concentrated to ca. 20 mL. Upon addition of hexane (500 mL), the mixture was shaken until the viscous residue solidified and precipitated. Filtration and recrystallization (90 mL, EtOAc and 30 mL, hexane) gave ketone **2a** as an off white solid (21.7 g, 72%). IR (NaCl, film): 1773 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.41 (d, $J$=8.4 Hz, 2H), 7.20 (d, $J$=8.4 Hz, 2H), 4.88 (d, $J$=5.1 Hz, 1H), 4.75 (d, $J$=10.5 Hz, 1H), 4.66–4.62 (m, 2H), 4.27 (d, $J$=13.5 Hz, 1H), 3.76 (d, $J$=10.5 Hz, 1H), 2.35 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 195.1, 151.2, 134.7, 134.5, 129.8, 118.8, 111.1, 99.2, 77.6, 75.6, 61.1, 50.0, 27.3, 26.2, 21.0. Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.75; N, 4.20. Found: C, 61.18; H, 5.86; N, 4.22.

In an another run, alcohol **6a** was used for oxidation directly without isolation described as follows:

A mixture of salt **5a** (186.0 g, 0.45 mol) and $NaHCO_3$ (336.0 g, 4.0 mol) in $CH_2Cl_2$ (1200 mL) was stirred (using mechanical stirrer) under $N_2$ at 0 °C for 1 h. Diisopropylamine (25.3 g, 0.25 mol) was then added. Upon stirring at 0 °C for 10 min, phosgene (20% solution in toluene, 310 mL, 0.58 mol) was added via addition funnel over 5 h. The reaction mixture was warmed to room temperature and stirred overnight, filtered, and washed with $CH_2Cl_2$ (3×200 mL). The filtrate was washed with satd $NaHCO_3$ (700 mL) and water (2×700 mL). The solution was used directly in the next step.

To the above solution was added $CH_2Cl_2$ (500 mL) and NaBr (51.5 g, 0.50 mol). After cooling to 0 °C, TEMPO (1.17 g, 0.0075 mol) was added, followed by freshly purchased 5% NaOCl (1400 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] with vigorous stirring (using mechanical stirrer) over 4 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C, the reaction was monitored by GC). After stirring for an additional 3 h at the same temperature, the layers of the reaction mixture were separated. The organic layers were washed with satd $Na_2S_2O_3$ (3×300 mL), water (5×250 mL), dried ($Na_2SO_4$), filtered through a pad of silica gel ($d$=9.5 cm, $h$=0.6 cm), washed with EtOAc (500 mL), and concentrated to 80–100 mL. Upon addition of hexane (800 mL), the mixture was vigorously shaken until the viscous residue solidified and precipitated. Filtration and recrystallization (250 mL, EtOAc and 200 mL, hexane) gave ketone **2a** as pale yellow solid (80.0 g). The mother liquor was concentrated and recrystallized (200 mL, EtOAc and 70 mL, hexane) to give ketone **2a** as yellow solid (15.0 g) (total 95.0 g, combined yields, 63% over two steps).

### 2.2. Synthesis of ketone 2b

To a mixture of D-glucose (270.0 g, 1.5 mol), 4-ethylaniline (218.1 g, 1.8 mol), and water (51.4 mL) was added HOAc (1.62 g, 0.027 mol). The mixture was rotated on a rotary evaporator (sealed without vacuum) at 90–93 °C for 70 min (during this time the product precipitated from the reaction mixture). After cooling to room temperature, ether–ethanol (3:1, 1600 mL) was added. Upon stirring at room temperature for an additional 2 h, the mixture was filtered, washed with ether (2×400 mL), ether–ethanol (5:1, 420 mL), ether (2×400 mL), and dried under vacuum to give aminoalcohol **3b** as a white solid (303.5 g, 72%).[10]

To a mixture of aminoalcohol **3b** (169.8 g, 0.6 mol) and 2,2-dimethoxypropane (222.0 mL, 1.8 mol) in acetone (1400 mL) while stirring (using mechanical stirrer) under Ar at 0 °C was added concd $H_2SO_4$ (48.0 mL, 0.86 mol) via addition funnel over 45 min. After stirring at 0 °C for an additional 1.5 h (the white solid product precipitated in the reaction mixture over the course of the reaction), ether (400 mL) was added. The mixture was filtered, washed with acetone–ether (1:4, 3×350 mL), ether (350 mL), and dried under vacuum for 2–3 h to give salt **5b** as a white solid (202.1 g, 80%) (Compound **5b** should be used immediately for the next step. Exhaustive vacuum drying and/or prolonged storage could lead to decomposition). IR (NaCl, film): 3349 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO) $\delta$ 8.09 (m, 4H), 7.24 (m, 4H), 4.23 (dd, $J$=5.7, 2.1 Hz, 1H), 4.15–4.01 (m, 2H), 3.90 (d, $J$=13.2 Hz, 1H), 3.49 (d, $J$=7.2 Hz, 1H), 3.43 (d, $J$=12.3 Hz, 1H), 3.27 (d, $J$=12.3 Hz, 1H), 2.58 (q, $J$=7.8 Hz, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 1.16 (t, $J$=7.8 Hz, 3H); $^{13}C$ NMR (75 MHz, DMSO) $\delta$ 143.0, 136.2, 128.9, 121.8, 107.9, 95.2, 76.1, 73.0, 70.6, 59.4, 56.4, 28.1, 27.8, 26.4, 15.7. Anal. Calcd for $C_{17}H_{27}NO_9S$: C, 48.45; H, 6.46; N, 3.32; S, 7.61. Found: C, 48.65; H, 6.60; N, 3.33; S, 7.62.

A mixture of salt **5b** (202.1 g, 0.48 mol) and $NaHCO_3$ (403.2 g, 4.8 mol) in $CH_2Cl_2$ (1000 mL) was stirred (using mechanical stirrer) under Ar at 0 °C for 1 h. Diisopropylamine (30.3 g, 0.30 mol) was then added. Upon stirring at

0 °C for 30 min, phosgene (20% solution in toluene, 377 mL, 0.71 mol) was added via addition funnel over 5.3 h. After stirring at 0 °C for an additional 1.5 h, the cold bath was removed. The reaction mixture stirred overnight, filtered, and washed with satd $NaHCO_3$ (200 mL), water (2×200 mL), brine (200 mL), dried ($Na_2SO_4$), filtered, concentrated to about 300 mL, and filtered to give **6b** as white solid (116.2 g). The filtrate was concentrated and recrystallized from hexane–$CH_2Cl_2$ (3:1, 260 mL) to give an additional 22.6 g of **6b** (combined yields, 83%). IR (NaCl, film): 3400, 1761 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.41 (d, $J$=8.4 Hz, 2H), 7.19 (d, $J$=8.4 Hz, 2H), 4.39–4.26 (m, 4H), 4.15 (d, $J$=13.5 Hz, 1H), 3.83–3.80 (m, 2H), 2.96 (br s, 1H), 2.63 (q, $J$=7.8 Hz, 2H), 1.57 (s, 3H), 1.40 (s, 3H), 1.22 (t, $J$=7.8 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 153.2, 140.5, 135.1, 128.4, 118.8, 109.8, 101.1, 76.4, 73.3, 71.4, 61.8, 53.3, 28.4, 28.2, 26.2, 15.8. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.93; H, 6.65; N, 4.03.

To a mixture of alcohol **6b** (31.4 g, 0.09 mol) and NaBr (9.26 g, 0.09 mol) in $CH_2Cl_2$–toluene (5:1, 360 mL) at 0 °C was added TEMPO (0.215 g, 0.0014 mol). Freshly purchased 5% NaOCl (270 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] was added with vigorous stirring (using mechanical stirrer) over 2.5 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C. The reaction was monitored by GC). The layers of the reaction mixture were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2×100 mL). The combined organic layers were washed with satd $Na_2S_2O_3$ (2×200 mL), water (6×100 mL), dried ($Na_2SO_4$), filtered through a pad of silica gel (40 g), washed with EtOAc (250 mL), and concentrated to ca. 20 mL. Upon addition of hexane (500 mL), the mixture was shaken until the viscous residue solidified and precipitated. Filtration and recrystallization (30 mL, EtOAc and 30 mL, hexane) gave ketone **2b** as an off white solid (18.4 g, 59%). IR (NaCl, film): 1773 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.41 (d, $J$=8.4 Hz, 2H), 7.19 (d, $J$=8.4 Hz, 2H), 4.85 (d, $J$=5.4 Hz, 1H), 4.71 (d, $J$=10.8 Hz, 1H), 4.64–4.56 (m, 2H), 4.23 (d, $J$=13.2 Hz, 1H), 3.72 (d, $J$=10.5 Hz, 1H), 2.61 (q, $J$=7.5 Hz, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.20 (t, $J$=7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 195.0, 151.2, 141.0, 134.6, 128.5, 118.8, 111.0, 99.1, 77.7, 75.5, 61.0, 50.0, 28.3, 27.2, 26.1, 15.7. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.48; H, 6.19; N, 4.06.

In an another run, alcohol **6b** was used for oxidation directly without isolation described as follows:

A mixture of salt **5b** (191.0 g, 0.45 mol) and $NaHCO_3$ (336.0 g, 4.0 mol) in $CH_2Cl_2$ (1200 mL) was stirred (using mechanical stirrer) under $N_2$ at 0 °C for 1 h. Diisopropylamine (25.3 g, 0.25 mol) was then added. Upon stirring at 0 °C for 10 min, phosgene (20% solution in toluene, 310 mL, 0.58 mol) was added via addition funnel over 5 h. The reaction mixture was warmed to room temperature and stirred overnight, filtered, and washed with $CH_2Cl_2$ (3×200 mL). The filtrate was washed with satd $NaHCO_3$ (700 mL) and water (2×700 mL). The solution was used directly for the next step.

To the above solution was added $CH_2Cl_2$ (500 mL) and NaBr (51.5 g, 0.50 mol). Upon cooling to 0 °C, TEMPO (1.17 g, 0.0075 mol) was added, followed by recently purchased 5% NaOCl (1400 mL, adjusted to pH 9.3 by $NaHCO_3$)[11] with vigorous stirring (using mechanical stirrer) over 4 h (during the addition, the internal temperature of the reaction mixture was kept at 4–8 °C, the reaction was monitored by GC). After stirring for an additional 3 h at the same temperature, the layers of the reaction mixture were separated. The organic layers were washed with satd $Na_2S_2O_3$ (3×300 mL), water (5×250 mL), dried ($Na_2SO_4$), filtered through a pad of silica gel ($d$=13.0 cm, $h$=1.4 cm), washed with EtOAc (800 mL), concentrated, and recrystallized (120 mL, EtOAc and 300 mL, hexane) to give ketone **2b** as a pale yellow solid (87.0 g). The mother liquor was concentrated and recrystallized (20 mL, EtOAc and 30 mL, hexane) to give ketone **2b** as brown solid (12.0 g) (total 99.0 g, combined yields, 63% over two steps).

### 2.3. General procedure for TPAP–NaOCl oxidation

To the solution of alcohol **6** (for **6a**: 50.3 g; for **6b**: 52.4 g, 0.15 mol) in EtOAc (375 mL), was added 0.1 M $NaHCO_3$–$Na_2CO_3$ buffer (pH=9.5, 495 mL)[12] followed by TPAP (0.53 g, 0.0015 mol). After stirring at room temperature for 10 min, recently purchased NaOCl (5%, 450 mL) was then added dropwise at rt over 4 h (reaction followed by GC). The mixture was then filtered through Celite and washed with EtOAc until no product came out. After separating the layers, the aqueous phase was extracted with EtOAc (2×150 mL). The combined organic layers were washed with water (2×150 mL), brine (150 mL), dried ($Na_2SO_4$), concentrated, and recrystallized from ethyl acetate–hexane (3:1, 200 mL for **2a**; 1:1, 120 mL for **2b**) to give the ketone **2** as a white solid (35.9 g, 72% for **2a**; 38.0 g, 73% for **2b**).

## Acknowledgements

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6. Other bases such as *tert*-butylamine, pyridine, 2,6-lutidine, imidazole, ammonium hydroxide, and ammonia (gas) were also tested. Among these bases, *tert*-butylamine worked well.
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8. The reaction was examined from pH 9.0 to 12.8 with 1% TEMPO in $CH_2Cl_2$. The optimal conversion was obtained around pH 9.3. Various solvents were also tested for the reaction. The conversions in these solvents (1.5% TEMPO at pH 9.3, for 4 h) are as following: acetone (<1%), EtOAc (6%), EtOAc–dioxane (1:1, v/v) (23%), EtOAc–DME (1:1, v/v) (27%), EtOAc–$CH_3CN$ (1:1, v/v) (67%), EtOAc–$CH_2Cl_2$ (4:1, v/v) (44%), EtOAc–$CH_2Cl_2$ (2:1, v/v) (82%), EtOAc–$CH_2Cl_2$ (1:1, v/v) (94%), $CH_2Cl_2$ (>99%), and $PhCH_3$–$CH_2Cl_2$ (1:5, v/v) (>99%). The amount of solvent can be reduced when $PhCH_3$–$CH_2Cl_2$ (1:5, v/v) (10 mL per gram of substrate) is used when compared to $CH_2Cl_2$ (20 mL per gram of substrate).
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11. NaOCl used was freshly purchased from Alfa (5%). Low conversion was obtained if poor quality NaOCl used. The control on pH of NaOCl solution is also very important for the oxidation. The pH was adjusted to 9.3 by addition of solid $NaHCO_3$ (carefully monitored by pH meter, ~24 mg $NaHCO_3$/mL NaOCl).
12. The buffer was prepared by mixing 0.1 M $NaHCO_3$ and 0.1 M $Na_2CO_3$ until pH 9.5 as monitored by the pH meter.

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# Diastereoselective Michael addition of (*S*)-mandelic acid enolate to 2-arylidene-1,3-diketones: enantioselective diversity-oriented synthesis of densely substituted pyrazoles

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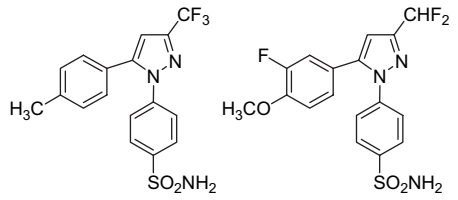
**Abstract**—A diversity-oriented approach to enantiomerically pure densely substituted pyrazoles, α-aryl-α-pyrazolylatrolactic acid and α-aryl-α-pyrazolylacetophenones has been developed. The approach utilises the conjugated addition of the lithium enolate of the (2*S*,5*S*)-*cis*-1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde to several 2-arylidene-1,3-diketones, which proceeds readily to give the corresponding Michael adducts in good yields and diastereoselectivities. The cyclocondensation of the 1,3-diketone moieties present in Michael adducts with several hydrazines leads to enantiomerically pure densely substituted pyrazoles. Subsequent basic hydrolysis of the dioxolanone moiety present in these products leads to enantiomerically pure α-aryl-α-pyrazolylatrolactic acids. Finally, oxidative decarboxylation of these using oxygen, pivalaldehyde and the Co(III)–$Me_2$opba complex as catalyst gives α-aryl-α-pyrazolylacetophenones. In this approach four points of diversity are introduced, one of them is the configuration of the (*S*)-mandelic acid, which acts as an umpoled chiral equivalent of the benzoyl anion.


## 1. Introduction

Substituted pyrazoles constitute an important class of heterocyclic compounds because this ring system is present in numerous compounds of therapeutic importance, including a number of marketed drugs, such as Celecoxib (Celebrex®) or Deracoxib (Fig. 1). These compounds are used with success for the treatment of inflammatory diseases with the advantage they present low ulcerogenic side effects commonly associated with the chronic use of other non-selective non-steroidal anti-inflammatory drugs (NSAIDs).[1] Due to the importance of these pharmacological properties, significant efforts toward the synthesis of this kind of compounds have been carried out in the last years.[2] However, to the best of our knowledge, preparation of optically active substituted pyrazoles has never been reported, despite chiral compounds could be used in pharmacological studies to explore the receptor topology.[3] In this paper we wish to report a general and diversity-oriented approach towards the syntheses of these compounds, including the construction of a stereogenic centre in the side chain.




Celecoxib Deracoxib

**Figure 1**. Some pyrazole-based marketed drugs.

Our approach to the synthesis of densely substituted pyrazoles, i.e., α-aryl-α-pyrazolylacetophenones, is shown in Figure 2. The pyrazole ring can be obtained by a variety of synthetic methods, including the 1,3-dipolar cycloaddition of diazo compounds onto triple bonds and the cyclocondensation of hydrazines with 1,3-difunctionalized compounds. This last procedure is the most commonly used strategy because of the availability of 1,3-difunctionalized compounds, and it is the one we used in our approach. According to this, we disconnected our target molecules into a hydrazine (fragment D) and a chiral 1,3-dicarbonyl component, which can be prepared from a 1,3-diketone (fragment C), an aromatic aldehyde (fragment B), and mandelic acid (fragment A).

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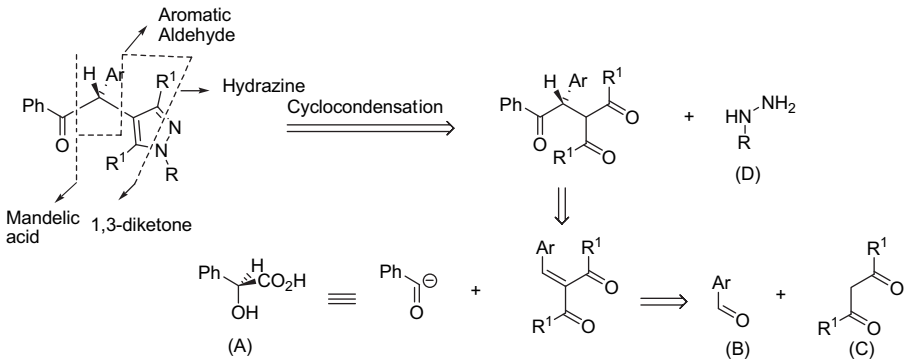



**Figure 2**. Retrosynthetic analysis.

Therefore, up to four points of diversity are possible in this scheme: R, $R^1$, Ar and the configuration of the stereogenic centre, which depends on mandelic acid.

The key step in the preparation of the chiral 1,3-dicarbonyl component is the conjugate addition of the enolate of (*S*)-mandelic acid to a 2-arylidene-1,3-diketone. Recently, we have described a highly diastereoselective Michael reaction of the enolate of (*S*)-(+)-mandelic acid to enones and the transformation of the resulting products into highly enantioenriched 2-substituted-1,4-diketones.[4]

## 2. Results and discussion

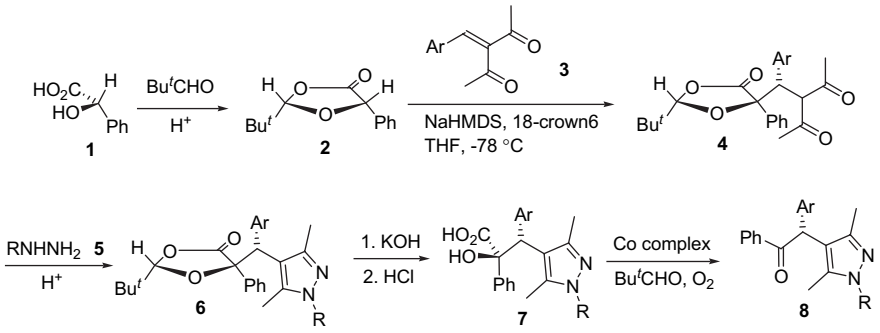
Our synthetic methodology is summarised in Scheme 1. The key step involves a Michael addition of the (*S*)-(+)-mandelic acid enolate to 2-arylidene-1,3-diketones **3**, which are easily prepared from aromatic aldehydes and pentane-2,4-dione via a Knoevenagel reaction.[5] These compounds are excellent Michael acceptors due to the strong anion-stabilising effect of the two carbonyl groups. Although the formation of the mandelic acid enolate leads to loss of chirality at the stereogenic centre, it is possible to regenerate the chiral information if (*S*)-(+)-mandelic acid (**1**) is previously transformed into (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**), according to the principle of self-regeneration of stereocentres,[6] as shown by Seebach[7] and us.[4,8,9]

The initial conditions tested for the Michael addition of **2** to 3-benzylidene-2,4-pentanedione **3a** were identical to those previously established by us for the addition of **2** to simple α,β-unsaturated ketones.[4] Compound **2** was deprotonated with a LDA solution at −78 °C in THF and then Michael acceptor **3a** was added to the resulting enolate solution. However, these conditions provided **4a** only with moderate yield and low diastereoselectivity (Table 1, entry 1). Next, the effect of the enolate aggregation state was examined. In most cases, the use of HMPA as an additive appreciably increases the reactivity as well as substantially modifies the selectivity. However, when 3 equiv of HMPA was used (entry 2) an important drop of the reaction yield was observed. The reaction was also examined in the presence of a crown ether as cation sequestering agent. When we carried out the reaction in the conditions reported recently by Dixon[10] for Michael addition to arylidene malonate esters, using 18-crown-6 and KHMDS as the base, the yield of **4a** was again very low (entry 3). However a change in the order of addition of the reagents brought about a spectacular increase in yield (90%) with a moderately good diastereoselectivity (77:23) (entry 4). Finally, the change of potassium to sodium

**Table 1**. Michael addition of (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**) and 3-benzylidene-2,4-pentanedione **3a** (optimisation of the conditions)

| Entry | Additive | Base | **4a** Yield (%)[a] | **4a** dr[b] |
|---|---|---|---|---|
| 1[c] | None | LDA | 60 | 60:40 |
| 2[c] | HMPA | LDA | 26 | 62:38 |
| 3[d] | 18-Crown-6 | KHMDS | 19 | 80:20 |
| 4[e] | 18-Crown-6 | KHMDS | 90 | 77:23 |
| 5[e] | 18-Crown-6 | NaHMDS | 84 | 94:6 |

[a] Yield of the major adduct after column chromatography.
[b] Determined by $^1$H NMR of the mixture prior purification.
[c] Our early protocol. See Ref. 4.
[d] Dixon's protocol. See Ref. 10.
[e] Our present protocol. See Section 3.




**Scheme 1**. Synthesis of compounds **4**–**8**.

hexamethyldisilazanide as the base increased the diastereoselectivity to 94:6, maintaining a good yield of **4a** (entry 5).

The Michael addition reaction with the enolate of **2** was carried out with several 2-arylidene-1,3-diketones **3** under these optimised conditions. In all cases the corresponding adducts **4** were obtained in good to excellent yields (81–94%) and diastereomeric ratios (from 89:11 to 97:3) (Table 2). It is important to note that the Michael adducts were obtained as only two diastereomers out of the four possible ones attending to the configuration of the two newly created stereogenic centres, one of the diastereomers being strongly predominant. The stereochemical structures of the major Michael adducts **4** were elucidated by NOE experiments. These experiments showed for all major diastereomers **4** a cis-relationship between the *t*-Bu group and the phenyl group from the original (*S*)-mandelic acid. The absolute configuration of the newly formed quaternary carbon atom was then assigned to be *S*, upon the consideration that the absolute configuration of the dioxolanone C-2 carbon atom bearing the *tert*-butyl group in **2** is *S* and remains unaltered from **2** to **4**. Furthermore, in the case of the *p*-chlorophenyl substituted adduct **4b**, the absolute stereochemistry of the major diastereomer was unambiguously determined by single X-ray diffraction (Fig. 3). According to the crystal structure the tertiary chiral carbon in **4b** had the *S* configuration. These results indicate that the major reaction pathway involves the approach of the *Re*-face of the 2-arylidene-1,3-diketone **3** to the *Re*-face of the lithium enolate of **2** (relative topicity *like*), in good agreement with the results reported by Seebach[7] and us[4,8,9] in related reactions.

The second step in our synthetic sequence was the preparation of the pyrazole ring system, which involves the cyclocondensation[11] of the 1,3-diketone moiety present in the Michael adducts **4** with different hydrazines **5**. Reaction of diketones **4a**, **4b** and **4e** with either phenylhydrazine (**5a**), or *p*-nitrophenylhydrazine (**5c**) using concd $H_2SO_4$ as catalyst in ethanol at reflux[11a] afforded pyrazoles **6aa** and **6ac**, **6ba** and **6bc**, **6ea** and **6ec**, respectively, with good yields (Table 3). The same diketones reacted with methylhydrazine (**5b**) at dioxane reflux in the presence of catalytic acetic acid[11b] to give pyrazoles **6ab**, **6bb** and **6eb** with acceptable yields (93–56%).

**Table 2**. Michael reaction of (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**) with 2-arylidene-1,3-diketones **3**

| Entry | **3** (Ar) | **4** (Ar) | **4** Yield (%)[a] | **4** dr[b] |
|---|---|---|---|---|
| 1 | **3a** (Ph) | **4a** (Ph) | 84 | 94:6 |
| 2 | **3b** (*p*-$ClC_6H_4$) | **4b** (*p*-$ClC_6H_4$) | 84 | 91:9 |
| 3 | **3c** (*p*-$BrC_6H_4$) | **4c** (*p*-$BrC_6H_4$) | 81 | 89:11 |
| 4 | **3d** (*p*-$MeC_6H_4$) | **4d** (*p*-$MeC_6H_4$) | 78 | 97:3 |
| 5 | **3e** (*p*-$MeOC_6H_4$) | **4e** (*p*-$MeOC_6H_4$) | 94 | 95:5 |

[a] Yield of the major adduct after column chromatography.
[b] Determined by $^1H$ NMR of the mixture prior purification.

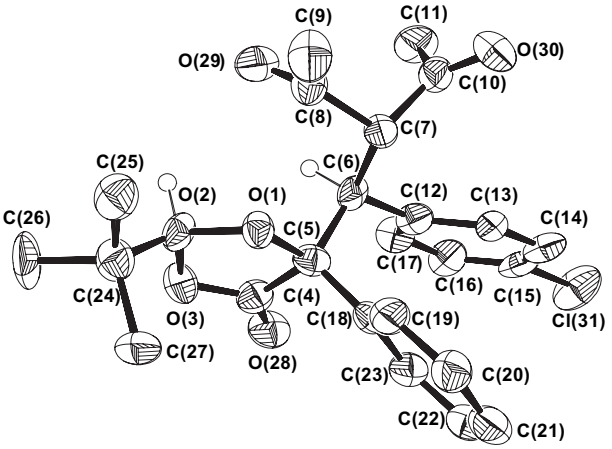



**Figure 3**. ORTEP drawing for compound **4b**.[14]

**Table 3**. Preparation of pyrazoles **6** from 1,3-diketones **4** and hydrazines **5**

| Entry | **4** (Ar) | **5** (R) | Pyrazoles **6** (Yield %) |
|---|---|---|---|
| 1 | **4a** (Ph) | **5a** (Ph) | **6aa** (77) |
| 2 | **4a** (Ph) | **5b** (Me) | **6ab** (93) |
| 3 | **4a** (Ph) | **5c** (*p*-$O_2NC_6H_4$) | **6ac** (74) |
| 4 | **4b** (*p*-$ClC_6H_4$) | **5a** (Ph) | **6ba** (86) |
| 5 | **4b** (*p*-$ClC_6H_4$) | **5b** (Me) | **6bb** (62) |
| 6 | **4b** (*p*-$ClC_6H_4$) | **5c** (*p*-$O_2NC_6H_4$) | **6bc** (74) |
| 7 | **4e** (*p*-$MeOC_6H_4$) | **5a** (Ph) | **6ea** (86) |
| 8 | **4e** (*p*-$MeOC_6H_4$) | **5b** (Me) | **6eb** (56) |
| 9 | **4e** (*p*-$MeOC_6H_4$) | **5c** (*p*-$O_2NC_6H_4$) | **6ec** (56) |

The next step in our synthetic sequence was the cleavage of the 1,3-dioxolan-4-one moiety present in compound **6**, which was achieved upon basic hydrolysis with ethanolic KOH and reprotonation to give the corresponding hydroxy acids, α-aryl-α-pyrazolylatrolactic acids **7**, with good yields (Table 4).

**Table 4**. Hydrolysis of the 1,3-dioxolan-4-one moiety in compounds **6** and oxidative decarboxylation of the hydroxy acid in compounds **7**

| Entry | **6** | **6**,**7**,**8** Ar | **6**,**7**,**8** R | **7** (Yield %) | **8** (Yield %) |
|---|---|---|---|---|---|
| 1 | **6aa** | Ph | Ph | **7aa** (94) | **8aa** (66) |
| 2 | **6ab** | Ph | Me | **7ab** (77) | **8ab** (87) |
| 3 | **6ac** | Ph | *p*-$O_2NC_6H_4$ | **7ac** (73) | **8ac** (—) |
| 4 | **6ba** | *p*-Cl–$C_6H_4$ | Ph | **7ba** (88) | **8ba** (62) |
| 5 | **6bb** | *p*-Cl–$C_6H_4$ | Me | **7bb** (86) | **8bb** (61) |
| 6 | **6ea** | *p*-MeO–$C_6H_4$ | Ph | **7ea** (99) | **8ea** (58) |
| 7 | **6eb** | *p*-MeO–$C_6H_4$ | Me | **7eb** (93) | **8eb** (74) |

Finally, the oxidative decarboxylation of the α-hydroxy acid moiety present in **7** to carbonyl compounds **8** was carried out by using a catalytic system developed in our laboratory that employs oxygen as terminal oxidant in the presence of pivalaldehyde and a catalytic amount of the Co(III)–$Me_2$opba complex (Fig. 4).[12] Under these conditions α-aryl-α-pyrazolylacetophenones **8** were obtained in good yields from α-aryl-α-pyrazolylatrolactic acids **7**, except in the case of the *N*-(*p*-nitrophenyl)pyrazole **7ac** that gave rise to a complex reaction mixture (Table 4).

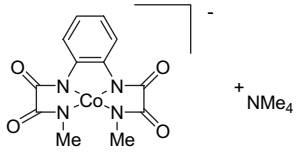



**Figure 4**. Co(III) *ortho*-phenylene-bis(*N*′-methyloxamidate) complex.

In summary, a practical, efficient and diversity-oriented synthesis of enantiomerically pure densely substituted pyrazoles, α-aryl-α-pyrazolylatrolactic acids and α-aryl-α-pyrazolylacetophenones has been developed. The key step in this synthesis is the conjugate addition of the lithium enolate of the (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one to 2-arylidene-1,3-diketones, which proceeds readily to give the corresponding Michael adducts in good yields and diastereoselectivities. The cyclocondensation of the 1,3-diketone moieties present in these adducts with several hydrazines leads to substituted pyrazoles. Subsequent basic hydrolysis of the 1,3-dioxolan-4-one moiety present in these products leads to enantiomerically pure α-aryl-α-pyrazolylatrolactic acids. Finally, oxidative decarboxylation of these using oxygen, pivalaldehyde and the Co(III)–$Me_2$opba complex as catalyst gives α-aryl-α-pyrazolylacetophenones. In this synthetic sequence four points of diversity, including the configuration of the stereogenic centre of the side chain, are introduced. Furthermore, it should be noted that by using other substituted mandelic acids as starting materials,[13] a fifth point of diversity could be introduced (the substituent of the benzoyl group). In this synthetic sequence (*S*)-mandelic acid acts as an umpoled chiral equivalent of the benzoyl carbanion determining the configuration of the stereogenic centre of the side chain.

## 3. Experimental

### 3.1. General

All melting points are uncorrected. Column chromatography was performed on silica gel (Merck, silica gel 60, 230–400 mesh). Commercial reagents and solvents were of analytical grade or were purified by standard procedures, prior to use. All reactions involving air or moisture sensitive materials were carried out under nitrogen atmosphere. Optical rotations were determined on a Perkin–Elmer 243 polarimeter. NMR spectra were recorded on a Bruker Advance 300 DPX spectrometer ($^1$H at 300 MHz and $^{13}$C at 75 MHz) or a Varian Unity 400 ($^1$H at 400 MHz and $^{13}$C at 100 MHz) and referenced to TMS as internal standard. The carbon type was determined by DEPT experiments. In the case of some pyrazoles **6** the $^{13}$C NMR was registered in DMSO-$d_6$ at 70 °C in order to observe all the expected signals. Mass spectra were run by electron impact at 70 eV, by chemical ionisation using methane as ionising gas, or FAB+ on a VG Autospec spectrometer (VG Analytical, Micromass Instruments). All new compounds were determined >95% pure by $^1$H NMR spectroscopy.

### 3.2. General procedure for the preparation of Michael adducts 4

A solution of 18-crown-6 (0.8 mmol) in dry THF (0.8 mL) was added to a solution of NaHMDS (1.0 mmol) in dry THF (10 mL) at −78 °C. The reaction mixture was then stirred for 15 min at −78 °C before a solution of (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolanone (**2**)[7a] (0.8 mmol) in dry THF (4.5 mL) was dropwise added. Stirring was maintained for 30 min at −78 °C before a solution of 2-arylidene-1,3-diketone **3** (0.67 mmol) in dry THF (5 mL) was added. The reaction was kept at this temperature until consumption of the 2-arylidene-1,3-diketone **3** as indicated by TLC. The reaction was then quenched with glacial acetic acid (80 μL, 2 mmol) via syringe at −78 °C. Once the mixture reached room temperature, water (15 mL) was added and extracted with diethyl ether (3×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was flash chromatographed on silica gel (hexane–diethyl ether) to afford adduct **4**.

**3.2.1. Michael adduct 4a.** White crystals; mp 177–178 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +296.9 (*c* 0.79, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.83 (9H, s), 1.61 (3H, s), 2.25 (3H, s), 4.45 (1H, d, *J*=11.4 Hz), 4.53 (1H, d, *J*=11.4 Hz), 4.92 (1H, s), 7.20–7.35 (10H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 26.9 (q), 30.5 (q), 34.6 (q), 51.8 (d), 70.2 (d), 82.4 (s), 107.8 (d), 126.9 (d), 127.6 (d), 128.0 (d), 128.2 (d), 128.6 (d), 133.7 (s), 134.2 (s), 170.4 (s), 201.1 (s), 202.0 (s); HRMS (CI) *m*/*z* 409.2015 ($M^+$+1, 62, $C_{25}H_{29}O_5$ required 409.2015), 323 (83), 220 (51), 147 (75), 105 (100).

**3.2.2. Michael adduct 4b.** White crystals; mp 197–198 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +286.3 (*c* 1.20, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.64 (3H, s), 2.28 (3H, s), 4.44 (2H, s), 5.01 (1H, s), 7.2–7.35 (9H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 27.0 (q), 30.6 (q), 34.6 (q), 51.2 (d), 70.0 (d), 82.0 (s), 107.9 (d), 126.9 (d), 127.7 (d), 128.2 (d), 128.8 (d), 132.7 (s), 133.3 (s), 134.3 (s), 170.3 (s), 200.8 (s), 201.7 (s); HRMS (CI) *m*/*z* 443.1682 ($M^+$+1, 13, $C_{25}H_{28}ClO_5$ required 443.1625), 445 (4), 359 (15), 357 (43), 220 (68), 219 (61), 105 (100).

**3.2.3. Michael adduct 4c.** White crystals; mp 202–203 °C (from hexane–diethyl ether); $[\alpha]_D^{25}$ +272.3 (*c* 0.67, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.64 (3H, s), 2.28 (3H, s), 4.41 (1H, d, *J*=11.4 Hz), 4.45 (1H, d, *J*=11.7 Hz), 5.01 (1H, s), 7.25–7.40 (9H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.2 (q), 27.0 (q), 30.5 (q), 34.6 (q), 51.2 (d), 70.0 (d), 81.9 (s), 107.9 (d), 122.5 (s), 126.8 (d), 127.7 (d), 128.8 (d), 131.1 (d), 131.2 (s), 133.2 (s), 170.2 (s), 200.8 (s), 201.6 (s); HRMS (CI) *m*/*z* 487.1147 ($M^+$+1, 1, $C_{25}H_{28}BrO_5$ required 487.1120), 489 (1), 403 (9), 401 (9), 220 (41), 219 (34), 105 (100).

**3.2.4. Michael adduct 4d.** White solid; mp 164–165 °C; $[\alpha]_D^{25}$ +299.2 (*c* 0.66, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.61 (3H, s), 2.25 (3H, s), 2.30 (3H, s), 4.41 (1H, d, *J*=11.1 Hz), 4.48 (1H, d, *J*=11.4 Hz), 4.95 (1H, s), 7.20–7.35 (9H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 21.1 (q), 23.1 (q), 26.8 (q), 30.5 (q), 34.5 (q), 51.3 (d), 70.2 (d), 82.3 (s), 107.6 (d), 126.9 (d), 127.5 (d), 128.5 (d), 128.6 (d), 130.9 (d), 133.6 (s), 137.9 (s), 170.4 (s), 201.2 (s), 202.0 (s); HRMS (CI) *m*/*z* 423.2268 ($M^+$+1, 69, $C_{26}H_{31}O_5$ required 423.2171), 337 (93), 220 (38), 203 (76), 161 (100), 105 (5).

**3.2.5. Michael adduct 4e.** White solid; mp 128–130 °C; $[\alpha]_D^{25}$ +272.0 (*c* 0.78, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.84 (9H, s), 1.62 (3H, s), 2.25 (3H, s), 3.78 (3H, s), 4.40 (1H, d, *J*=11.4 Hz), 4.45 (1H, d, *J*=11.4 Hz), 4.96 (1H, s), 7.20–7.30 (9H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.2

(q), 26.7 (q), 30.6 (q), 34.5 (q), 50.9 (d), 55.1 (q), 70.3 (d), 82.4 (s), 107.7 (d), 113.2 (d), 113.3 (d), 125.9 (s), 126.9 (d), 127.5 (d), 128.5 (d), 159.3 (s), 170.5 (s), 201.2 (s), 202.1 (s); HRMS (CI) *m/z* 339.1614 ($M^+$+1−$C_5H_7O_2$, 9, $C_{21}H_{23}O_4$ required 339.1596), 219 (25), 177 (100), 105 (5).

### 3.3. General procedure for the preparation of pyrazoles 6

**3.3.1. Procedure A (reaction with arylhydrazines).** To a solution of compound **4** (0.24 mmol) in absolute EtOH (3 mL), acidified with a drop of concd $H_2SO_4$, was dropwise added a solution of arylhydrazine **5** ($PhNHNH_2$ or *p*-$NO_2PhNHNH_2$) (0.48 mmol) in absolute EtOH (2 mL). The reaction mixture was heated at reflux temperature until complete transformation of compound **4** into pyrazole **6**, as shown by TLC. Then, the reaction mixture was neutralised with saturated aqueous $NaHCO_3$, extracted with $CH_2Cl_2$, washed with brine, dried over $Na_2SO_4$, concentrated and flash chromatographed on silica gel (hexane–diethyl ether) to afford pyrazoles **6**.

**3.3.2. Procedure B (reaction with methylhydrazine).** A solution of compound **4** (0.49 mmol), methylhydrazine **5b** (0.98 mmol) and $CH_3CO_2H$ (56 μL, 0.98 mmol) in dioxane (8 mL), was heated at reflux temperature until complete transformation of compound **4** into pyrazole **6**, as shown by TLC (in some cases additional amounts of reagent were added). Then, the dioxane was removed in vacuo, and the residue was diluted with water, extracted with EtOAc, washed with saturated aqueous $NaHCO_3$ and with brine, dried over $Na_2SO_4$, concentrated and flash chromatographed on silica gel (hexane–diethyl ether) to afford pyrazoles **6**.

**3.3.3. Pyrazole 6aa.** Yellow oil; $[\alpha]_D^{25}$ +253.0 (*c* 0.78, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (9H, s), 2.15 (3H, br s), 2.41 (3H, br s), 4.97 (1H, s), 5.03 (1H, s), 7.06–7.45 (13H, m), 7.83 (2H, d, *J*=7.2 Hz); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.00 (9H, s), 2.13 (3H, s), 2.29 (3H, s), 5.01 (1H, s), 5.03 (1H, s), 7.02 (1H, tt, *J*=7.4, 1.4 Hz), 7.12 (2H, t, *J*=7.6 Hz), 7.20 (2H, dt, *J*=7.6, 1.2 Hz), 7.31 (2H, d, *J*=8 Hz), 7.35 (2H, d, *J*=7.6 Hz), 7.40 (2H, d, *J*=8 Hz), 7.41 (1H, d, *J*=7.2 Hz), 7.5 (2H, t, *J*=7.8 Hz), 7.83 (2H, d, *J*=8 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$, 70 °C) $\delta$ 10.7 (q), 12.5 (q), 23.0 (q), 34.3 (q), 48.5 (d), 86.2 (s), 109.4 (d), 115.0 (s), 124.4 (d), 125.3 (d), 125.5 (d), 126.9 (d), 127.0 (d), 127.2 (d), 127.3 (d), 128.5 (d), 129.4 (d), 137.2 (s), 137.4 (s), 137.5 (s), 139.1 (s), 147.0 (s), 172.4 (s); HRMS (FAB+) *m/z* 481.2497 ($M^+$+1, 33, $C_{31}H_{33}N_2O_3$ required 481.2491), 262 (36), 261 (100), 147 (15).

**3.3.4. Pyrazole 6ab.** Colourless oil; $[\alpha]_D^{25}$ +270.4 (*c* 0.71, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.01 (9H, s), 2.01 (3H, br s), 2.33 (3H, br s), 3.67 (3H, s), 4.85 (1H, s), 4.97 (1H, s), 6.96 (1H, t, *J*=7.2 Hz), 7.05 (2H, t, *J*=7.8 Hz), 7.13 (1H, t, *J*=7.2 Hz), 7.25 (2H, m), 7.81 (2H, dd, *J*=7.5, 1.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.1 (q), 13.6 (q), 23.8 (q), 35.1 (q), 36.1 (q), 49.6 (d), 87.0 (s), 110.5 (d), 114.0 (s), 125.7 (d), 125.8 (d), 127.4 (d), 127.6 (d), 127.8 (d), 129.9 (d), 137.5 (s), 137.9 (s), 138.0 (s), 146.4 (s), 173.8 (s); HRMS (FAB+) *m/z* 419.2341 ($M^+$+1, 34, $C_{26}H_{31}N_2O_3$ required 419.2335), 281 (12), 221 (13), 199 (100), 147 (71).

**3.3.5. Pyrazole 6ac.** Yellow oil; $[\alpha]_D^{25}$ +241.0 (*c* 0.72, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (9H, s), 2.13 (3H, br s), 2.54 (3H, br s), 4.97 (1H, s), 5.01 (1H, s), 7.05–7.20 (5H, m), 7.29 (3H, t, *J*=7.5 Hz), 7.65 (2H, d, *J*=8.7 Hz), 7.84 (2H, d, *J*=7.5 Hz), 8.33 (2H, d, *J*=9 Hz); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.00 (9H, s), 2.15 (3H, s), 2.45 (3H, s), 5.03 (1H, s), 5.06 (1H, s), 7.03 (1H, t, *J*=7.4 Hz), 7.12 (2H, t, *J*=7.4 Hz), 7.21 (1H, t, *J*=7.2 Hz), 7.32 (2H, t, *J*=7.8 Hz), 7.36 (2H, d, *J*=7.6 Hz), 7.77 (2H, d, *J*=8.8 Hz), 7.85 (2H, dd, *J*=8.4, 1.2 Hz), 8.32 (2H, d, *J*=9.2 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$, 70 °C) $\delta$ 11.1 (q), 12.6 (q), 23.0 (q), 34.3 (q), 48.4 (d), 86.0 (s), 109.4 (d), 116.9 (s), 124.0 (d), 124.1 (d), 125.3 (d), 125.6 (d), 127.0 (d), 127.2 (d), 127.3 (d), 129.5 (d), 137.2 (s), 137.3 (s), 138.0 (s), 144.0 (s), 145.3 (s), 148.9 (s), 172.3 (s); HRMS (FAB+) *m/z* 526.2383 ($M^+$+1, 70, $C_{31}H_{32}N_3O_5$ required 526.2342), 306 (100), 260 (15), 105 (14).

**3.3.6. Pyrazole 6ba.** Colourless oil; $[\alpha]_D^{25}$ +228.9 (*c* 0.75, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.95 (9H, s), 2.03 (3H, s), 2.35 (3H, s), 4.85 (1H, s), 4.94 (1H, s), 7.00 (2H, d, *J*=8.4 Hz), 7.12–7.41 (10H, m), 7.73 (2H, d, *J*=7.5 Hz), $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.00 (9H, s), 2.15 (3H, s), 2.30 (3H, s), 5.00 (1H, s), 5.04 (1H, s), 7.16 (2H, d, *J*=8.8 Hz), 7.22 (1H, td, *J*=7.4, 1.2 Hz), 7.33 (2H, t, *J*=8.4 Hz), 7.37 (2H, d, *J*=8.8 Hz), 7.43–7.39 (3H, m), 7.51 (2H, t, *J*=7.6 Hz), 7.82 (2H, dd, *J*=8.4, 1.2 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$, 70 °C) $\delta$ 10.7 (q), 12.5 (q), 23.0 (q), 29.5 (s), 47.9 (d), 86.0 (s), 109.5 (d), 124.4 (d), 125.2 (d), 126.9 (d), 127.0 (d), 127.3 (d), 127.4 (d), 128.6 (d), 130.3 (s), 131.3 (d), 136.5 (s), 137.2 (s), 137.3 (s), 139.0 (s), 146.9 (s), 172.1 (s); HRMS (FAB+) *m/z* 515.2119 ($M^+$+1, 15, $C_{31}H_{32}ClN_2O_3$ required 515.2101), 517 (5), 297 (34), 296 (44), 295 (86), 267 (15), 221 (46), 147 (100).

**3.3.7. Pyrazole 6bb.** Colourless oil; $[\alpha]_D^{25}$ +260.1 (*c* 1.03, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.01 (9H, s), 2.00 (3H, s), 2.34 (3H, s), 3.71 (3H, s), 4.81 (1H, s), 4.95 (1H, s), 7.03 (2H, d, *J*=8.4 Hz), 7.18–7.30 (5H, m), 7.78 (d, *J*=7.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 10.1 (q), 14.2 (q), 23.8 (q), 35.1 (s), 36.2 (q), 49.1 (d), 86.9 (s), 110.6 (d), 113.6 (s), 125.7 (d), 127.7 (d), 127.9 (d), 128.0 (d), 131.3 (d), 131.7 (s), 137.60 (s), 137.63 (s), 146.3 (s), 173.0 (s); HRMS (FAB+) *m/z* 453.1951 ($M^+$+1, 49, $C_{26}H_{30}ClN_2O_3$ required 453.1945), 455 (16), 235 (33), 233 (100), 147 (44).

**3.3.8. Pyrazole 6bc.** Yellow oil; $[\alpha]_D^{25}$ +236.2 (*c* 0.75, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (9H, s), 2.10 (3H, br s), 2.55 (3H, br s), 4.92 (1H, s), 5.00 (1H, s), 7.1 (2H, d, *J*=8.7 Hz), 7.23 (3H, t, *J*=6.9 Hz), 7.31 (2H, t, *J*=7.5 Hz), 7.66 (2H, d, *J*=8.7 Hz), 7.81 (2H, d, *J*=9 Hz), 8.34 (2H, d, *J*=9 Hz); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.00 (9H, s), 2.17 (3H, s), 2.46 (3H, s), 5.02 (1H, s), 5.07 (1H, s), 7.17 (2H, d, *J*=8.8 Hz), 7.23 (1H, tt, *J*=7.4, 1.2 Hz), 7.34 (2H, t, *J*=7.6 Hz), 7.38 (2H, d, *J*=8.4 Hz), 7.77 (2H, d, *J*=9.2 Hz), 7.84 (2H, dd, *J*=8.8, 1.2 Hz), 8.32 (2H, d, *J*=9.1 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$, 70 °C) $\delta$ 11.1 (q), 12.6 (q), 22.9 (q), 34.3 (q), 47.8 (d), 85.8 (s), 109.5 (d), 116.3 (s), 124.1 (d), 124.2 (d), 125.3 (d), 127.0 (d), 127.39 (d), 127.42 (d), 130.4 (s), 131.3 (d), 136.2 (s), 137.0 (s), 138.1 (s), 143.9 (s), 145.3 (s), 148.8 (s), 172.0 (s); HRMS (FAB+) *m/z* 560.1956 ($M^+$+1, 81, $C_{31}H_{31}ClN_3O_5$ required 560.1952), 562 (33), 342 (42), 340 (100), 169 (38).

**3.3.9. Pyrazole 6ea.** Yellow oil; $[\alpha]_D^{25}$ +270.8 (*c* 0.77, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (9H, s), 2.14 (3H, br s), 2.40 (3H, br s), 3.68 (3H, s), 4.91 (1H, s), 5.02 (1H, s), 6.63 (2H, d, *J*=8.7 Hz), 7.15–7.3 (5H, m), 7.35–7.48 (5H, m), 7.82 (2H, d, *J*=7.5 Hz); $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 1.00 (9H, s), 2.15 (3H, s), 2.29 (3H, s), 3.64 (3H, s), 4.97 (1H, s), 5.01 (1H, s), 6.68 (2H, d, *J*=9.2 Hz), 7.21 (1H, tt, *J*=8.6, 1.4 Hz), 7.26 (2H, d, *J*=8.4 Hz), 7.32 (2H, t, *J*=7.6 Hz), 7.37–7.43 (3H, m), 7.47–7.53 (2H, m), 7.82 (2H, dd, *J*=8.4, 1.2 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$, 70 °C) $\delta$ 10.7 (q), 12.5 (q), 23.0 (q), 34.2 (q), 47.8 (d), 54.4 (q), 86.3 (s), 109.4 (d), 112.6 (d), 115.3 (s), 124.4 (d), 125.2 (d), 126.9 (d), 127.1 (d), 127.3 (d), 128.5 (d), 129.5 (s), 130.5 (d), 137.0 (s), 137.5 (s), 139.1 (s), 147.0 (s), 156.9 (s), 172.4 (s); HRMS (FAB+) *m/z* 511.2584 ($M^+$+1, 70, $C_{32}H_{35}N_2O_4$ required 511.2597), 291 (100), 169 (12).

**3.3.10. Pyrazole 6eb.** Colourless oil; $[\alpha]_D^{25}$ +246.9 (*c* 0.82, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.94 (9H, s), 1.97 (3H, br s), 2.25 (3H, br s), 3.59 (3H, s), 3.63 (3H, s), 4.72 (1H, s), 4.89 (1H, s), 6.52 (2H, d, *J*=9.0 Hz), 7.09 (1H, t, *J*=6.9 Hz), 7.10 (2H, d, *J*=9 Hz), 7.19 (2H, d, *J*=7.5 Hz), 7.72 (2H, d, *J*=7.5 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 10.2 (q), 14.1 (q), 23.9 (q), 35.1 (q), 36.1 (q), 48.9 (d), 54.9 (q), 87.2 (s), 110.5 (d), 112.8 (d), 114.3 (s), 125.7 (d), 127.6 (d), 127.9 (d), 130.2 (s), 130.9 (d), 137.4 (s), 138.0 (s), 146.4 (s), 157.4 (s), 173.9 (s); HRMS (FAB+) *m/z* 449.2447 ($M^+$+1, 11, $C_{27}H_{33}N_2O_4$ required 449.2440), 281 (40), 229 (18), 221 (54), 147 (100).

**3.3.11. Pyrazole 6ec.** Yellow oil; $[\alpha]_D^{25}$ +288.4 (*c* 0.70, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.02 (9H, s), 2.13 (3H, br s), 2.54 (3H, br s), 3.69 (3H, s), 4.90 (1H, s), 5.00 (1H, s), 6.65 (2H, d, *J*=6.9 Hz), 7.20 (3H, t, *J*=7.2 Hz), 7.30 (2H, t, *J*=7.6 Hz), 7.66 (2H, d, *J*=8.7 Hz), 7.82 (2H, d, *J*=7.5 Hz), 8.33 (2H, d, *J*=9.3 Hz); $^1H$ NMR (400 MHz, DMSO-$d_6$, 70 °C) $\delta$ 1.00 (9H, s), 2.16 (3H, s), 2.45 (3H, s), 3.64 (3H, s), 4.99 (1H, s), 5.02 (1H, s), 6.68 (2H, d, *J*=8.8 Hz), 7.22 (1H, t, *J*=7.2 Hz), 7.26 (2H, d, *J*=8.8 Hz), 7.33 (2H, t, *J*=7.6 Hz), 7.77 (2H, d, *J*=9.2 Hz), 7.83 (2H, d, *J*=7.6 Hz), 8.32 (2H, d, *J*=8.8 Hz); $^{13}C$ NMR (100 MHz, DMSO-$d_6$, 70 °C) $\delta$ 11.2 (q), 12.6 (q), 23.0 (q), 34.3 (q), 47.6 (d), 54.4 (q), 86.2 (s), 109.4 (d), 112.6 (d), 117.2 (s), 124.1 (d), 124.1 (d), 125.3 (d), 127.2 (d), 127.3 (d), 129.1 (s), 130.5 (d), 137.4 (s), 137.9 (s), 144.0 (s), 145.2 (s), 148.9 (s), 157.0 (s), 172.3 (s). HRMS (FAB+) *m/z* 556.2436 ($M^+$+1, 71, $C_{32}H_{34}N_3O_6$ required 556.2448), 336 (100), 238 (27), 169 (62).

### 3.4. General procedure for the hydrolysis of the 1,3-dioxolan-4-one moiety in compound 6

Compound **6** (0.5 mmol) was treated with 5% ethanolic KOH (1.1 mL, 1 mmol) at 60 °C until complete reaction of the starting material (TLC). The reaction mixture was poured into ice and acidified with 1 M HCl until pH ~2. The aqueous mixture was extracted with EtOAc (4×25 mL), and the organic layers were washed with brine (2×15 mL), dried ($NaSO_4$), filtered and concentrated under reduced pressure to give α-hydroxy acids **7**.

**3.4.1. Compound 7aa.** White solid; mp 225–227 °C (from ether–methanol); $[\alpha]_D^{25}$ +179.6 (*c* 0.77, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.04 (3H, s), 2.25 (3H, s), 5.10 (1H, s), 6.93–6.97 (3H, m), 7.06–7.18 (10H, m), 7.60 (2H, d, *J*=7.2 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 12.1 (q), 12.4 (q), 47.3 (d), 81.3 (s), 117.8 (s), 125.6 (d), 126.5 (d), 127.0 (d), 127.48 (d), 127.78 (d), 128.0 (d), 128.78 (d), 128.83 (d), 130.0 (d), 138.0 (s), 139.34 (s), 139.99 (s), 141.7 (s), 148.0 (s), 176.2 (s); HRMS (FAB+) *m/z* 413.1875 ($M^+$+1, 5, $C_{26}H_{25}N_2O_3$ required 413.1865), 282 (22), 261 (100), 147 (74).

**3.4.2. Compound 7ab.** White solid; mp 255–257 °C (from chloroform–methanol); $[\alpha]_D^{25}$ +261.0 (*c* 1.8, $CH_3OH$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.15 (3H, s), 2.49 (3H, s), 3.58 (3H, s), 5.23 (1H, s), 6.98–7.04 (3H, m), 7.16–7.27 (5H, m), 7.76 (2H, d, *J*=7.5 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$–MeOH-$d_4$) $\delta$ 10.5 (q), 11.9 (q), 34.9 (q), 46.8 (d), 80.8 (s), 115.5 (s), 125.0 (d), 126.1 (d), 126.8 (d), 127.0 (d), 127.5 (d), 129.6 (d), 138.6 (s), 139.4 (s), 141.0 (s), 146.1 (s), 176.1 (s); HRMS (FAB+) *m/z* 351.1711 ($M^+$+1, 41, $C_{21}H_{23}N_2O_3$ required 351.1709), 281 (36), 221 (45), 199 (38), 147 (100).

**3.4.3. Compound 7ac.** Oil; $[\alpha]_D^{25}$ −150.0 (*c* 1.0, $CH_3OH$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.08 (3H, s), 2.20 (3H, s), 5.12 (1H, s), 6.90–7.00 (3H, m), 7.10–7.30 (7H, m), 7.57 (2H, d, *J*=7.2 Hz), 7.93 (2H, d, *J*=8.4 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 12.7 (q), 12.8 (q), 47.0 (d), 81.3 (s), 119.4 (s), 124.4 (d), 124.9 (d), 125.9 (d), 126.3 (d), 127.4 (d), 127.6 (d), 128.0 (d), 129.9 (d), 138.6 (s), 140.0 (s), 141.2 (s), 143.5 (s), 146.0 (s), 150.2 (s), 176.2 (s); HRMS (FAB+) *m/z* 458.1711 ($M^+$+1, 7, $C_{26}H_{24}N_3O_5$ required 458.1716), 412 (8), 281 (32), 147 (100).

**3.4.4. Compound 7ba.** White solid; mp 240–243 °C (from chloroform–methanol); $[\alpha]_D^{25}$ +201.8 (*c* 1.2, $CH_3OH$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.10 (3H, s), 2.24 (3H, s), 5.11 (1H, s), 6.99 (2H, d, *J*=8.1 Hz), 7.10–7.25 (10H, m), 7.64 (2H, d, *J*=6.6 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 12.1 (q), 12.3 (q), 46.8 (d), 81.1 (s), 115.3 (d), 117.2 (s), 125.6 (d), 126.4 (d), 127.6 (d), 127.9 (d), 128.9 (d), 129.5 (d), 131.4 (d), 137.9 (s), 139.9 (s), 141.3 (s), 147.9 (s), 155.9 (s), 176.1 (s); HRMS (FAB+) *m/z* 447.1495 ($M^+$+1, 20, $C_{26}H_{24}ClN_2O_3$ required 447.1475), 449 (5), 294 (44), 281 (29), 154 (100).

**3.4.5. Compound 7bb.** Pale yellow solid; mp 230–232 °C (from ether–methanol); $[\alpha]_D^{25}$ +202.1 (*c* 1.4, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.04 (3H, s), 2.33 (3H, s), 3.44 (3H, s), 5.09 (1H, s), 6.93 (2H, d, *J*=9.0 Hz), 7.05–7.19 (5H, m), 7.66 (2H, d, *J*=6.9 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.4 (q), 11.6 (q), 34.9 (q), 46.6 (d), 81.2 (s), 116.5 (s), 126.4 (d), 127.14 (d), 127.64 (d), 127.95 (d), 131.24 (d), 131.32 (s), 138.3 (s), 140.3 (s), 141.8 (s), 145.1 (s), 177.2 (s); HRMS (FAB+) *m/z* 385.1316 ($M^+$+1, 9, $C_{21}H_{22}ClN_2O_3$ required 385.1319), 387 (3), 281 (40), 221 (40), 207 (45), 147 (100).

**3.4.6. Compound 7ea.** Pale yellow solid; mp 248–251 °C (from ether–methanol); $[\alpha]_D^{25}$ +164.8 (*c* 1.0, $CH_3OH$); $^1H$ NMR (300 MHz, $CDCl_3$-25% $CD_3OD$) $\delta$ 2.14 (3H, s), 2.24 (3H, s), 3.57 (3H, s), 5.09 (1H, s), 6.51 (2H, d, *J*=8.4 Hz), 7.07–7.31 (10H, m), 7.65 (2H, d, *J*=7.8 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$-25% $CD_3OD$) $\delta$ 12.4 (q), 12.5 (q), 46.7 (d),

54.9 (q), 81.3 (s), 112.8 (d), 117.5 (s), 124.4 (d), 125.4 (d), 127.1 (d), 127.6 (d), 128.8 (d), 130.45 (d), 130.90 (d), 131.5 (s), 138.5 (s), 139.1 (s), 141.3 (s), 148.5 (s), 157.1 (s), 176.5 (s); HRMS (FAB+) *m/z* 443.1944 ($M^+$+1, 25, $C_{27}H_{27}N_2O_4$ required 443.1971), 281 (92), 207 (100), 147 (100).

**3.4.7. Compound 7eb.** Pale yellow solid; mp 230–231 °C (from ether–methanol); $[\alpha]_D^{25}$ +203.9 (*c* 1.6, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.13 (3H, s), 2.38 (3H, s), 3.49 (3H, s), 3.66 (3H, s), 5.14 (1H, s), 6.58 (2H, d, *J*=8.7 Hz), 7.08–7.26 (5H, m), 7.76 (2H, d, *J*=6.6 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.3 (q), 11.7 (q), 34.9 (q), 46.4, (d), 54.9 (q), 81.5 (s), 112.8 (d), 117.2 (s), 126.5 (d), 126.9 (d), 127.8 (d), 130.8 (d), 131.8 (s), 140.1 (s), 142.3 (s), 145.2 (s), 157.2 (s), 177.7 (s); HRMS (FAB+) *m/z* 381.1823 ($M^+$+1, 54, $C_{22}H_{25}N_2O_4$ required 381.1814), 281 (86), 229 (83), 207 (63), 147 (100).

### 3.5. General procedure for the oxidative decarboxylation of α-hydroxy acid moiety of compound 7

A solution of compound **7** (0.22 mmol), Co(III)–$Me_2$opba complex (5.3 mg, 0.013 mmol) and pivalaldehyde (74 μL, 0.66 mmol) in acetonitrile (1.5 mL) and DMF (0.2 mL) was stirred under an oxygen atmosphere until consumption of the starting material (TLC). Water was added, the mixture was extracted with ethyl ether (3×20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (2×10 mL) and dried ($MgSO_4$). The reaction products were purified by flash chromatography on silica gel (hexane–ethyl acetate) to afford compound **8**.

**3.5.1. Compound 8aa.** Orange oil; $[\alpha]_D^{25}$ −34.8 (*c* 0.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.12 (3H, s), 2.22 (3H, s), 5.92 (1H, s), 7.19 (2H, d, *J*=6.6 Hz), 7.55–7.26 (13H, m), 8.00 (2H, d, *J*=7.2 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.5 (q), 12.5 (q), 50.0 (d), 125.2 (d), 125.5 (d), 126.7 (d), 127.6 (d), 128.5 (d), 128.89 (d), 128.94 (d), 129.2 (d), 133.2 (d), 136.1 (s), 136.7 (s), 137.6 (s), 138.4 (s), 139.4 (s), 147.9 (s), 198.1 (s); HRMS (FAB+) *m/z* 367.1829 ($M^+$+1, 100, $C_{25}H_{23}N_2O$ required 367.1810), 277 (20), 261 (64).

**3.5.2. Compound 8ab.** Yellow oil; $[\alpha]_D^{25}$ −71.0 (*c* 1.2, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.06 (3H, s), 2.14 (3H, s), 3.70 (3H, s), 5.83 (1H, s), 7.11 (2H, d, *J*=6.6 Hz), 7.55–7.25 (8H, m), 7.95 (2H, d, *J*=7.2 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 10.1 (q), 12.1 (q), 27.1 (q), 35.9 (q), 49.9 (d), 126.9 (d), 128.30 (s), 128.4 (d), 128.6 (d), 128.9 (d), 130.0 (s), 133.0 (d), 136.7 (s), 138.6 (s), 145.7 (s), 198.2 (s); HRMS (FAB+) *m/z* 305.1643 ($M^+$+1, 100, $C_{20}H_{21}N_2O$ required 305.1654), 215 (25), 199 (62).

**3.5.3. Compound 8ba.** Yellow oil; $[\alpha]_D^{25}$ −19.1 (*c* 1.3, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.12 (3H, s), 2.21 (3H, s), 5.86 (1H, s), 7.11 (2H, d, *J*=8.4 Hz), 7.30–7.37 (5H, m), 7.41–7.47 (4H, m), 7.56 (1H, t, *J*=7.4 Hz), 7.98 (2H, d, *J*=7.5 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.4 (q), 12.5 (q), 49.5 (d), 111.3 (s), 114.5 (s), 125.2 (d), 127.7 (d), 128.6 (d), 128.7 (d), 129.0 (d), 130.3 (d), 132.9 (s), 133.3 (s), 136.5 (s), 136.9 (s), 137.5 (s), 147.7 (s), 197.7 (s); HRMS (EI) *m/z* 400.1317 ($M^+$, 2, $C_{25}H_{21}ClN_2O$ required 400.1342), 297 (33), 295 (100).

**3.5.4. Compound 8bb.** Yellow oil; $[\alpha]_D^{25}$ −35.4 (*c* 1.2, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.05 (3H, s), 2.13 (3H, s), 3.69 (3H, s), 5.77 (1H, s), 7.04 (2H, d, *J*=8.7 Hz), 7.28 (2H, d, *J*=8.7), 7.41 (2H, t, *J*=7.5 Hz), 7.53 (1H, tt, *J*=7.8, 1.5 Hz), 7.92 (2H, dd, *J*=7.2, 1.5 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 10.1 (q), 12.2 (q), 36.0 (q), 49.4 (d), 112.6 (s), 128.47 (d), 128.55 (d), 128.63 (d), 130.2 (d), 130.3 (s), 132.7 (s), 133.2 (d), 136.5 (s), 137.1 (s), 145.6 (s), 197.8 (s); HRMS (EI) *m/z* 338.1168 ($M^+$, 2, $C_{20}H_{19}ClN_2O$ required 338.1186), 247 (15), 233 (100).

**3.5.5. Compound 8ea.** Pale yellow oil; $[\alpha]_D^{25}$ −52.2 (*c* 0.7, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.04 (3H, s), 2.13 (3H, s), 3.72 (3H, s), 5.78 (1H, s), 6.80 (2H, d, *J*=8.7 Hz), 7.02 (2H, d, *J*=9.3 Hz), 7.23–7.38 (7H, m), 7.45 (1H, tt, *J*=7.8, 1.5 Hz), 7.91 (2H, d, *J*=8.7 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.4 (q), 12.6 (q), 49.4 (d), 55.2 (q), 113.9 (d), 115.2 (s), 125.2 (d), 127.5 (d), 128.6 (d), 128.9 (d), 130.0 (d), 130.4 (d), 133.0 (d), 136.8 (s), 137.3 (s), 139.6 (s), 147.9 (s), 158.5 (s), 198.4 (s); HRMS (EI) *m/z* 396.1847 ($M^+$, 1, $C_{26}H_{24}N_2O_2$ required 396.1838), 336 (11), 291 (100).

**3.5.6. Compound 8eb.** Pale yellow oil; $[\alpha]_D^{25}$ −70.5 (*c* 1.7, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.05 (3H, s), 2.13 (3H, s), 3.69 (3H, s), 3.77 (3H, s), 5.77 (1H, s), 6.84 (2H, d, *J*=8.7 Hz), 7.04 (2H, d, *J*=8.7 Hz), 7.40 (2H, t, *J*=7.2 Hz), 7.51 (1H, t, *J*=7.5 Hz), 7.94 (2H, d, *J*=7.2 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 10.1 (q), 12.2 (q), 35.9 (q), 49.2 (d), 55.2 (q), 113.5 (s), 113.8 (d), 128.52 (d), 128.54 (d), 129.8 (d), 130.6 (s), 132.9 (d), 136.7 (s), 137.3 (s), 145.6 (s), 158.4 (s), 198.4 (s); HRMS (EI) *m/z* 334.1678 ($M^+$, 1, $C_{21}H_{22}N_2O_2$ required 334.1681), 244 (21), 149 (63).

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# A general synthetic route to chiral dihydroxy-9,9′-spirobifluorenes

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**Abstract**—$C_2$-Symmetric 9,9′-spirobifluorenes with 2,2′-, 3,3′-, and 4,4′-dihydroxyls were conveniently prepared from 1,2-dibromobenzene. The palladium-catalyzed coupling reaction of 1,2-dibromobenzene with methoxyphenylmagnesium bromide or methoxyphenylboronic acid provided methoxy substituted 2-bromobiphenyls. Lithium–bromine exchange with *n*-butyllithium, followed by reaction with dimethyl carbonate afforded di[2-(methoxyphenyl)phenyl]ketones as the key intermediates. A continuous ring-closure induced by a strong Lewis acid and demethylation gave dihydroxy-9,9′-spirobifluorenes. The racemic dihydroxy products were resolved by inclusion crystallization using chiral resolving reagents or separated by chiral HPLC.


## 1. Introduction

Compounds containing a spirobifluorene backbone have been widely applied in molecular electronics,[1] light-emitting materials,[2] enantioselective molecular recognition,[3] and other areas.[4] In the spirobifluorene family, chiral dihydroxy-spirobifluorene was an important branch because the hydroxy group could be easily converted to other groups using well-established protocols.[5] Though the preparation of spirobifluorene itself was realized in 1930 by Gomberg,[6] synthesis of its 2,2′-dihydroxy derivative was not achieved until the 1970s.[7] Both procedures used the same strategy; the addition of biphenyl Grignard reagents to 9-fluorenone, followed by a ring-closure to generate the spirobifluorene skeleton. In this procedure, the position of substituents of spirobifluorene depended directly on that in the parent 9-fluorenone, which restricted its use in the synthesis of various spirobifluorene compounds. An alternative strategy used Friedel–Crafts acylation[8] to construct disubstituted spirobifluorene, but it was limited to the preparation of 2,2′-disubstituted spirobifluorenes. In fact, development of a general method for the synthesis of the spirobifluorene compounds with 1,1′-, 2,2′-, 3,3′-, or 4,4′-disubstituents is still a challenge. Recently, we reported the synthesis and resolution of 1,1′-dihydroxy-9,9′-spirobifluorene. Two features of the method are crucial: (1) dimethyl carbonate was employed to condense with 2-bromo-biphenyl to create a diaryl ketone, which was a key intermediate; (2) methanesulfonic acid was used to close both rings of spirobifluorene in one step and the ring-closure proceeded exclusively at the 'bay' position as directed by the methoxy group.[9] Further studies revealed that this method also allowed the synthesis of 9,9′-spirobifluorene structures with disubstituents at the *ortho*, *meta*, and *para* positions. Here we wish to report the synthesis and resolution of 2,2′-, 3,3′-, and 4,4′-dihydroxy-9,9′-spirobifluorenes.

## 2. Result and discussion

2,2′-Dihydroxy-9,9′-spirobifluorene was prepared with the protocol described below. 2-Bromo-4′-methoxybiphenyl (**1**) was prepared by the Kumada coupling of 1,2-dibromobenzene with 4-methoxyphenylmagnesium bromide catalyzed by $Pd(PPh_3)_4$. The lithium–bromine exchange, followed by reaction with dimethyl carbonate gave the key intermediate **2** in 60% yield. Owing to the lack of an electron-donating group at the *ortho* or *para* position to the 'bay' carbon, the electrophilic ring-closure of compound **2** can only be accomplished at 120 °C. It was found that the demethylation of the methoxy group also took place at this temperature, producing the target molecule **3** directly (Scheme 1). So, the construction of the spirobifluorene skeleton and the deprotection of the diol were realized in one reaction, which shortened the synthesis of 2,2′-dihydroxy-9,9′-spirobifluorene from five steps[9] to only three steps with 21% overall yield. The diol **3** was first resolved by Toda[10] in 1988 and its absolute configuration was determined by Lützen.[11]

3,3′-Dihydroxy-9,9′-spirobifluorene was obtained in a similar procedure by using 3-methoxyphenylmagnesium bromide (Scheme 2). In the ring-closure step, though there were two different 'bay' positions in molecule **5** and two different ring-closure products could be formed, the electrophilic attack occurred at the carbon *para* to the methoxy

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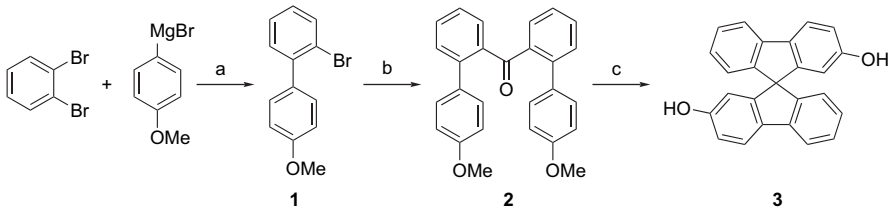
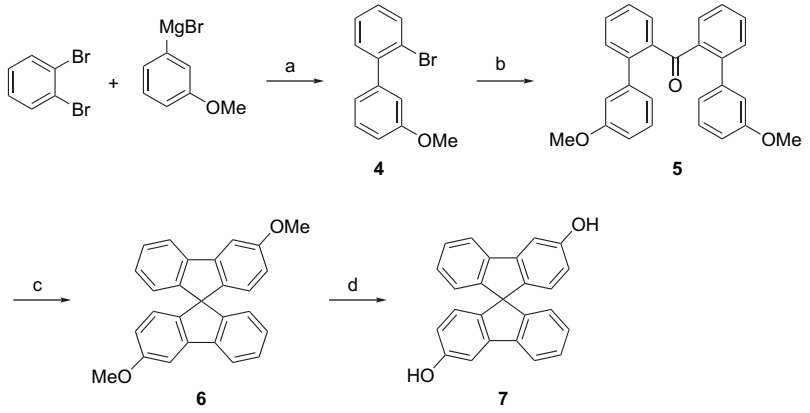


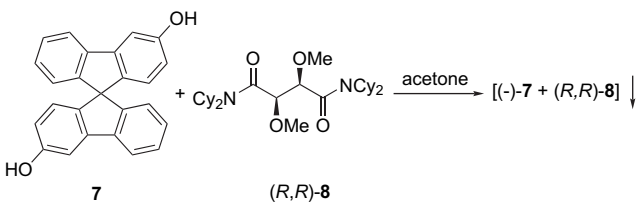

**Scheme 1**. Reagents and conditions: (a) $Pd(PPh_3)_4$, THF, 40 °C, 50%. (b) (i) *n*-BuLi, THF, −78 °C; (ii) MeOCOOMe, THF, 60%. (c) MsOH, 120 °C, 70%.




**Scheme 2**. Reagents and conditions: (a) (i) $Pd(PPh_3)_4$, THF, 40 °C, 60%. (b) (i) *n*-BuLi, THF, −78 °C; (ii) MeOCOOMe, THF, 75%. (c) MsOH, 35 °C, 4 h, 96%. (d) $BBr_3$, added at −78 °C, and reacted at rt 8 h, 90%.

group to give the spirobifluorene compound **6** with 100% selectivity at 35 °C. Using boron tribromide, the protecting methyl group was removed smoothly at room temperature, affording the product 3,3′-dihydroxy-9,9′-spirobifluorene (**7**). The overall yield from 1,2-dibromobenzene was 39%.

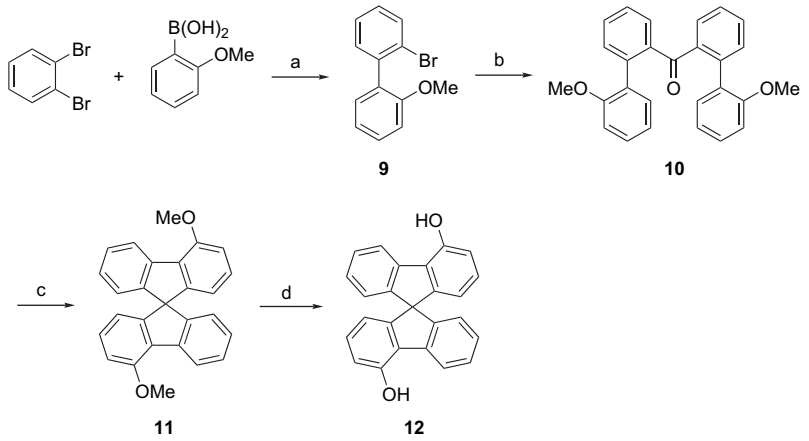
In order to prepare the pure enantiomer of diol **7**, (*R*,*R*)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetracyclohexylsuccinamide (**8**), which has successfully resolved 1,1′- and 2,2′-dihydroxy-9,9′-spirobifluorene, was chosen as inclusion resolving reagent to recrystallize with racemic **7**. As expected, (*R*,*R*)-**8** could selectively recognize (−)-**7** in the solution of acetone and formed a white inclusion precipitate, which decomposed in aqueous NaOH to release (−)-**7** in 60% ee (Scheme 3). The enantiomerically pure (−)-**7** was obtained after repeating the resolution procedure two more times. Elementary analysis of inclusion complex showed that (*R*,*R*)-**8** and (−)-**7** assembled in a 1:1 manner. Unfortunately, the crystal structure of the inclusion complex of [(*R*,*R*)-**8**/(−)-**7**] was too complicated to determine the absolute configuration of (−)-**7**. The enantiomerically pure (+)-**7** was gained by resolution with (*S*,*S*)-**8**.



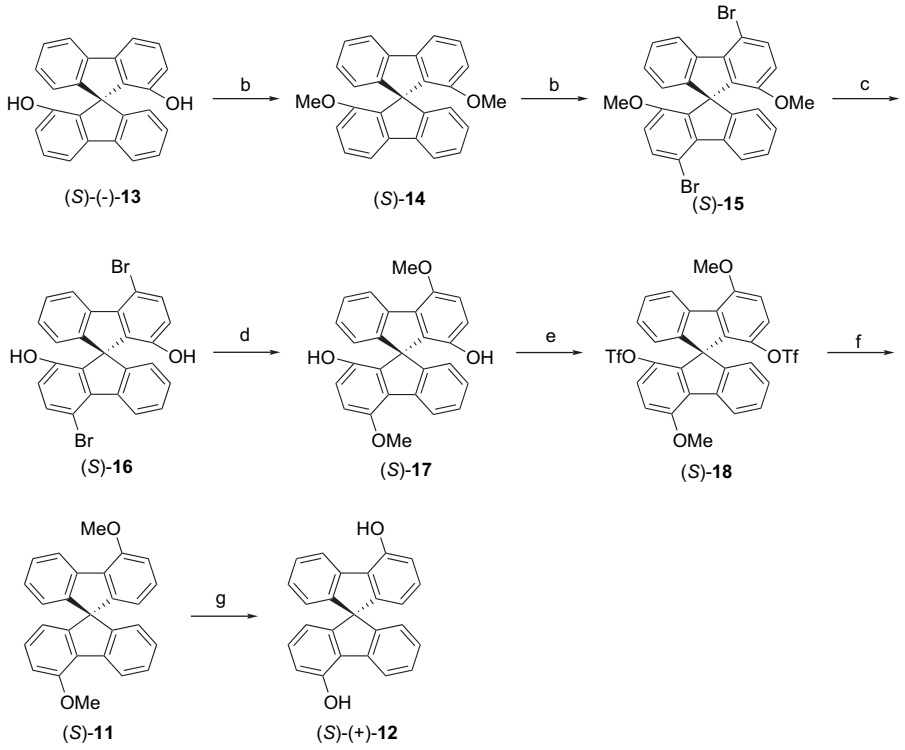

**Scheme 3**.

For the synthesis of 4,4′-dihydroxy-9,9′-spirobifluorene (**12**), the Kumada coupling of 2-methoxyphenylmagnesium bromide with 1,2-dibromobenzene was first attempted to prepare the intermediate 2-bromo-2′-methoxy-biphenyl (**9**), but no reaction took place. Fortunately, the Suzuki coupling reaction of 2-bromophenylboronic acid with 1,2-dibromobenzene catalyzed by $Pd(PPh_3)_4$ was found to be an efficient method to give the desired coupling product **9** in 71% yield. Following the procedure used in the synthesis of the dihydroxy-9,9′-spirobifluorenes described above, the diaryl ketone **10** was prepared from biphenyl **9** in 65% yield. However, the ring-closure of biphenyl **9** prompted by MsOH was sluggish at room temperature and 80 °C. When the reaction temperature was increased to 120 °C, the reaction became complicated. Alternatively, the 4,4′-dimethoxy-9,9′-spirobifluorene (**11**) was successfully achieved in 79% yield when PPA (polyphosphoric acid) was used to replace the MsOH as ring-close reagent. Finally, the treatment of compound **11** with boron tribromide afforded 4,4′-dihydroxy-9,9′-spirobifluorene (**12**) in high yield (Scheme 4).

The resolution of racemic **12** was unsuccessful by inclusion recrystallization with chiral host molecules such as (*R*,*R*)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetracyclohexylsuccinamide (**8**) and *N*-benzylcinchonidinium chloride. We therefore turned to the direct separation of racemic **12** in preparative chiral HPLC. By using chiral column AD-H two enantiomers of **12** were separated. The absolute configuration of 4,4′-dihydroxy-9,9′-spirobifluorene (**12**) was determined by chemical correlation with (*S*)-(−)-1,1′-dihydroxy-9,9′-spirobifluorene as illustrated in Scheme 5. The optically pure (*S*)-(−)-1,1′-dihydroxy-9,9′-spirobifluorene (**13**)[9] was methylated with iodomethane to yield **14**, which was brominated in the presence of sodium bromide and hydroperoxide, followed by demethylation to give the (*S*)-4,4′-dibromo-1,1′-dihydroxy-9,9′-spirobifluorene (**16**) in 73% yield in three steps. The diol **16** was converted to (*S*)-1,1′-dihydroxy-4,4′-dimethoxy-9,9′-spirobifluorene (**17**) by reaction with sodium




**Scheme 4**. Reagents and conditions: (a) $Pd(PPh_3)_4$, dioxane, 50 °C, 71%. (b) (i) *n*-BuLi, THF, −78 °C; (ii) MeOCOOMe, THF, 70%. (c) PPA, 150 °C, 79%. (d) $BBr_3$, $CH_2Cl_2$, −78 °C to rt, 89%.




**Scheme 5**. Reagents and conditions: (a) KOH, MeI, water, rt, 4 h, 97%. (b) NaBr, $H_2O_2$, HAc, rt, 10 h, 88%. (c) $BBr_3$, $CH_2Cl_2$, −78 °C to rt, 8 h, 85%. (d) NaOMe, CuCl, DMF, 120 °C, 10 h, 59%. (e) $Tf_2O$, Py, $CH_2Cl_2$, 0 °C, 70%. (f) Pd/C/$H_2$, $K_2CO_3$, *i*-PrOH, 45%. (g) $BBr_3$, $CH_2Cl_2$, −78 °C to rt, 73%.

methoxide catalyzed by copper(I) chloride with 59% yield.[12] The esterification of compound **17** with $Tf_2O$, followed by palladium-catalyzed hydrogenation and demethylation with $BBr_3$ finally gave (*S*)-(+)-**12** with 23% yield in three steps (Scheme 5).

## 3. Experimental

### 3.1. General

All reactions and manipulations were performed using standard Schlenk techniques. THF was distilled from sodium benzophenone ketyl. $CH_2Cl_2$ was distilled from $CaH_2$. Melting points were measured on a RY-I apparatus and uncorrected. $^1H$, $^{13}C$ and $^{31}P$ NMR spectra were recorded on Varian Mercury Vx-300 or Bruker 300 MHz spectrometers. Chemical shifts were reported in parts per million down field from internal $Me_4Si$. Optical rotations were determined using a Perkin–Elmer 341 MC polarimeter. Elemental analyses were performed on Yanaca CDRDER MT-3 instrument. Mass spectra were recorded on a VG-7070E spectrometer. HPLC analyses were performed on a Hewlett–Packard Model HP 1100 Series or a Waters 600E.

### 3.2. Synthesis of racemic 2,2′-dihydroxy-9,9′-spirobifluorene

**3.2.1. Preparation of 2-bromo-4′-methoxybiphenyl (1).** A solution of 4-methoxy-1-bromobenzene (16.6 g, 89 mmol)

in 40 mL of THF was added dropwise to the magnesium scraps under nitrogen atmosphere at 40 °C over 30 min. The reaction mixture was refluxed for 1 h and transferred into a nitrogen flushed flask charged with 1,2-dibromobenzene (20.0 g, 92 mmol) and tetrakis(triphenylphosphine)palladium (1.5 g, 1.3 mmol) in 100 mL of THF. The mixture was stirred for 30 h at 40 °C and quenched with saturated $NH_4Cl$ solution, diluted with $Et_2O$, washed with 3 M HCl and brine, dried over $MgSO_4$. Evaporation of the solvent under reduced pressure yielded the crude product that was purified by chromatography on silica gel with PE/EA (30:1, v/v). The product **1** was obtained as a colorless liquid (11.8 g, 50%), which solidified after standing at room temperature. Mp 53–54 °C (lit. 55 °C);[13] $^1$H NMR ($CDCl_3$) $\delta$ 3.85 (s, 3H, Ar-$OCH_3$), 6.96 (d, 2H, $J$=9 Hz, Ar-H), 7.13–7.19 (m, 1H, Ar-H), 7.31–7.36 (m, 4H, Ar-H), 7.65 (d, 1H, $J$=7.5 Hz, Ar-H).

**3.2.2. Preparation of bis(4′-methoxybiphenyl-2-yl)-methanone (2).** To a solution of **1** (5.9 g, 22.4 mmol) in 40 mL of THF at −78 °C was added *n*-BuLi (13.5 mL, 27 mmol, 2.0 M in hexane), and the yellow solution was stirred for another 0.5 h. After slow addition of dimethyl carbonate (0.91 g, 10.1 mmol) in 20 mL of THF, this mixture was gradually warmed to −50 to −45 °C and kept at this temperature for 4 h resulting in a yellow slurry. This slurry was warmed to room temperature and quenched with saturated $NH_4Cl$ solution. The solvent was then removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$, washed with 3 M HCl and brine, dried over $MgSO_4$, concentrated under reduced pressure to afford a yellow solid. The solid was washed with petroleum ether, recrystallized with PE/EA (2:1, v/v) to give **2** as a white solid (2.3 g, 60%). Mp 153–154 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.76 (s, 6H, Ar-$OCH_3$), 6.73 (d, 4H, $J$=8.7 Hz, Ar-H), 7.03 (d, 4H, $J$=8.7 Hz, Ar-H), 7.13 (d, 2H, $J$=7.8 Hz, Ar-H), 7.18 (t, 2H, $J$=7.5 Hz, Ar-H), 7.32 (t, 2H, $J$=7.5 Hz, Ar-H), 7.42 (d, 2H, $J$=7.5 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.3, 113.4, 126.3, 130.1, 130.6, 130.7, 133.0, 139.1, 141.2, 158.8; MS (ESI) (*m*/*z*, %): 386 (M+H$^+$, 100%); Anal. Calcd for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.47; H, 5.80.

**3.2.3. Preparation of 2,2′-dihyroxy-9,9′-spirobifluorene (3).** Well-powdered **2** (1.05 g, 3.7 mmol) was added to MsOH (7 mL) and heated at 120 °C for 8 h. The reaction mixture was diluted with water, extracted with EA. The organic phase was dried over $Na_2SO_4$ and concentrated to give a brown solid that was subjected to chromatography on silica gel with PE/EA (1:1, v/v) to offer **3** as a white solid (0.65 g, yield 70%). Mp 284–287 °C (lit. 286–287 °C);[7b] $^1$H NMR ($CDCl_3$) $\delta$ 4.77 (s, 2H, OH), 6.17 (s, 2H, Ar-H), 6.71 (d, 2H, $J$=7.8 Hz, Ar-H), 6.81 (d, 2H, $J$=8.4 Hz, Ar-H), 7.04 (t, 2H, $J$=7.5 Hz, Ar-H), 7.33 (t, 2H, $J$=7.5 Hz, Ar-H), 7.67 (d, 2H, $J$=8.4 Hz, Ar-H), 7.73 (d, 2H, $J$=7.5 Hz, Ar-H).

### 3.3. Synthesis and resolution of racemic 3,3′-dihydroxy-9,9′-spirobifluorene (7)

**3.3.1. Preparation of 3,3′-dimethoxy-9,9′-spirobifluorene (6).**[14] The well-powdered **5** (1.0 g, 2.5 mmol) was added to MsOH (30 mL) and warmed at 35 °C for 3 h. The reaction mixture was poured into ice water and extracted twice with EA. The organic phase was washed with aqueous $Na_2CO_3$, dried over $Na_2SO_4$, and concentrated. The crude product was chromatographed on silica gel with PE/EA (3:1, v/v) to afford **6** as a white solid (0.92 g, 96%). Mp 187–189 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.88 (s, 6H, Ar-$OCH_3$), 6.66–6.72 (m, 6H, Ar-H), 7.09 (t, 2H, $J$=7.5 Hz, Ar-H), 7.32–7.37 (m, 4H, Ar-H), 7.79 (d, 2H, $J$=7.5 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.5, 64.7, 105.2, 113.9, 119.9, 123.9, 124.6, 127.5, 127.9, 140.8, 141.5, 143.0, 149.9, 159.8; MS (EI) (*m*/*z*, %): 376 (M$^+$, 100%); Anal. Calcd for $C_{27}H_{20}O_2$: C, 86.14; H, 5.36. Found: C, 85.98; H, 5.30.

**3.3.2. Preparation of 3,3′-dihyroxy-9,9′-spirobifluorene (7).** To a flask charged with **6** (2.9 g, 7.7 mmol) in 40 mL of $CH_2Cl_2$ at −78 °C under a nitrogen atmosphere, a solution of $BBr_3$ (3 mL, 32 mmol) in 10 mL of $CH_2Cl_2$ was added dropwise with stirring. After addition, the reaction was spontaneously warmed to room temperature and kept at this temperature for 8 h. The dark solution was washed with $NaHSO_3$ and $NaHCO_3$. The organic phase was dried over $Na_2SO_4$ and concentrated under reduced pressure. After chromatography on silica gel with PE/EA (2:1, v/v) product **7** was obtained as a white solid (2.4 g, yield 90%). Mp 237–241 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.30 (s, 2H, Ar-OH), 6.43 (d, 2H, $J$=8.4 Hz, Ar-H), 6.55 (d, 2H, $J$=7.6 Hz, Ar-H), 7.03 (t, 2H, $J$=7.6 Hz, Ar-H), 7.27–7.35 (m, 4H, Ar-H), 7.77 (d, 2H, $J$=7.6 Hz, Ar-H); $^{13}$C NMR ($CD_3OD$) $\delta$ 64.8, 106.4, 114.9, 119.9, 123.6, 124.3, 127.4, 139.9, 141.8, 143.2, 150.3, 157.4, 127.5; MS (ESI) (*m*/*z*, %): 347 (M−H$^+$, 60%); Anal. Calcd for $C_{25}H_{20}O_2$: C, 86.19; H, 4.63. Found: C, 85.98; H, 5.03.

**3.3.3. Resolution of 3,3′-dihydroxy-9,9′-spirobifluorene (7).** To a well-powdered mixture of racemic **7** (500 mg, 1.44 mmol) and (*R*,*R*)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetracyclohexylsuccinamide (**8**) (755 mg, 1.50 mmol) was added 1 mL of acetone to give a clear solution. After a white precipitate appeared a further 1 mL of acetone was added to the mixture and stirred at room temperature for 8 h. The mixture was filtrated and the solid was dissolved in $Et_2O$ and washed with 1 M NaOH three times. The organic phase was dried over $Na_2SO_4$ and concentrated to recover the resolving reagent **8**. The aqueous phase was acidified with 12 M HCl to pH=3 and extracted with $CH_2Cl_2$ twice. The organic phase was dried over $Na_2SO_4$ and concentrated to give product **7** as a white solid (0.16 g, 30% recovery). The optical purity was determined to be 60% ee by chiral HPLC [AD-H (25 cm×0.46 cm i.d.), hexane/2-PrOH = 75:25, $t_R$ of (+)-isomer is 8.9 min, $t_R$ of (−)-isomer is 17.7 min]. A sample of **7** with predominant (−)-configuration was subjected to the resolution procedure twice to give enantiomerically pure (−)-**7** in 15% total recovery. Mp 239–241 °C, $[\alpha]_D^{25}$ −1.82 (*c* 0.66, acetone).

### 3.4. Synthesis and resolution of 4,4′-dihydroxy-9,9′-spirobifluorene

**3.4.1. Preparation of 2′-bromo-2-methoxy-biphenyl (9).** To a flask charged with $Pd(PPh_3)_4$ (0.21 g, 0.19 mmol), $K_2CO_3$ (2.75 g, 19.9 mmol) was added 6 mL of dioxane and 1,2-dibromobenzene (2.28 g, 9.66 mmol), the mixture was heated at 50 °C and 2-methoxy-1-benzeneboronic acid (1 g, 6.45 mmol, in 6 mL of dioxane) was added over 4 h. The reaction was then quenched with 3 M HCl and extracted

with EA. The organic phase was dried over $Na_2SO_4$ and concentrated. After chromatography on silica gel with PE/EA (30:1, v/v), 1.2 g (71% yield) white solid was obtained. Mp 58 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.79 (s, 3H, Ar-$OCH_3$), 6.97–7.05 (m, 2H, Ar-H), 7.15–7.23 (m, 2H, Ar-H), 7.27–7.41 (m, 3H, Ar-H), 7.65 (d, 1H, $J$=8.1 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.6, 110.1, 120.3, 124.3, 127.0, 128.6, 129.3, 130.3, 130.8, 131.6, 132.4, 139.8, 156.6; MS (EI) (*m*/*z*, %): 262, 264 ($M^+$, 100%); Anal. Calcd for $C_{13}H_{11}BrO$: C, 59.34; H, 4.21. Found: C, 59.35; H, 4.10.

**3.4.2. Preparation of bis(2′-methoxybiphenyl-2-yl)-methanone (10).** To a flask charged with **9** (5 g, 19.0 mmol) and 30 mL of THF was added *n*-BuLi (10 mL, 2.1 M in hexane, 21 mmol) at −78 °C. The mixture was stirred at −78 °C for 20 min, and a solution of dimethyl carbonate (0.727 g, 8.08 mmol) was added dropwise over 5 min. The reaction mixture was allowed to warm to room temperature spontaneously and quenched with aqueous $NH_4Cl$. After concentration under reduced pressure the residue was dissolved in $CH_2Cl_2$ and washed with 3 M HCl. The organic phase was dried over $Na_2SO_4$ and concentrated. The residue was washed with PE/EA (5:1, v/v) to give a pale yellow solid (2.5 g, 70%). Mp 235–237 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.50 (s, 6H, Ar-$OCH_3$), 6.69 (d, 2H, $J$=7.8 Hz, Ar-H), 6.94 (t, 3H, $J$=7.5 Hz, Ar-H), 7.14–7.32 (m, 8H, Ar-H), 7.47 (t, 2H, $J$=7.5 Hz, Ar-H), 7.58 (d, 2H, $J$=7.2 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 54.6, 110.2, 120.8, 126.0, 128.6, 129.9, 130.4, 130.5, 130.7, 131.3, 138.6, 139.3, 155.3; MS (EI) (*m*/*z*, %): 394 ($M^+$, 35%); Anal. Calcd for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.11; H, 5.57.

**3.4.3. Preparation of 4,4′-dimethoxy-9,9′-spirobifluorene (11).** To a flask were added PPA (polyphosphoric acid, 20 mL) and bis(2′-methoxybiphenyl-2-yl)methanone (2.0 g, 5.2 mmol). The mixture was heated at 150 °C for 2 h and was poured into ice. The aqueous slurry was extracted with EA. The organic phase was dried over $Na_2SO_4$ and concentrated, followed by chromatography on silica gel with PE/EA (4:1, v/v) to afford **11** as a white solid (1.5 g, 79%). Mp 212–213 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.07 (s, 6H, Ar-$OCH_3$), 6.35 (d, 2H, $J$=7.2 Hz, Ar-H), 6.71 (d, 2H, $J$=7.5 Hz, Ar-H), 6.87 (d, 2H, $J$=8.4 Hz, Ar-H), 7.06 (t, 4H, $J$=7.8 Hz, Ar-H), 7.34 (t, 2H, $J$=7.5 Hz, Ar-H), 8.18 (d, 2H, $J$=7.8 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 55.4, 100.0, 109.6, 116.2, 123.4, 123.7, 126.9, 127.6, 128.8, 141.0, 148.0, 150.6, 155.7; MS (EI) (*m*/*z*, %): 376 ($M^+$, 100%); Anal. Calcd for $C_{27}H_{20}O_2$: C, 86.14; H, 5.36. Found: C, 86.08; H, 5.43.

**3.4.4. Preparation of 4,4′-dihydroxy-9,9′-spirobifluorene (12).** To a solution of **11** (1.4 g, 3.8 mmol) in 20 mL of $CH_2Cl_2$ at −78 °C under nitrogen atmosphere was added $BBr_3$ (1.4 mL, 14 mmol) in 10 mL of $CH_2Cl_2$. The mixture was allowed to warm to ambient temperature spontaneously and washed with aqueous $NaHSO_3$ and $NaHCO_3$, dried over $Na_2SO_4$, and concentrated. The residue was subjected to chromatography on silica gel with PE/EA (2:1, v/v) to give **12** as a pale yellow solid (1.2 g, 89%). Mp 125–127 °C; $^1$H NMR ($CDCl_3$) $\delta$ 5.43 (s, 2H, Ar-OH), 6.34 (d, 2H, $J$=7.5 Hz, Ar-H), 6.71–6.74 (m, 4H, Ar-H), 6.96 (t, 2H, $J$=7.8 Hz, Ar-H), 7.08 (t, 2H, $J$=7.5 Hz, Ar-H), 7.36 (t, 2H, $J$=7.5 Hz, Ar-H), 8.15 (d, 2H, $J$=7.5 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$) $\delta$ 30.9, 114.8, 116.5, 123.5, 123.6, 127.0, 127.7, 128.4, 128.6, 140,7, 148,1, 151.2, 151.1; MS (ESI) (*m*/*z*, %): 347 ($M-H^+$, 30%); Anal. Calcd for $C_{25}H_{16}O_2$: C, 86.10; H, 4.63. Found: C, 85.95; H, 4.69.

**3.4.5. Resolution of 4,4′-dihyroxy-9,9′-spirobifluorene (12).** The racemic sample of **11** was directly subjected to HPLC resolution with a preparative Daicel AD-H column [HPLC conditions: hexane/2-PrOH = 85:15 (v/v); fluent rate, 3 mL/min; $t_R$ of (+)-isomer is 12.9 min, $t_R$ of (−)-isomer is 15.5 min]. The first peak corresponded to (+)-**11**. Mp 125–127 °C, $[\alpha]_D^{25}$ +2.7 (*c* 1.7, acetone).

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# A novel approach to the synthesis of diaza-bridged heterocycle derivatives

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**Abstract**—A novel synthetic route of diaza-bridged heterocycles based on natural 3,9-diazabicyclo[3.3.1]non-6-ene scaffold has been accomplished. The synthetic approach consists of a Pictet–Spengler condensation of the L-Dopa–OMe with an appropriate aldehyde, Fmoc–Aa–H, followed by intramolecular lactamization. This approach generated two configurationally distinct products (cis and trans-isomers), increasing the stereochemical diversity of these compounds. The synthesized compounds are potentially useful in the discovery of novel pharmacologically active compounds.


## 1. Introduction

In the process of identifying of useful scaffolds for medicinal chemistry, one possible approach is the use of diversity pool of natural products as a guideline to generate new templates. Among the natural products subjected to structural modification, tetrahydroisoquinoline alkaloids occupy a special position owing to their biological and pharmaceutical relevance.[1] In fact, some of these natural products, like saframycin, renieramycin, and ecteinascidin families show potent cytotoxic activity against a variety of tumor cell lines in vitro, against several rodent tumors and human tumor xenografts in vivo.[2–4] In all these families, a common 3,9-diazabicyclo[3.3.1]non-6-ene core structure is present (**A** and **B**, Fig. 1). In this context we directed our attention towards the synthesis of new diazatricyclic analogues as scaffold for design of potential antitumoral agents (structure **C**).

The usual strategy for the synthesis of **A** and **B** core structures consists to produce first a (di)ketopiperazine derivative and then to generate an acyl iminium intermediate for the cyclization on an appropriate scaffold.[5,6] Regarding the compounds correlated to scaffold **C**, Koch, Giger, and co-workers reported the synthesis in solution and solid phase of an indole 3,9-diazabicyclo[3.3.1]non-6-en-2-one derivate, starting from L-tryptophan, via sequential Dakin–West/Pictet–Spengler reactions.[7] Nevertheless, this strategy does not allow the formation of the phenolic tricyclic scaffold (structure **C**). More recently, Park et al. described the formation of the phenolic tricyclic scaffold via a sequential cyclic iminium formation and a Pictet–Spengler cyclization under acid condition (Scheme 1). This intramolecular reaction proceeds under strict control of regio- and diastereoselectivity with the formation of a single diastereoisomer.[8]

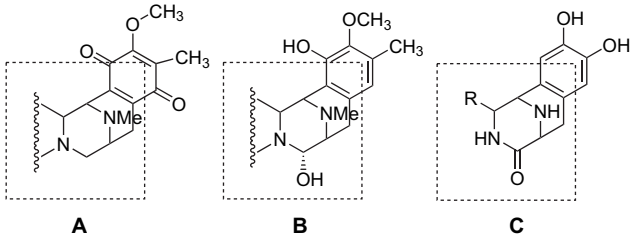


**Figure 1**. 3,9-Diazabicyclo[3.3.1]non-6-ene core structure present in saframycin and renieramycin (**A**), ecteinascidin (**B**), and the proposed structure 3,9-diazabicyclo[3.3.1]non-6-en-2-one (**C**).

In this communication we report an efficient and improved synthetic methodology to obtain molecules containing the **C** core structure (diaza-bridged heterocycle) starting from enantiopure amino acid derivatives. During the preparation of this manuscript Aubry et al. have reported a similar approach for the synthesis of diaza-bridged heterocycle derivatives.[9]

*Keywords*: Amino acids; Intramolecular cyclization; Molecular diversity; Antitumor agents.
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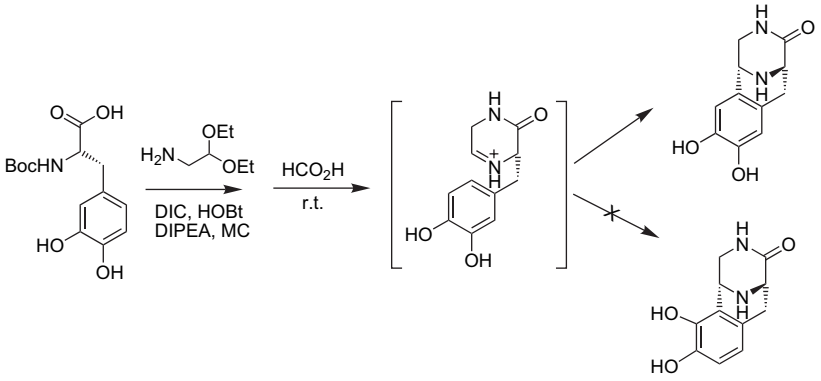
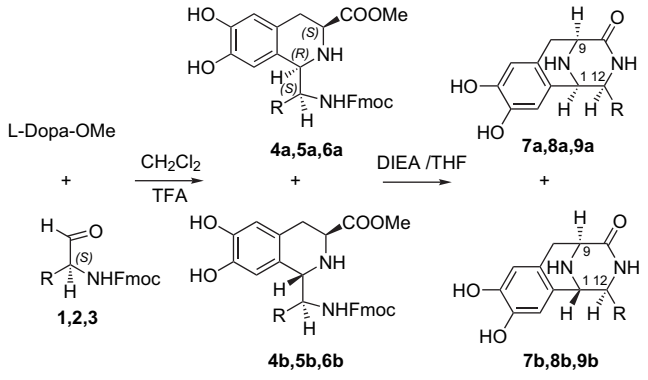


**Scheme 1**. Formation of the phenolic tricyclic scaffold proposed by Park et al.[8]

## 2. Results and discussion

Our approach involves the formation of a tetrahydroisoquinoline derivative via Pictet–Spengler[10] reaction between an appropriate enantiopure Fmoc–Aa–H and L-Dopa–OMe, and consecutive intramolecular lactamization to ketopiperazine. Conveniently protected 1,3-disubstituted tetrahydroisoquinolines were initially selected as intermediates for the preparation of the dihydroxydiazatricyclic derivatives. As shown in Scheme 2, compounds **4**–**6** were synthesized via Pictect–Spengler reaction. Accordingly, the Fmoc–Gly–H (**1**), and the enantiomeric pure Fmoc–L-Phe–H (**2**) and Fmoc–L-Ala–H (**3**), prepared from the corresponding Fmoc–L-amino acids reported in literature,[11,12] were condensed with L-Dopa–OMe in dichloromethane to generate the imine intermediates, which were treated with TFA to induce cyclization.[10,12]



**Scheme 2**. Solution synthesis of diazatricyclic lactam derivatives for **1**,**4**,**7**: R=H; **2**,**5**,**8**: R=$CH_3$; **3**,**6**,**9**: R=$CH_2$Ph.

After 6 h of reaction at room temperature, the desired tetrahydroisoquinolines were obtained as diastereoisomeric mixtures **4a**, **b** (a/b=3:2), **5a**, **b** (a/b=3:2), and **6a**, **b** (a/b=1:1) in 48, 50, and 51% yield, respectively. These results suggest that under these conditions, the Pictet–Spengler reaction is not diastereoselective. The diastereoisomeric a/b ratio (cis/trans, relative configuration between C-1 and C-3 protons) were determined from the crude reaction mixtures by HPLC or $^1$H NMR (Table 1).

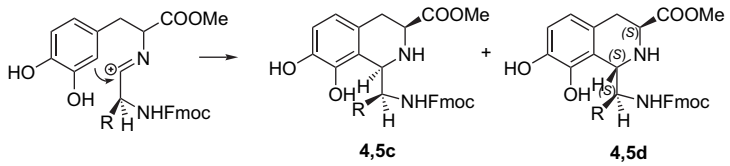
The diastereoisomeric mixture **4**, **5**, and **6** were chromatographically resolved and their configuration at C-1 were confirmed by NMR analysis.[13] In addition, a third series of compounds were also detected and isolated from the crude **4** and **5** (≈10 and 7% yield), while no additional compounds were detected from crude **6**. These additional compounds were identified by NMR analysis as cis and trans mixture of the 1,2,3,4-tetrahydro-7,8-hydroxy-isoquinoline regioisomers **4c**, **4d** (**c**/**d**=3:1) and **5c**, **5d** (**c**/**d**=3:1). The formation of compounds **4c**, **4d** and **5c**, **5d** might be explained by condensation between the iminium ion and the aromatic C-2 by nucleophile reaction (Scheme 3).

When the regioisomeric mixtures **4c**, **4d** and **5c**, **5d** were subjected to further purification process only the cis-regioisomers **4c** and **5c** were isolated as pure (see experimental data). Finally, the diazatricyclic derivatives **7a**, **7b**; **8a**, **8b** and **9a**, **9b** were easily obtained, in quantitative yields, by intramolecular lactamization of the corresponding tetrahydroisoquinolines in condition of cleavage of Fmoc protecting group, using 33% DIEA/THF solution at room temperature. This kind of cyclization, concomitant with removal of the *N*-protecting group, has already been described

**Table 1**. Tetrahydroisoquinoline (**4**–**6**) and diazatricyclic derivatives (**7**–**9**)

| Amino aldehyde | R | Tetrahydroisoquinoline | Yield[a] (%) | a/b Ratio | HPLC[b] $t_r$ (min) | Diazatricyclic derivative | Yield (%) | HPLC[b] $t_r$ (min) |
|---|---|---|---|---|---|---|---|---|
| 1 | H | **4a** | 29 | 1.5:1 | 24.13 | **7a** | 91 | 16.32 |
| | | **4b** | 19 | | 24.36 | **7b** | 92 | 16.47 |
| 2 | $CH_3$ | **5a** | 28 | 1.2:1 | 23.43 | **8a** | 91 | 14.86 |
| | | **5b** | 23 | | 23.57 | **8b** | 89 | 15.21 |
| 3 | $CH_2$Ph | **6a** | 26 | 1:1 | 22.47 | **9a** | 92 | 13.72 |
| | | **6b** | 25 | | 22.78 | **9b** | 90 | 13.98 |

[a] Isolated yield for chromatographically purified compounds.
[b] Analytical RP-HPLC was performed on a C18 column (Vydac 218TP54) using a gradient of acetonitrile in 0.1% aqueous TFA (10–40%) in 45 min at 1 mL/min.




**Scheme 3**. Formation of compounds **c** and **d**.

during the *N*-deprotection of Z- and Boc–aminomethylene pseudo-dipeptide methyl esters under catalytic hydrogenation or acidic conditions.[13]

To confirm the relative configuration of the heterocyclic core structures, extensive NMR studies, including $^{1}$H COSY, ROESY, HSQC, and HMBC experiments, were carried out on final compounds (see Supplementary information). The C-1 stereochemistry in all compounds was assigned on the basis of ROESY studies (Fig. 2).

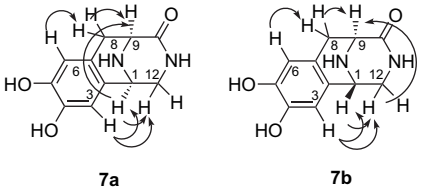



**Figure 2**. NOEs observed for compounds **7a** and **7b**.

Thus, weak exchanges of magnetization among the H-1 and H-9 protons in compound **7a**, **8a**, and **9a** indicated that these protons were in cis disposition. On the contrary, these NOEs were not observed in the diastereoisomer **7b**, **8b**, and **9b**, in which the H-1 proton has a trans-relationship with respect to the H-9. Since the synthesis starts from DOPA, the absolute configuration at C-9 is *S*, consequently we assigned the configuration as *R* at C-1 in compounds **7**, **8**, and **9a** and as *S* in compounds **7**, **8**, and **9b**. For the cis diastereoisomers other significant NOE effects were observed between H-12′/H-1, H-12′/H-8, H-12′/H-9 (**9a**), and H-12′/H-3 (**8a**) whereas for the trans diastereoisomers, NOE effects were also observed between H-9/H-12 (**8b**, **9b**) and H-3/H-12′ (**8b**) (Table 2).

In the $^{1}$H NMR spectra, the main differences between 1*R* (**a**) and 1*S* (**b**)-diastereoisomers were found for the chemical shifts of the H-1 and H-9. Thus, the H-1 and H-9 resonance in compounds having *R* configuration appeared shielded when compared to the same protons in the 1*S*-isomers (0.3–0.8 and 0.2–0.8 ppm). In addition, the C-1 and C-9 resonance in the 1*S* derivatives appear at higher field than the corresponding carbons of the 1*R*-isomers.

The final enantiomeric purity of the synthesized compounds was checked by HPLC analysis using chiral Shiseido Ceramospher RU-2 column, using as gradient acetonitrile/water (90:10)+0.1% diethylamine in 30 min.

Compared to previous synthetic methods described in literature for the preparation of similar bicyclo[3.3.1]nonane systems, this approach contains noteworthy features. In fact, the reaction conditions used allow the formation of two configurationally distinct products (cis and trans-isomers) increasing the stereochemical diversity of these compounds. In addition, this route provides access to the diversification of core skeleton at C-12 starting from synthetically available enantiopure aminoaldehydes.

In conclusion, we have described an efficient synthetic approach to diazatricyclic lactam derivatives, which can be used as core building blocks for combinatorial synthesis as well as for further exploration of their chemistry and pharmaceutical properties. Biological testing of the obtained compounds and the potential diversification of our scaffold is currently under way.

## 3. Experimental

### 3.1. General

Reagents, starting material, and solvents were purchased from commercial suppliers and used as received. Analytical TLC was performed on a 0.25 mm layer of silica gel 60 $F_{254}$ Merck and preparative TLC on 20×20 cm glass plates coated with a 2 mm layer of silica gel $PF_{254}$ Merck. Silica gel 60 (300–400 mesh), Merck, was used for flash

**Table 2**. Significant $^{1}$H and $^{13}$C NMR data for the diazatricyclic lactam derivatives (**7**, **8**, and **9**)

| | | **7a**[a] | **7b**[a] | **8a**[a] | **8b**[a] | **9a**[b] | **9b**[b] |
|---|---|---|---|---|---|---|---|
| $^{1}$H NMR | 1-H | 3.90 | 4.74 | 3.82 | 4.08 | 3.73 | 4.03 |
| | 8-H | 2.50, 2.82 | 2.86, 3.17 | 2.58, 2.90 | 2.73, 3.01 | 2.72, 3.05 | 2.78, 3.10 |
| | 9-H | 3.46 | 4.22 | 3.65 | 3.81 | 3.51 | 3.73 |
| | 12-H | 2.95 | 3.17 | 3.77 | 4.11 | 3.70 | 4.21 |
| | $J_{1,12}$ | 3.6 | 4.0 | 1.7 | 2.0 | 1.6 | 2.0 |
| | $J_{8,9}$ | 5.6 | 5.2, 0.0 | 5.6, 0.0 | 4.9 | 7.6, 0.0 | 6.8, 0.0 |
| $^{13}$C NMR | C-1 | 48.49 | 47.54 | 49.61 | 48.45 | 52.46 | 51.85 |
| | C-8 | 32.63 | 29.95 | 31.32 | 31.40 | 31.53 | 32.04 |
| | C-9 | 53.37 | 51.06 | 58.23 | 56.40 | 62.03 | 59.26 |
| | C-12 | 50.83 | 46.86 | 51.43 | 53.34 | 49.62 | 52.51 |

[a] Registered in DMSO-$d_6$.
[b] Registered in $CD_3OD$.

chromatography (FC). Melting points were taken on a Kofler apparatus and are uncorrected. Optical rotations were determined by a Perkin–Elmer-241MC polarimeter using methanol as solvent. $^1$H NMR spectra were recorded with a Varian 400 spectrometer, operating at 400 MHz. Chemical shifts are reported in $\delta$ values (ppm) relative to internal $Me_4Si$ and $J$ values are reported in Hertz (Hz). Analytical RP-HPLC was performed on a C18 column (Vydac 218TP54) using a gradient of acetonitrile in 0.1% aqueous TFA (10–40%) in 45 min at 1 mL/min. Mass spectra were obtained using a FABMS spectrometer. Starting Fmoc–Gly–H, Fmoc–L-Phe–H, and Fmoc–L-Ala–H were prepared according to the procedure as previously described.[11,12a]

### 3.2. General procedure for the synthesis of (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*)-1-[(*N*-fluorenyl)metoxycarbonyl]amino-substituted-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (4–6a and b)

To a solution of Fmoc–L-amino aldehydes **1** or **2** or **3** (3.40 mmol) in dichloromethane (30 mL) were added L-Dopa–OMe (3.40 mmol) and TFA (3.40 mmol), and the mixture was stirred at room temperature for 6 h. Then, the mixture was concentrated in vacuo and dichloromethane was added. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$, and evaporated. The title compounds were purified by flash chromatography (FC) using different eluent systems.

**3.2.1. (1*R*,3*S*) and (1*S*,3*S*)-1-[(*N*-fluorenyl)metoxycarbonyl]aminomethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (4a and 4b).** FC AcOEt/*n*-hexane (3/1). Isomer **4a**: 0.47 g, 29%. White solid, mp 145–147 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.67–2.86 (m, 2H, H-4); 3.26 (m, 1H, H-1′); 3.52 (dd, $J_1$=2.9 Hz, $J_2$=10.4 Hz, 1H, H-3); 3.72 (s, 3H, OC$H_3$); 3.80 (m, 1H, H-1″); 3.97 (m, 1H, H-1); 4.35 (m, 2H, C$H_2$ Fmoc); 4.41 (m, 1H, C*H* Fmoc); 6.60 (s, 1H, H-5); 6.69 (s, 1H, H-8); 7.03–7.18 (m, 2H, aryl); 7.29–7.62 (m, 4H, aryl); 7.64–7.83 (m, 2H, aryl). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 29.72 (C-4); 43.63 (C-1′); 57.90 (C-1); 67.78 (C-3); 112.43 (C-5); 116.35 (C-8); 122.72, 123.81, 126.56, 127.80, 127.45, 128.30, 130.22, 145.51, 146.71 (aryl), 156.13, 170.49 (C=O). ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 474.18, found 474.21.

Isomer **4b**: 0.30 g, 19%. White solid, mp 129–130 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.67–2.86 (m, 2H, H-4); 3.27 (m, 1H, H-1′); 3.51 (dd, $J_1$=2.9 Hz, $J_2$=10.4 Hz, 1H, H-3); 3.67 (m, 1H, H-1″); 3.71 (s, 3H, OC$H_3$); 4.01 (m, 1H, H-1); 4.39 (m, 2H, C$H_2$ Fmoc); 4.50 (m, 1H, C*H* Fmoc); 6.53 (s, 1H, H-5); 6.67 (s, 1H, H-8); 7.00–7.19 (m, 2H, aryl); 7.24–7.61 (m, 4H, aryl); 7.63–7.82 (m, 2H, aryl). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 31.72 (C-4); 45.75 (C-1′); 55.86 (C-1); 66.63 (C-3); 111.98 (C-5); 115.24 (C-8); 123.65, 123.81, 125.82, 127.35, 127.69, 128.19, 130.12, 145.42, 146.73 (aryl), 156.03, 171.03 (C=O). ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 474.18, found 474.31.

The mixture of the corresponding 1,2,3,4-tetrahydro-7,8-dihydroxyisoquinoline (**4c** and **4d**) was submitted to further purification by FC using AcOEt/*n*-hexane (5/1). Isomer **4c**: 0.05 g, 3%. White solid, mp 113–115 °C. Significant data $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 2.63 (dd, $J$=11.6 and 15.6 Hz, 1H, H-4); 2.88–2.93 (m, 2H, H-4′and H-1′); 3.36 (dd, $J$=3.6 and 14.4 Hz, 1H, H-1″); 3.64–3.68 (m, 5H, H-3, and $CH_3$ ester); 3.98 (m, 1H, H-1); 6.45 (d, $J$=8.0 Hz, 1H, H-5); 6.62 (d, 1H, H-6). $^{13}$C NMR (100 MHz, $CD_3OD$): 25.70 (C-4); 44.63 (C-1′); 52.60 (C-3); 53.99 (C-1). ROESY data: NOE effects between H-1/H-3, H-4/H-5, and H-1′/H-4 were observed. ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 474.18, found 474.23. Mixture **4c** and **4d** 0.11 g, 7%, (**c**/**d** ratio 2:1). $^1$H NMR **4d** (400 MHz, $CD_3Cl$, from the **4c**+**4d** mixture): $\delta$ 2.58–2.62 (m, $J$=15.6 Hz, 2H, H-4); 2.91 (m, 1H, H-1′); 3.40 (dd, $J$=5.8 and 14.3 Hz, 1H, H-1″); 3.72 (s, 3H, $CH_3$ ester); 3.79 (m, 1H, H-3); 4.03 (m, 1H, H-1); 6.52 (d, $J$=8.0 Hz, 1H, H-5); 6.64 (d, 1H, H-6).

**3.2.2. (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*)-1-[1′-(*N*-fluorenyl)-metoxycarbonyl]amino]ethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (5a and 5b).** FC AcOEt/*n*-hexane (3/1). Isomer **5a**: 0.46 g, 28%. White solid, mp 141–43 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.01 (d, 3H, C$H_3$); 2.75 (m, 1H, H-4a); 3.07 (m, 1H, H-4b,); 3.70 (m,1H, H-3); 3.85 (s, 3H, OC$H_3$); 4.30–4.33 (m, 2H, H-1, H-1′); 4.47 (m, 2H, C$H_2$ Fmoc); 4.78 (m, 1H, C*H* Fmoc); 6.38 (s, 1H, H-5); 6.50 (s, 1H, H-8); 7.10–7.19 (m, 2H, aryl); 7.26–7.59 (m, 4H, aryl); 7.65–7.85 (m, 2H, aryl). $^{13}$C NMR (100 MHz, $CDCl_3$): 13.31 (C-2′); 25.43 (C-4); 49.29 (C-1′); 51.42 (ester); 56.40 (C-3); 56.50 (C-1); 112.00 (C-5); 115.26 (C-8); 123.04, 124.79, 125.19, 127.56, 127.92, 128.87, 130.19, 141.70, 144.26, 149.09 (aryl), 155.47 and 174.16 (C=O). ESMS *m*/*z* calcd for $C_{28}H_{28}N_2O_6$ 488.19, found 488.31.

Isomer **5b**: 0.38 g, 23%. White solid, mp 134–135 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.35 (d, 3H, H2′); 3.15–3.29 (m, 2H, H-4); 3.61 (s, 3H, ester C$H_3$); 4.02 (m, 1H, H-3); 4.34 (d, $J$=6.4 Hz, 1H, H-1′); 4.50 (d, $J$=6.4 Hz, 1H, H-1); 4.45 (m, 2H, C$H_2$ Fmoc); 4.77 (m, 1H, C*H* Fmoc); 6.51 (s, 1H, H-5); 6.65 (s, 1H, H-8). $^{13}$C NMR (100 MHz, $CDCl_3$): 18.27 (C-2′); 23.74 (C-4); 47.40 (C-3); 47.51 (C-1′); 52.64 (ester); 53.42 (C-1); 111.00 (C-5); 114.86 (C-8); 123.21, 124.79, 125.20, 127.43, 127.58, 127.93, 128.67, 128.97, 130.43, 141.68, 144.47, 149.01 (aryl), 154.92 and 174.26 (C=O). ESMS *m*/*z* calcd for $C_{28}H_{28}N_2O_6$ 488.19, found 488.25.

The mixture of the corresponding 1,2,3,4-tetrahydro-7,8-dihydroxyisoquinoline (**5c** and **5d**) was submitted to further purification by FC using AcOEt/*n*-hexane (5/1). Isomer **5c**: 0.03 g, 2%. White solid, mp 124–126 °C. Significant data $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 1.35 (d, 3H, H2′); 2.85 (m, $J$=15.3 Hz, 1H, H-4); 3.06 (m, 2H, H-4′); 3.70 (m, 1H, H-3); 3.85 (s, 3H, ester C$H_3$); 4.30–4.33 (m, 2H, H-1, H-1′); 6.33 (d, $J$=8.0 Hz, 1H, H-5); 6.46 (d, 1H, H-6). $^{13}$C NMR (100 MHz, $CD_3OD$): 13.31 (C-2′); 25.43 (C-4); 49.29 (C-1′); 56.40 (C-3); 56.50 (C-1). ROESY data: NOE effects between H-1/H-3, H-4/H-5, and H-2′/H-4 were observed. ESMS *m*/*z* calcd for $C_{28}H_{28}N_2O_6$ 488.19, found 488.25. Mixture **5c** and **5d** 0.075 g, 5%, (**c**/**d** ratio 2:1). $^1$H NMR **5d** (400 MHz, $CD_3Cl$, from the **5c**+**5d** mixture): $\delta$ 1.33 (d, 3H, H2′); 3.15–3.29 (m, 2H, H-4); 3.71 (s, 3H, ester C$H_3$); 3.81 (m, 1H, H-3); 4.20 (m, 1H, H-1′); 4.35 (m, 1H, H-1); 6.50 (d, $J$=8.0 Hz, 1H, H-5); 6.61 (d, 1H, H-6).

**3.2.3. (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*)-1-[1′-(*N*-fluorenyl)-metoxycarbonyl]amino]phenylethyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (6a and 6b).** FC $CHCl_3$/MeOH (95/5). Isomer **6a**: 0.49 g, 26%. White solid, mp 165–167 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.87–2.95 (m, 2H, H-2′); 2.99–3.08 (m, 2H, H-4); 3.54 (s, 3H, $OCH_3$); 3.79 (d, *J*=10.0 Hz, 1H, H-3); 4.20 (m, 1H, H-1); 4.27 (d, *J*=8.8 Hz, 1H, H-1′); 4.41 (m, 2H, C*H*$_2$ Fmoc); 4.69 (m, 1H, C*H* Fmoc); 6.60 (s, 1H, H-5); 6.70 (s, 1H, H-8); 7.09–7.22 (m, 4H, aryl); 7.26–7.63 (m, 7H, aryl); 7.65–7.85 (m, 2H, aryl). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 30.19 (C-4); 38.92 (C-2′); 50.12 (C-3); 54.71 (C-1); 58.34 (C-1′); 113.87 (C-8); 115.65(C-5); 123.20, 124.77, 125.19, 126.11, 127.43, 127.58, 127.93, 128.14, 128.67, 128.97, 130.43, 138.52, 141.68, 144.47, 149.01 (aryl); 153.72 and 173.26 (C═O). ESMS *m*/*z* calcd for $C_{34}H_{32}N_2O_6$ 564.23, found 564.34.

Isomer **6b**: 0.48 g, 25%. White solid, mp 148–150 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 2.82(m, 1H, H-4a); 2.87–2.99 (m, 2H, H-2′, H-4b); 3.08 (m, 1H, H-2″); 3.57 (s, 3H, $OCH_3$); 3.92 (d, *J*=12.4 Hz, 1H, H-3); 4.15–4.22 (m, 2H, H-1 and H-1′); 4.28 (m, 2H, C*H*$_2$ Fmoc); 4.63 (m, 1H, C*H* Fmoc); 6.59 (s, 1H, H-5); 6.63 (s, 1H, H-8); 7.11–7.24 (m, 4H, aryl); 7.28–7.59 (m, 7H, aryl); 7.65–7.80 (m, 2H, aryl). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 32.12 (C-4); 40.11 (C-2′); 58.66 (C-1); 58.69 (C-3); 114.98 (C-5); 117.24 (C-8); 122.94, 124.57, 125.19, 126.34, 127.41, 127.58, 127.89, 128.14, 128.67, 128.56, 131.13, 138.12, 141.63, 144.29, 149.00 (aryl); 154.12 and 172.98 (C═O). ESMS *m*/*z* calcd for $C_{27}H_{26}N_2O_6$ 564.23, found 564.39.

### 3.3. Synthesis of (1*R*,3*S*,1′*S*) and (1*S*,3*S*,1′*S*) 12-substituted-4,5-dihydroxy-11,13-diazatricyclo-[7.3.1.0$^{2,7}$]trideca-3,5,7-trien-10-one (7–9a and 9b)

To a solution of tetrahydroisoquinoline **4a** or **4b**, or **5a** or **5b** or **6a** or **6b** (0.60 mmol) in dry tetrahydrofuran (7 mL), diethylamine (3 mL) was added and the mixture was stirred at room temperature for 2 h. Then the solution was evaporated under reduced pressure and the corresponding diazatricyclic derivatives (**8a** and **8b**, **9a** and **9b**) were precipitated by treatment of the crude residue with EtOAc/*n*-hexane.

**3.3.1. (1*R*,3*S*)-4,5-Dihydroxy-11,13-diazatricyclo[7.3.1.0$^{2,7}$]trideca-3,5,7-trien-10-one (7a).** Purified by FC $CHCl_3$/MeOH (95/5). Oil, 120 mg, 91%. $[\alpha]_D^{20}$ −30.0 (*c*=1.0, acetone). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.49 (m, 1H, H-8,); 2.81 (dd, *J*=5.6 Hz, 1H, H-8′); 2.94 (m, *J*=11.2 Hz, 1H, H-12); 3.45 (d, *J*=5.6 Hz, 1H, H-9); 3.56 (dd, *J*=3.6 Hz, 1H, H-12′); 3.90 (d, *J*=3.6 Hz, 1H, H-1); 6.38 (s, 1H, H-6); 6.50 (s, 1H, H-3). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 32.63 (C-8); 48.49 (C-1); 50.83 (C-12); 53.37 (C-9); 114.19 (C-3); 115.64 (C-6); 124.94 (C-7); 128.58 (C-2); 144.19 (C-4); 144.92 (C-5); 172.33 (C═O). ESMS *m*/*z* calcd for $C_{11}H_{12}N_2O_3$ 220.08, found 220.21.

**3.3.2. (1*S*,3*S*)-4,5-Dihydroxy-11,13-diazatricyclo-[7.3.1.0$^{2,7}$]trideca-3,5,7-trien-10-one (7b).** Purified by FC $CHCl_3$/MeOH (95/5). Oil, 0.12 g, 92%. $[\alpha]_D^{20}$ −14.3 (*c*=1.0, acetone). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.83–2.87 (dd, *J*=16.8 and 0.0 Hz, 1H, H-8); 3.14–3.19 (m, 2H, H-8′ and H-12); 3.74–3.78 (dd, *J*=12.2 and 4.0 Hz, 1H, H-12′); 4.21 (d, *J*=5.2 Hz, 1H, H-9); 4.74 (d, *J*=2.0 Hz, 1H, H-1); 6.54 (s, 1H, H-6); 6.69 (s, 1H, H-3). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 29.94 (C-8); 46.86 (C-12); 47.54 (C-1); 51.06 (C-9); 114.25 (C-6); 115.26 (C-3); 121.72 (C-7); 121.81 (C-2); 145.51 (C-4); 146.74 (C-5); 166.49 (C═O). ESMS *m*/*z* calcd for $C_{11}H_{12}N_2O_3$ 220.08, found 220.26.

**3.3.3. (1*R*,3*S*,1′*S*) 12-Methyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0$^{2,7}$]trideca-3,5,7-trien-10-one (8a).** 0.13 g, 91%. White solid, mp 208–210 °C. $[\alpha]_D^{20}$ −13.6 (*c*=1.2, acetone). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.38 (d, 3H, $CH_3$); 2.58 (m, 1H, H-8); 2.90 (dd, *J*=5.6 Hz, 1H, H-8′); 3.65 (d, *J*=5.6 Hz, 1H, H-9); 3.77 (d, *J*=1.7 Hz, 1H, H-12); 3.82 (d, *J*=1.7 Hz, 1H, H-1); 6.40 (s, 1H, H-6); 6.51 (s, 1H, H-3). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 16.23 (C-12′); 31.32 (C-8); 49.61 (C-1); 51.43 (C-12); 58.23 (C-9); 113.29 (C-3); 114.64 (C-6); 127.84 (C-7); 129.52 (C-2); 144.25 (C-4); 144.91 (C-5); 172.63 (C═O). ESMS *m*/*z* calcd for $C_{12}H_{14}N_2O_3$ 234.10, found 234.21.

**3.3.4. (1*S*,3*S*,1′*S*) 12-Methyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0$^{2,7}$]trideca-3,5,7-trien-10-one (8b).** 0.12 g, 89%. White solid, mp 192–193 °C. $[\alpha]_D^{20}$ +2.7 (*c*=1.2, acetone). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.35 (d, 3H, $CH_3$); 2.73 (m, 1H, H-8); 3.01 (dd, *J*=4.9 Hz, 1H, H-8′); 3.81 (d, *J*=4.9 Hz, 1H, H-9); 4.08 (d, *J*=2.0 Hz, 1H, H-1); 4.11 (d, *J*=2.0 Hz, 1H, H-12); 6.43 (s, 1H, H-6); 6.49 (s, 1H, H-3). $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 18.00 (C-12′); 31.40 (C-8); 48.45 (C-1); 53.34 (C-12); 56.40 (C-9); 114.19 (C-3); 114.64 (C-6); 127.81 (C-7); 129.62 (C-2); 144.15 (C-4); 144.83 (C-5); 171.59 (C═O). ESMS *m*/*z* calcd for $C_{12}H_{14}N_2O_3$ 234.10, found 234.20.

**3.3.5. (1*R*,3*S*,1′*S*) 12-Benzyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0$^{2,7}$]trideca-3,5,7-trien-10-one (9a).** 0.17 g, 92%. White solid, mp 259–260 °C. $[\alpha]_D^{20}$ −52.7 (*c*=1.00, acetone). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.84–2.86 (m, 2H, H-8, H-12′); 3.07 (dd, 1H, H-12″); 3.25 (dd, 1H, H-8′); 3.57 (t, *J*=4.0 Hz, 1H, H-9); 4.23–4.26 (m, 2H, H-1, H-12); 6.18 (s, 1H, H-3); 6.53 (s, 1H, H-6); 7.22–7.32 (m, 5H, aryl). $^1$H NMR (400 MHz, $CD_3OD$): δ 2.72 (dd, *J*=16 and 0.0 Hz, 1H, H-8); 3.03–3.08 (m, 3H, H-12′, H-12″, H-8′); 3.51 (t, *J*=7.6 Hz, 1H, H-9); 3.70 (d, *J*=6.4 Hz, 1H, H-12); 3.73 (d, *J*=1.6 Hz, 1H, H-1); 6.19 (s, 1H, H-3); 6.47 (s, 1H, H-6); 7.23–7.39 (m, 5H, aryl). $^{13}$C NMR (100 MHz, $CD_3OD$): δ 31.53 (C-8); 40.41 (C-12′); 49.62 (C-12); 52.49 (C-1); 62.03 (C-9); 112.65 (C-3); 114.81 (C-6); 123.68 (C-2); 127.79 (C-7); 126.73, 128.70, 129.31, and 138.31 (C-aryl); 143.92 (C-4); 144.36 (C-5); 172.04 (C═O). ESMS *m*/*z* calcd for $C_{18}H_{18}N_2O_3$ 310.13, found, 310.27.

**3.3.6. (1*S*,3*S*,1′*S*) 12-Benzyl-4,5-dihydroxy-11,13-diazatricyclo[7.3.1.0$^{2,7}$]trideca-3,5,7-trien-10-one (9b).** 0.16 g, 90%. White solid, mp 220–221 °C. $[\alpha]_D^{20}$ −37.2 (*c*=1.00, acetone). $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.61–2.65 (m, *J*=5.2 and 14.2 Hz, 1H, H-12′); 2.73 (m, 1H, H-12″); 2.87 (m, *J*=17.6 Hz, 1H, H-8); 3.19 (dd, *J*=6.0 Hz, 1H, H-8′); 4.18 (d, *J*=6.0 Hz, 1H, H-9); 4.36 (m, 1H, H-12); 4.50 (d, *J*=4.0 Hz, 1H, H-1); 6.52 (s, 1H, H-6 or H-3); 6.59 (s, 1H, H-3 or H-6); 7.24–7.36 (m, 5H, aryl). $^1$H NMR (400 MHz, $CD_3OD$): δ 2.31–2.37 (dd, *J*=9.6 and 13.6 Hz, 1H, H-12′); 2.78 (dd, *J*=16.8 and 0.0 Hz, 1H, H-8); 2.93–3.03 (m, 1H,

H-12″); 3.07–3.13 (dd, $J$=6.8 Hz, 1H, H-8′); 3.73 (d, $J$=6.8 Hz, 1H, H-9); 4.03 (d, $J$=2.0 Hz, 1H, H-1); 4.21 (m, $J$=4.0 Hz, 1H, H-12); 6.57 (s, 1H, H-6); 6.60 (s, 1H, H-3); 7.20–7.36 (m, 5H, aryl). $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 32.04 (C-8); 38.29 (C-12′); 51.85 (C-1); 52.51 (C-9); 59.26 (C-12); 115.11 (C-6); 115.69 (C-3); 121.72 (C-2); 123.74 (C-7); 126.89, 128.92, 129.04, and 136.90 (C-aryl); 143.02 (C-4); 145.80 (C-5); 174.00 (C=O). ESMS $m/z$ calcd for $C_{18}H_{18}N_2O_3$ 310.13, found 310.17.

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## Supplementary data

As example are reported the experimental NMR spectral data for final compounds **7a**, **7b** and **9a**, **9b**. Supplementary information associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.010.

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# Dendrimers with peripheral stilbene chromophores

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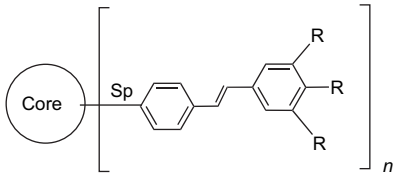
**Abstract**—Two types of dendritic nanoparticles were prepared, which contain (*E*)-stilbene chromophores in the terminal positions of the dendrons. The compounds showed a highly efficient photoreactivity in the course of which statistical CC bond formations led to a crosslinking of the particles. Finally, all stilbene chromophores reacted and the typical (*E*)-stilbene absorption and fluorescence disappeared completely.


## 1. Introduction

The stilbene chromophore is a very useful building block for many applications in photochemistry since *E*/*Z* isomerization, [$\pi^6$a] cyclization, [$\pi^2$s+$\pi^2$s] cyclodimerization, and statistical CC bond formations (polymerization, crosslinking) offer various reaction possibilities in synthetic chemistry as well as in materials science.[1] A fast and efficient CC bond formation of stilbenoid compounds can be applied as basic process for imaging and photoresist techniques. A high density of stilbene chromophores on the periphery of dendritic particles is certainly a good precondition for this purpose. Scheme 1 visualizes the fundamental structure of such multi-arm or dendritic compounds in which (*E*)-stilbene chromophores are linked directly or via (saturated and possibly branched) spacers Sp to the core. Anthracene,[2] binaphthyl,[3] porphyrin,[2] and even various stilbenoid systems[4–15] were used as core for such systems.




**1** ( R = H, alkyl, alkoxy)

**Scheme 1**. Star-shaped compounds or dendrimers having (*E*)-stilbene chromophores linked by (branched) spacers Sp to the core.

When the absorption of the core chromophore ($S_0 \rightarrow S_1$) overlaps with the emission (deactivation) $S_1' \rightarrow S_0'$ of the (*E*)-stilbene chromophores one has to face an energy transfer (Förster mechanism), which competes with the photochemistry of the stilbene units. The majority of the before-mentioned systems[2–15] shows such processes, which can be avoided, when the absorption of the core lies far in the UV.[16] Amines as core are typical examples for the latter case.[17] We tried now to attach (*E*)-stilbene chromophores in terminal positions to propylene imine or benzene triester cores.

## 2. Results and discussion

The preparation of a dendrimer with (*E*)-stilbene chromophores fixed on an oligoamine core was based on 3,4,5-tripropoxybenzaldehyde (**2**),[12,18] *N*-(4-iodophenyl)-phthalimide (**3**),[19] and the commercially available amine DAB-Astramol Am-4® (**4**) (Scheme 2). Aldehyde **2** was transformed by a Wittig reaction to 3,4,5-tripropoxystyrene (**5**). A Heck coupling of **5** and iodo compound **3** yielded the stilbene derivative **6**, which was carefully purified by column chromatography. The pure (*E*)-isomer was then subjected to a hydrazinolysis **6** → **7**. The obtained aminostilbene **7** was finally transformed with bis(trichloromethyl)carbonate [triphosgene] to the red isocyanate **8**, which was directly added to amine **4**. A molar ratio **7**:**4** of 4.75:1 was used in order to achieve the complete fourfold coupling of the stilbene chromophore via urea functionalities to the core. The beige solid **9** was obtained in a yield of 93% related to **7**. It showed in the field desorption mass spectrum (FD MS) the expected peak for the [M+H$^+$] molecular ions at *m*/*z*=1900 (calculated *m*/*z* values for the peak group of [$C_{112}H_{156}N_{10}O_{16}$+H$^+$]: 1898–1903, maximum at 1899). The $^1$H and $^{13}$C NMR spectra of **9** revealed a uniform, symmetrical compound. So we are sure that all four $NH_2$ groups of **4** were transformed to NH–CO–NH tethers for the stilbene units. The detection limit for a by-product with less than four stilbene units is about 5%. Table 1 summarizes the $^1$H and $^{13}$C NMR data of the central $^1$H and $^{13}$C nuclei of **9**, compared to **4**. The signals listed in Table 1 are sharp for **4**, but, due to a restricted mobility broad for **9**. The signals of the stilbene units in **9** are sharp and well resolved.

*Keywords*: Crosslinking; Dendrimers; Photochemistry.
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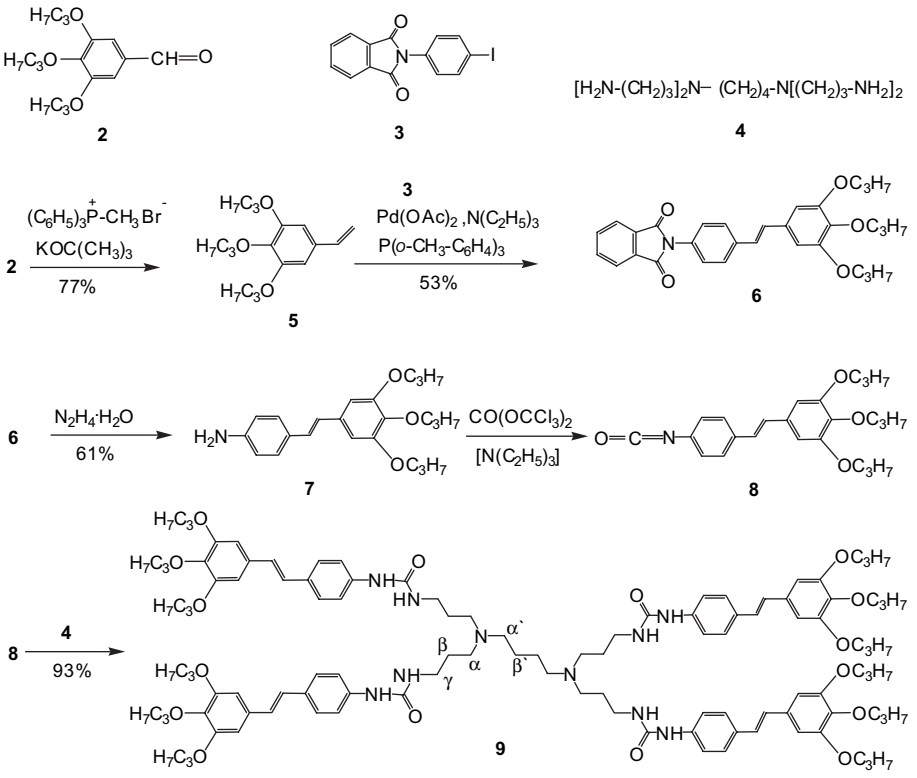



**Scheme 2**. Preparation of dendrimer **9**.

Scheme 3 shows the preparation of dendrimers of first generation, which have six (*E*)-stilbene chromophores. NBS bromination of the stilbenes **10a**,**b** led to **11a**,**b**,[5,20] which were used for the twofold benzylation of resorcinol **12** in the presence of $K_2CO_3$ and 18-crown-6.[5] The products **13a**,**b**, which are primary alcohols, reacted then with 1,3,5-benzenetricarboxylic acid trichloride (**14**) in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine. High yields (90–70%) of the corresponding triesters **15a**,**b** were obtained. The mass spectra revealed the correct *m*/*z* values. A MALDI-TOF measurement (dithranol, $Ag^+$) of **15a** gave *m*/*z*=1837 (calculation for $[C_{120}H_{96}O_{12}+Ag^+]$ leads to a peak group with a maximum at *m*/*z*=1837). The FD MS spectroscopy of **15b** showed a molecular ion at *m*/*z*=2268 (calculated peak group maximum: *m*/*z*=2269). The base peak (100%) in the latter spectrum is owing to the doubly charged molecular ion $M^{2+}$ (*m*/*z*=1134). The $^1H$ and $^{13}C$ NMR spectra of **15a**,**b** are in accordance with $D_{3h}$ symmetry, that means with the attachment of three dendrons to the benzene core. The NMR data reveal constitutionally and configurationally pure dendrimers **15a**,**b**. The detection limit of a by-product with less than six stilbene units or with a (*Z*)-configured double bond is about 5%. Most typical for the threefold ester formation is the change of $^1H/^{13}C$ signals ($\delta$ values) of the central benzene ring from 9.02/135.5 for **14** to 8.91/131.3 for **15a** and 8.91/131.2 for **15b**.

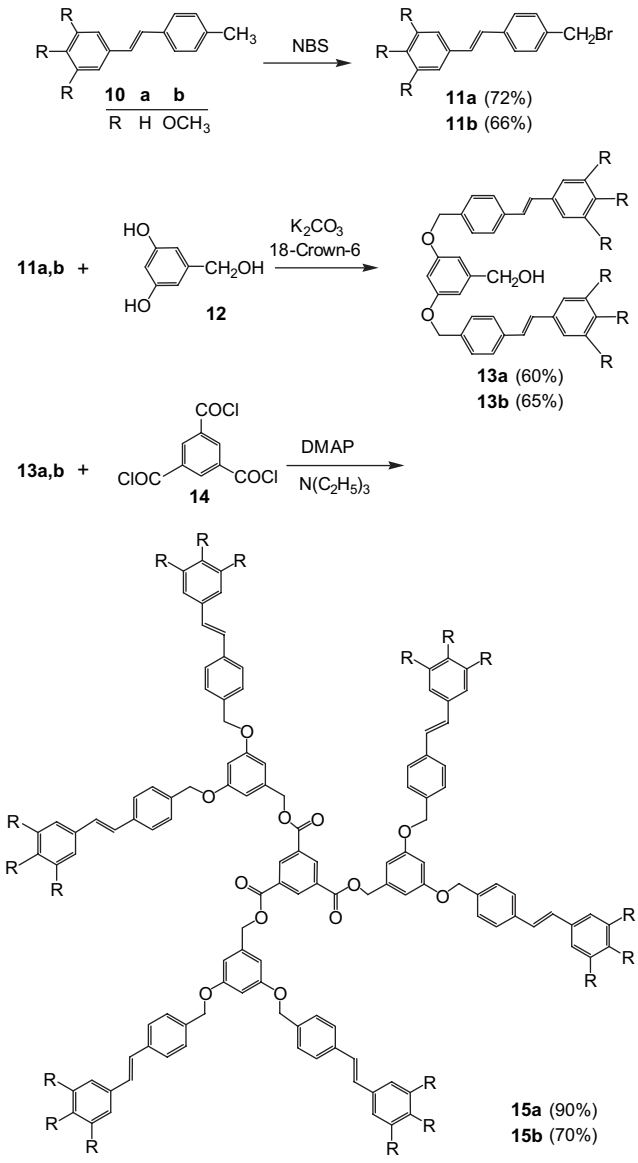
**Table 1**. $^1H$ and $^{13}C$ NMR data of **4** and the core of **9** ($\delta$ values in $CDCl_3$, related to TMS as internal standard)

| Compound | NMR | α | β | γ | α′ | β′ |
|---|---|---|---|---|---|---|
| **4** | $^1H$ | 2.40 | 1.55 | 2.67 | 2.36 | 1.38 |
| | $^{13}C$ | 51.1 | 28.8 | 39.5 | 53.4 | 23.9 |
| **9** | $^1H$[a] | 2.8 | 1.6 | 3.2 | 2.7 | 1.5 |
| | $^{13}C$[a] | 50.7 | 24.3 | 36.6 | 52.2 | 21.3 |

[a] Broad signals.

The long-wavelength absorption of dendrimer **9** shows a maximum at 342 nm ($\varepsilon=11.48\times10^4$ L mol$^{-1}$ cm$^{-1}$). The fluorescence band of **9** has its maximum at 399 nm and overlaps with the absorption band in the range of the $0\rightarrow0$ transition at 370 nm (measurements in $CHCl_3$). Irradiation of a $1.1\times10^{-5}$ M solution of **9** with the unfiltered light of a Xenon high-pressure lamp leads to a fast alteration of the absorption. Figure 1 shows that the band at 342 nm decreases and changes its shape because of the primary generation of (*Z*)-configured stilbene chromophores with a maximum at around 320 nm. A low-intensity maximum appears at 460 nm. More striking is the formation of a new maximum far in the visible range. We assign these new bands to quinoid species with a short half-life.[21,22] The band at $\lambda_{max}=614$ nm reaches the highest intensity after 15 s and disappears then with a half-life of about 100 s—too fast for an NMR study. Finally, all stilbene chromophores have participated in [2π+2π]photocycloaddition reactions and statistical CC bond formations. The crosslinking of the nanoparticles[23] occurs even much faster in more concentrated solutions.

Dendrimers **15a**,**b** behave similar to **9** on irradiation. Figure 2 demonstrates the degradation of the (*E*)-stilbene chromophores of **15a**. The original $\lambda_{max}$ value of 316 nm decreases and a new maximum, assigned to the (*Z*)-configuration, appears at about 289 nm. Prolonged irradiation causes then the complete degradation of all stilbene chromophores.




**Scheme 3**. Preparation of dendrimers **15a**,**b**.

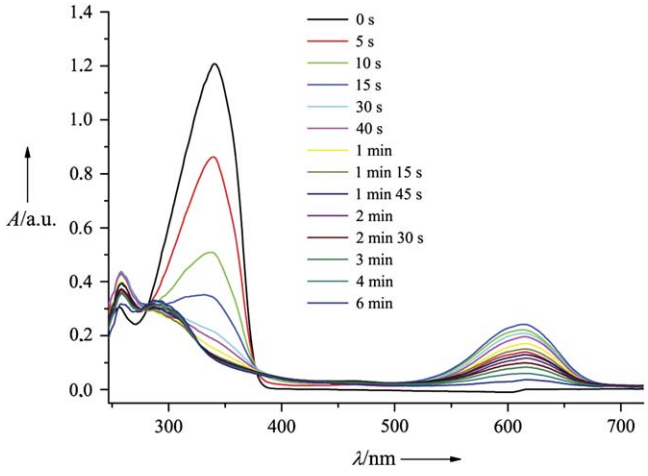



**Figure 1**. Reaction spectra of the irradiation of a $1.1\times10^{-5}$ M solution of **9** in $CHCl_3$.

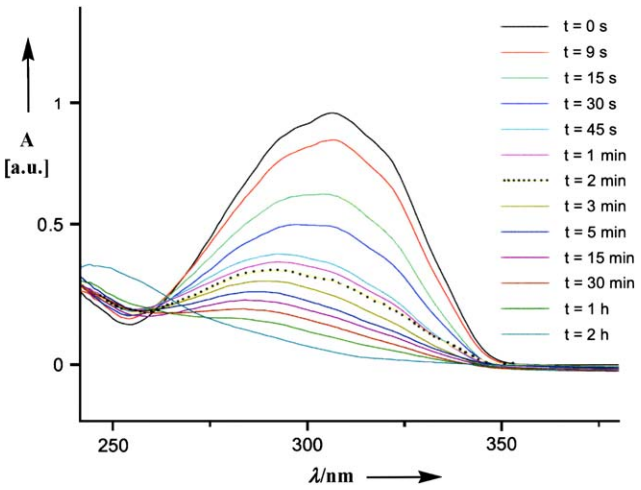
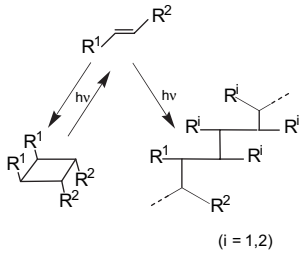



**Figure 2**. Photodegradation of **15a** in a $3\times10^{-6}$ M solution in $CH_2Cl_2$ performed by irradiation with monochromatic light ($\lambda$=320 nm).

What remains, is the band at about 250 nm, which is typical for benzene systems. An intermediate quinoid structure could not be detected. This difference may be due to the fact that the stilbene chromophores in **9** have on both sides in 4- and 4′-position heteroatoms, whereas they are fixed in **15a**,**b** on a saturated C atom. Simultaneously with the change of the absorption, the fluorescence of **15a** ($\lambda_{max}$=359 nm in $CH_2Cl_2$) disappears. The same behavior is observed for **15b**. The absorption with $\lambda_{max}$=310 nm ($CH_2Cl_2$) and the fluorescence with $\lambda_{max}$=404 nm ($CH_2Cl_2$, excitation at 310 nm) decrease steadily on monochromatic irradiation at 340 nm.[24]

The course of the photoreactions can be nicely followed by $^1$H NMR spectroscopy. Signals, which appear in the range between 6.4 and 6.8 ppm, indicate the primary generation of (*Z*)-stilbene units. Upcoming signals between 4.4 and 4.8 ppm prove then tertiary protons on a saturated carbon atom. In principle, CC bond formation in **9** and **15a**,**b** can occur intra- and intermolecularly. The easily soluble product portions have still the molecular masses of the monomers. The amount of less soluble oligomers increases with the concentration of the solution and the energy of the applied UV light. The latter effect may be due to the fact that the formation of four-membered rings in head-to-head [$\pi^2$s+$\pi^2$s] cycloadducts is partly reversible (Scheme 4).




**Scheme 4**. Photoreactivity of the stilbenoid compounds **9** and **15a**,**b**.

The photooligomers give $^1$H NMR spectra with very broad signals. Molecular masses could not be determined by FD, FAB or ESI mass spectroscopy.[25]

## 3. Conclusion

The synthetic procedures described in Schemes 2 and 3 afforded dendrimers **9** and **15a**,**b** with (*E*)-stilbene chromophores in peripheral positions of the dendrons. Since an intramolecular energy transfer to the core can be excluded, the excited singlet states $S_1$ of **9** and **15a**,**b** are deactivated by photophysical processes (fluorescence and radiationless internal conversion) and by photochemical processes (*E*/*Z* isomerization and inter- and intramolecular CC bond formations). The CC bond formation can be realized in head-to-head [$\pi^2$s+$\pi^2$s] cycloadditions and statistical crosslinking. The latter photoreaction provokes a fast and complete degradation of all stilbene chromophores indicated by the total loss of the stilbene absorption and fluorescence. In the case of compound **9**, in which the stilbene units are bound by a urea functionality, a short-lived intermediate with an absorption maximum far in the vis region at 614 nm can be detected. It is tentatively assigned to a quinoid species.

## 4. Experimental

### 4.1. General remarks

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. The UV/vis spectra were obtained with a Zeiss MCS 320/340 and the fluorescence spectra with a Perkin–Elmer LS 50B spectrometer. The $^1$H and $^{13}$C NMR spectra were recorded with the Bruker spectrometers AMX 400 and ARX 400. The mass spectra were obtained on a Finnigan MAT-95 (FD and EI technique) or on a Micromass TOF spec E (MALDI-TOF) spectrometer. The elemental analyses were determined in the Microanalytical Laboratory of the Chemistry Department of the University of Mainz.

**4.1.1. 3,4,5-Tripropoxybenzaldehyde (2).** Preparation according to the literature.[12,18]

**4.1.2. *N*-(4-Iodophenyl)phthalimide (3).** Preparation according to the literature.[19] $^1$H NMR ($CDCl_3$): $\delta$=7.21/7.81 (AA′BB′, 4H, phenyl), 7.78/7.93 (AA′BB′, 4H, phthalimide); $^{13}$C NMR ($CD_3SOCD_3$): $\delta$=94.1 ($C_q$I), 123.6, 129.5, 134.9, 137.8 (aromat. CH), 131.6, 131.8 (aromat. $C_q$), 166.8 (CO). Anal. Calcd for $C_{14}H_8INO_2$ (349.1): C, 48.46; H, 2.31; N, 4.01. Found: C, 48.26; H, 2.29; N, 3.98.

**4.1.3. 3,4,5-Tripropoxystyrene (5).** Aldehyde **2** (8.24 g, 29.0 mmol) and methyltriphenyl-phosphonium bromide (15.75 g, 44.0 mmol) were treated in 120 mL THF with $KO(CH_3)_3$ (4.95 g, 44.0 mmol). After 12 h at 25 °C, the mixture was poured on ice and neutralized with HCl. Extraction with $CH_2Cl_2$ led to the raw product, which was purified by column filtration (13×10 cm $SiO_2$, $CH_2Cl_2$). Yield: 6.29 g (77%) oil. $^1$H NMR ($CDCl_3$): $\delta$=0.99 (t, 3H, $CH_3$), 1.03 (t, 6H, $CH_3$), 1.75–1.82 (m, 6H, $CH_2$), 3.91 (t, 2H, $OCH_2$), 3.94 (t, 4H, $OCH_2$), 5.16 (d, $^3J$=10.7 Hz, 1H, olefin. H), 5.60 (d, $^3J$=17.6 Hz, 1H, olefin. H), 6.59 (dd, $^3J$=17.6 Hz, $^3J$=10.7 Hz, 1H, olefin. H), 6.60 (s, 2H, aromat. H); $^{13}$C NMR ($CDCl_3$): $\delta$=10.6, 10.6 ($CH_3$), 22.7, 23.5 ($CH_2$), 70.7, 75.1 ($OCH_2$), 105.0 (aromat. CH), 112.7 (olefin. $CH_2$), 132.8, 138.4, 153.2 (aromat. $C_q$), 138.4 (olefin. CH); FD MS: *m*/*z* (%)=278 (100) [$M^+$]. Anal. Calcd for $C_{17}H_{26}O_3$ (278.4): C, 73.35; H, 9.41. Found: C, 72.76; H, 10.01.

**4.1.4. *N*-[4-((*E*)-3,4,5-Tripropoxystyryl)-phenyl]phthalimide (6).** The Heck reaction was performed with **5** (4.14 g, 14.9 mmol), **3** (4.19 g, 12.0 mmol), $Pd(OAc)_2$ (25 mg, 0.1 mmol), P(*o*-$CH_3$–$C_6H_4)_3$ (123 mg, 0.4 mmol), and $N(C_2H_5)_3$ (1.7 mL, 12.2 mmol) in 20 mL dry DMF. The reaction mixture was degassed and kept for 12 h at 80 °C. The volatile parts of the filtered solution were evaporated. Repeated column chromatography (8×20 cm $SiO_2$, $CH_2Cl_2$) yielded 3.17 g (53%) **6**, which melted at 134 °C. $^1$H NMR ($CDCl_3$): $\delta$=1.01 (t, 3H, $CH_3$), 1.05 (t, 6H, $CH_3$), 1.76–1.84 (m, 6H, $CH_2$), 3.95 (t, 2H, $OCH_2$), 3.99 (t, 4H, $OCH_2$), 6.72 (s, 2H, aromat. H), 6.98 (d, $^3J$=16.2 Hz, 1H, olefin. H), 7.02 (d, $^3J$=16.2 Hz, 1H, olefin. H), 7.42/7.48 (AA′BB′, 4H, phenylene), 7.78/7.94 (AA′BB′, 4H, phthalimide); $^{13}$C NMR ($CDCl_3$): $\delta$=10.6, 10.6 ($CH_3$), 22.8, 23.5 ($CH_2$), 70.8, 75.1 ($OCH_2$), 105.4, 123.7, 126.5, 126.9, 134.4 (aromat. CH), 126.6, 129.9 (olefin. CH), 130.6, 131.8, 132.2, 137.3, 138.5, 159.5 (aromat. $C_q$), 167.3 (CO); EI MS: *m*/*z* (%)=499 (100) [$M^+$], 457 (45) [$M^+-C_3H_6$]. Anal. Calcd for $C_{23}H_{17}NO_3$ (499.6): C, 74.53; H, 6.66; N, 2.80. Found: C, 74.57; H, 6.63; N, 2.88.

**4.1.5. 4-((*E*)-3,4,5-Tripropoxystyryl)aniline (7).** Phthalimide **6** (3.17 g, 6.3 mmol) was treated in 70 mL ethanol under Ar at 50 °C with $N_2H_4\cdot H_2O$ (8.0 mL, 8.24 g, 160 mmol). During refluxing for 1 h, a grey solid precipitated. Crystallization from ethanol yielded 1.42 g (61%) of yellowish product, which melted at 122 °C and turned pink on staying in the air. $^1$H NMR ($CDCl_3$): $\delta$=1.00 (t, 3H, $CH_3$), 1.04 (t, 6H, $CH_3$), 1.75–1.83 (m, 6H, $CH_2$), 3.93 (t, 2H, $OCH_2$), 3.97 (t, 4H, $OCH_2$), 6.66 (s, 2H, aromat. H), 6.82/6.86 (AB, $^3J$=16.2 Hz, 2H, olefin. H), 6.73/7.31 (AA′BB′, 4H, aromat. H); $^{13}$C NMR ($CDCl_3$): $\delta$=10.6, 10.6 ($CH_3$), 22.8, 23.5 ($CH_2$), 70.7, 75.1 ($OCH_2$), 104.9 (aromat. CH), 115.6, 127.6 (aromat. CH), 125.6, 127.6 (olefin. CH), 128.6, 133.1, 137.8, 145.1, 153.2 (aromat. $C_q$); FD MS: *m*/*z* (%)=369 (100) [$M^+$]. Above room temperature, the decomposition of **7** is very fast so that a correct elemental analysis could not be obtained.

**4.1.6. Dendrimer 9.** To 418 mg (1.4 mmol) bis(trichloromethyl)carbonate (triphosgene) in 7 mL dry $CH_2Cl_2$, **7** (1.42 g, 3.8 mmol) and $N(C_2H_5)_3$ (0.59 mL, 428 mg, 4.2 mmol) in 24 mL $CH_2Cl_2$ were added under Ar within 3 h. The temperature was kept at 0 °C and the mixture vigorously stirred. The volatile parts were removed at 1 Torr (133 Pa). Two cooled flasks with propanol were put between vessel and pump in order to remove excess amounts of phosgene. The red residue was then dissolved in 5 mL dry $CH_2Cl_2$ and treated under Ar with Astramol Am-4® **4** (243 mg, 0.8 mmol) dissolved in 10 mL $CH_2Cl_2$. After 12 h at ambient temperature, 4 mL $CH_3OH$ were added and the stirring continued for further 12 h. Column chromatography (50×3 cm $SiO_2$, $CH_2Cl_2$) afforded a beige solid (1.36 g, 93%), which melted at 137 °C. $^1$H NMR ($CDCl_3$): $\delta$=0.98 (t, 36H, $CH_3$), 1.40–1.85 (m, 36H, $CH_2$), 2.53–3.30 (m, 20H, $NCH_2$), 3.89 (t, 24H, $OCH_2$), 6.63 (s, 8H, aromat. H), 6.84 (m, 8H, olefin. H), 7.31/7.42 (AA′BB′, 16H, aromat. H), 8.80 (s, 4H, NH), 9.90 (s, 4H, NH); $^{13}$C

NMR ($CDCl_3$): $\delta$=10.5, 10.6 ($CH_3$), 21.3, 22.7, 23.4, 24.3 ($CH_2$), 36.7, 50.7, 52.2 ($NCH_2$), 70.6, 75.0 ($OCH_2$), 104.9, 118.7, 127.0 (aromat. CH), 127.0, 127.1 (olefin. CH), 131.4, 132.7, 137.9, 139.1, 153.2 (aromat. $C_q$), 156.5 (CO); FD MS: *m/z* (%)=1900 (68) [$M^+$], 951 (100) [$M^{2+}$].[27]

**4.1.7. (*E*)-4-Bromomethylstilbenes (11a,b).** The NBS bromination of the corresponding (*E*)-4-methylstilbenes was performed according to the literature.[5,20]

**4.1.8. 3.5-Bis{4-[(*E*)-2-(phenyl)ethenyl]benzyloxy}benzyloxybenzyl alcohol (13a).** Compound **13a** was prepared as described for **13b**.[5] Compound **11a** (11.34 g, 41.5 mmol), **12** (2.32 g, 16.6 mmol), $K_2CO_3$ (5.5 g, 40 mmol), and catalytic amounts of 18-crown-6 yielded 13.06 g (60%) of colorless crystals, which melted (after recrystallization from methanol) at 173–176 °C. $^1$H NMR ($CDCl_3$): $\delta$=4.62 (s, 2H, $CH_2OH$), 5.03 (s, 4H, $OCH_2$), 6.54 (t, $^4J$=2.1 Hz, 1H, aromat. H), 6.62 (d, $^4J$=2.1 Hz, 2H, aromat. H), 7.08/7.10 (AB, $^3J$=16.5 Hz, 4H, olefin. H), 7.26–7.53 (m, 18H, aromat. H); $^{13}$C NMR ($CDCl_3$): $\delta$=65.3 ($CH_2OH$), 69.8 ($OCH_2$), 101.3, 105.8, 126.5, 126.7, 127.7, 127.9, 128.2, 128.7, 129.0 (aromat. and olefin. CH), 136.1, 137.1, 137.2, 143.4, 160.1 (aromat. $C_q$); FD MS: *m/z* (%)=524 (100, $M^+$). Anal. Calcd for $C_{37}H_{32}O_3$ (524.7): C, 84.70; H, 6.15. Found: C, 84.80; H, 6.45.

**4.1.9. *all*-(*E*)-Tris(3,5-bis{4-[2-(phenyl)ethenyl]benzyloxy}benzyl)benzene-1,3,5-tri-carboxylate (15a).** A solution of **13a** (0.5 g, 0.95 mmol), benzene-1,3,5-tricarboxylic acid trichloride (**14**)[26] (0.079 g, 0.30 mmol), triethylamine (0.67 g, 6.60 mmol), and 4-dimethylaminopyridine (0.03 g, 0.24 mmol) in 25 mL dry THF was refluxed under Ar for 6 h. The filtered mixture was concentrated and purified by column chromatography (50×4 cm $SiO_2$, petroleum ether bp 40–70 °C/ethyl acetate 1:1). Yield: 1.94 g (90%) of a colorless solid which melted at 168–170 °C. $^1$H NMR ($CDCl_3$): $\delta$=4.62 (s, 12H, $OCH_2$), 5.30 (s, 6H, $CH_2OCO$), 6.50 (t, $^4J$=1.8 Hz, 3H, aromat. H), 6.67 (d, $^4J$=1.8 Hz, 6H, aromat. H), 7.03–7.07 (AB, $^3J$=16.5 Hz, 12H, olefin. H), 7.31–7.47 (m, 54H, aromat. H), 8.91 (s, 3H, aromat. H, central benzene ring); $^{13}$C NMR ($CDCl_3$): $\delta$=67.2 ($CH_2OCO$), 69.9 ($OCH_2$), 102.2, 107.3, 126.6, 126.7, 127.1, 127.7, 128.2, 128.7, 129.0 (aromat. and olefin. CH), 131.3, 135.0, 136.0, 137.2, 137.2, 137.9 (aromat. $C_q$ and CH of central benzene ring), 160.2 (aromat. $C_qO$), 164.7 (CO); MALDI-TOF: *m/z* (%)=1837 (100) [M+$Ag^+$]. Anal. Calcd for $C_{120}H_{96}O_{12}$ (1730.1): C, 85.31; H, 5.59. Found: C, 85.45; H, 5.90.

**4.1.10. *all*-(*E*)-Tris(3,5-bis{4-[2-(3,4,5-trimethoxyphenyl)-ethenyl]benzyloxy}benzyl)benzene-1,3,5-tricarboxylate (15b).** The preparation was performed according to the procedure described for **15a**. Compound **13b** (0.75 g, 1.06 mmol), **14** (0.085 g, 0.32 mmol), $Et_3N$ (0.87 g, 8.7 mmol), and DMAP (0.03 g, 0.24 mmol) afforded 1.68 g (70%) of **15b**, a glassy material. $^1$H NMR ($CDCl_3$): $\delta$=3.83 (s, 18H, $OCH_3$), 3.87 (s, 36H, $OCH_3$), 4.99 (s, 12H, $OCH_2$), 5.30 (s, 6H, $CH_2OCO$), 6.50 (t, $^4J$=1.8 Hz, 3H, aromat. H), 6.67 (d, $^4J$=1.8 Hz, 6H, aromat. H), 6.70 (s, 12H, aromat. H), 6.94/7.00 (AB, $^3J$=16.5 Hz, 12H, olefin. H), 7.36/7.46 (AA′BB′, 24H, aromat. H), 8.91 (s, 3H, aromat. H, central benzene ring); $^{13}$C NMR ($CDCl_3$): $\delta$=56.1, 60.9 ($OCH_3$), 67.1 ($CH_2OCO$), 69.9 ($OCH_2$), 102.1, 103.7, 107.3, 126.6, 127.6, 127.9, 128.9 (aromat. and olefin. CH), 131.2, 132.9, 134.9, 135.9, 137.0, 137.9, 138.1, 153.4, 160.1 (aromat. $C_q$ and CH of central benzene ring), 164.6 (CO); FD MS: *m/z* (%)=2265 (11) [$M^+$], 1133 (100) [$M^{2+}$]. Anal. Calcd for $C_{138}H_{132}O_{30}$ (2270.6): C, 73.00; H, 5.86. Found: C, 72.84; H, 5.90.

*Irradiations*: The irradiations for the UV/vis reaction spectra were performed with a xenon high-pressure lamp (LTI LPS1000X) with or without interference filters. Preparative samples for $^1$H NMR control were irradiated with a Hanovia 450-W middle-pressure lamp. $CH_2Cl_2$ or $CHCl_3$ served as solvent in both cases.

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22. See also the behavior of related stilbenoid compounds in Ref. 13.
23. According to molecular models, the diameter of **9** amounts to 5.3 nm when the dendrons are maximally stretched.
24. Measurements of thin spin-coated films of **15a**,**b** exhibit small bathochromic shifts of the absorption to $\lambda_{max}$=324 and 328 nm, respectively; the fluorescence maxima however are strongly red-shifted to 430 and 476 nm. The photodegradation works in the film as well.
25. AFM measurements of related oligomers revealed the participation of many monomers in the photocrosslinking.[5]
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27. Inclusion of solvent molecules even in carefully dried samples did not permit a correct elemental analysis.

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# Total synthesis of (+)-massarinolin B and (+)-4-*epi*-massarinolin B, fungal metabolites from *Massarina tunicata*

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**Abstract**—The Cr(II)- and Ni(II)-mediated coupling of several tricyclic chiral aldehydes with (*E*)-β-iodomethacrylates (Nozaki–Hiyama–Kishi reaction) was successfully applied to the preparation of some valuable key intermediates of our synthetic strategy to the fungal metabolites (+)-massarinolin B, (+)-4-*epi*-massarinolin B and (+)-massarinolin C.


## 1. Introduction

Massarinolins A–C (**1**–**3**) are novel bioactive sesquiterpenoids isolated from the freshwater aquatic fungus *Massarina tunicata* Shearer & Fallah (A-25-1; Lophiostomataceae) by Gloer and Shearer in 1999 (Fig. 1).[1] Massarinolins A and B are presumably cyclization products of massarinolin C and all of them appear to be sesquiterpenoids biosynthesized from a farnesyl-type precursor. Compounds **1** and **2** were active against *Bacillus subtillis* (ATCC 6051), and possess unusual tricyclic and bicyclic ring systems, exhibiting similar functionalization within the lateral chain derived from (*E*)-4-hydroxy-2-methyl-2-pentenoic acid.

Although, the absolute configuration at C-4 of **2** and **3** has been determined by NMR studies on (*R*)-phenylbutyric acid (PBA) derivatives carried out by the discoverers,[1] it has not been possible yet to correlate the stereochemistry of the tricyclic portion of **2** and **3** with that of the side chain, so the absolute stereochemistry of the ring systems in massarinolins B and C still need to be ascertained. Since the absolute stereochemistry of the bicyclo[3.1.1]heptane subunit common to **2** and **3** has not yet been reported, the total synthesis of these two sesquiterpenoids remains a challenge.

On the basis of our retrosynthetic analysis, access to the lateral chain functionalities of these sesquiterpenoids was

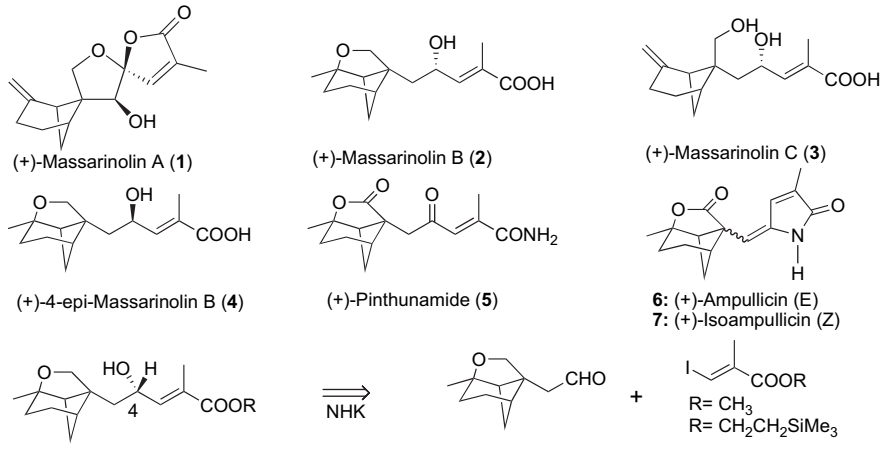


**Figure 1**. Bioactive sesquiterpenoids from *Massarina tunnicata* and *Ampulliferina Sp 27*. Retrosynthetic analysis of (+)-massarinolin B.

*Keywords*: Sesquiterpenes; β-Iodomethacrylates; (+)-Massarinolin B; *R*-(−)-carvone.
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envisioned to take place by Cr(II)- and Ni(II)-mediated coupling of the corresponding chiral aldehyde with (*E*)-β-iodomethacrylates (Nozaki–Hiyama–Kishi NHK reaction).[2]

We wish to report the results obtained for the coupling reaction of chiral aldehydes **12** and **15** with different (*E*)-β-iodomethacrylates and the application of these transformations to the synthesis of (+)-massarinolin B (**2**), (+)-massarinolin C (**3**) and (+)-4-*epi*-massarinolin B (**4**). The formal synthesis of (+)-pinthunamide (**5**)[3] will also be described as an application of the same coupling process to the chiral aldehyde **9**.

## 2. Results and discussion

On the basis of our retrosynthetic analysis, access to the lateral chain functionalities of sesquiterpenoids **3**–**5** was envisioned to take place by Cr(II)- and Ni(II)-mediated coupling of the corresponding chiral aldehyde with (*E*)-β-iodomethacrylates (Nozaki–Hiyama–Kishi NHK reaction).

The preparation of the chiral aldehydes **9**, **12** and **15** was easily achieved by multistep sequences starting from lactone **8** (Scheme 1), which was first described by Mori[4] and we have previously reported from *R*-(−)-carvone with occasion of the synthesis of (+)-ampullicin (**6**) and (+)-isoampullicin (**7**).[5]

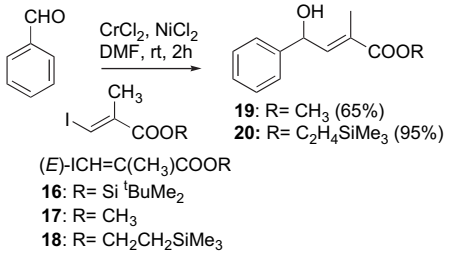
Ozonolysis of **8** followed by treatment with dimethyl sulfide afforded the aldehyde **9** in nearly quantitative yields.

The LAH reduction of **8** followed by tosylation of the primary alcohol **10** allowed us to isolate the tricyclic ether **11**, which was further ozonolyzed to yield aldehyde **12** with 80% overall yield.

On the other hand the diol **10** was sequentially protected by treatment with acetic anhydride followed by trimethylsilyl chloride in triethyl amine and DMAP to afford the unsaturated ester **14**, which was further ozonolyzed to yield aldehyde **15** with 76% yield (three steps).

The preparation of functionalized allylic alcohols has been successfully achieved by Cr(II)- and Ni(II)-mediated coupling of olefinic halides or triflates to aldehydes.[6] The insertion of chromium(II) chloride to β-iodomethacrylates in DMF furnishes the functionalized chromium(III) organometallics, which react with aldehydes to afford γ-hydroxy-α,β-unsaturated esters. This process appears to involve the activation of the carbon–iodine bond via Ni(0) or Ni(I), transmetallation of Ni to Cr and carbon–carbon bond formation via the organochromium reagent. The exceptional chemo- and stereoselectivity displayed by the d[3] organometallic reagent precludes any protection of the ester group or the double bond.

We first studied the coupling reaction of (*E*)-β-iodomethacrylates **16**–**18** with an achiral aldehyde. The Cr(II)- and Ni(II)-mediated coupling of β-iodomethacrylates **17**[7] and **18**[8] with benzaldehyde took place at room temperature in DMF with moderate to excellent yields (See Scheme 2). However, under these conditions the coupling with **16** failed.

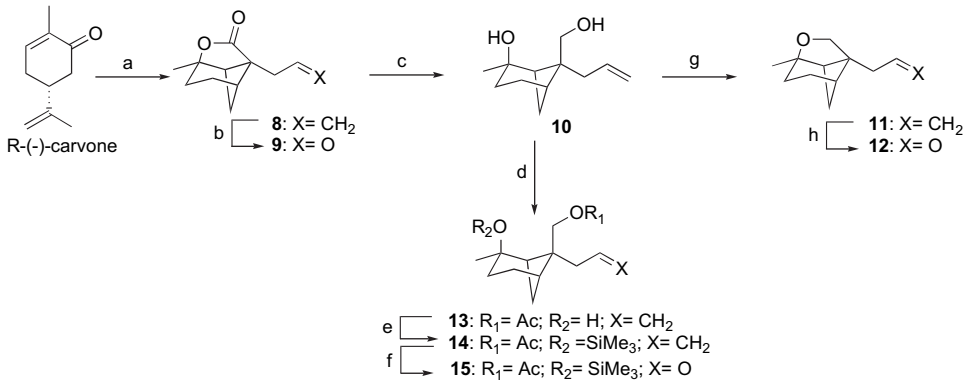



**Scheme 2**. Coupling reactions of (*E*)-β-iodomethacrylates with benzaldehyde.

Isolation of the methyl and trimethylsilylethyl esters **19** and **20** by flash chromatography[9] on silica gel took place with 65 and 95% yields, respectively. Yields were lower in both THF (15–45%) and $CH_3CN$ (5–15%).

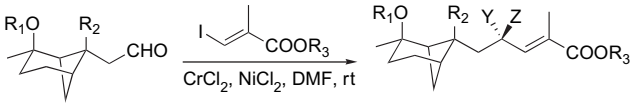
The Cr(II)- and Ni(II)-mediated coupling of aldehydes **9**, **12** and **15** with (*E*)-β-iodomethacrylates **17** and **18** took place with moderate yields but with poor diastereoselectivity (Table 1). However, the isolation and structural elucidation of the reaction products was possible in all cases.

The Cr(II)- and Ni(II)-mediated coupling of aldehyde **9** with β-iodomethacrylate **18** in DMF at room temperature afforded a mixture of diastereomers (**21**:**22**=1:1) with 56% yield.[10] Isolation of both isomers by flash chromatography was followed by Dess–Martin oxidation of each diastereomer to afford the enone **23** with 75 and 80 yields, respectively.

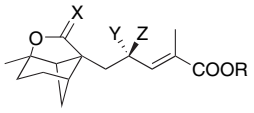



**Scheme 1**. Reagents and conditions: (a) Ref. 5; (b) $O_3$, −78 °C, $Me_2S$, 97%; (c) LAH, ether, rt, 91% (X=$CH_2$); (d) $Ac_2O$, Py, 95%; (e) $Me_3SiCl$, $Et_3N$, DMAP, $CH_2Cl_2$, 84%; (f) $O_3$, −78 °C, $Me_2S$, 95%; (g) TsCl, Py, DMAP, $CH_2Cl_2$, rt, 90%; (h) $O_3$, −78 °C, $Me_2S$, 98%.

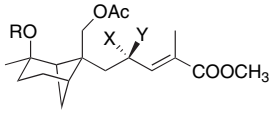
**Table 1**. Coupling reaction of aldehydes **9**, **12** and **15** with (*E*)-β-iodomethacrylates **17** and **18**[a]




| Aldehyde | Methacrylate | dr[b] | Yield (%)[c] |
|---|---|---|---|
| **9**: $R_1$,$R_2$=CO | **18**: $R_3$=$CH_2CH_2SiMe_3$ | **21**:**22**=1:1 | 56 |
| **12**: $R_1$,$R_2$=$CH_2$ | **17**: $R_3$=$CH_3$ | **24**:**25**=3:2 | 65 |
| **12**: $R_1$,$R_2$=$CH_2$ | **18**: $R_3$=$CH_2CH_2SiMe_3$ | **27**:**28**=1.2:1 | 95 |
| **15**: $R_1$=$SiMe_3$; $R_2$=$CH_2OAc$ | **17**: $R_3$=$CH_3$ | **29**:**30**=1.2:1 | 87 |




**21**: X= O; Y= OH, Z= H; R= $CH_2CH_2Si(CH_3)_3$
**22**: X= O ; Y= H, Z= OH; R= $CH_2CH_2Si(CH_3)_3$
**24**: X= $H_2$; R= $CH_3$; Y= OH, Z= H
**25**: X= $H_2$; R= $CH_3$; Y= H, Z= OH
**27**: X= $H_2$; R= $CH_2CH_2SiMe_3$; Y= OH; Z= H
**28**: X= $H_2$; R= $CH_2CH_2SiMe_3$; Y= H; Z= OH




**29:** R= $SiMe_3$ ; X= OH; Y= H
**30**: R= $SiMe_3$ ; X= H; Y= OH

**23**: X= O; Y, Z= O; R= $CH_2CH_2Si(CH_3)_3$
**26**: X= $H_2$; Y, Z= O; R= $CH_3$

**31**[d]: R= $SiMe_3$ ; X= $OSi^tBuPh_2$; Y= H
**32**[d]: R= H; X= $OSi^tBuPh_2$; Y= H

[a] All reactions were run in DMF at room temperature with $CrCl_2$/haloester/aldehyde=4:2:1 ratio.
[b] Determined by GLPC (3% silicone OV-17, 1.5 m).
[c] Isolated yields.

Transformation of the enone **23** into (+)-pinthunamide (**5**) has been described previously.[4]

The Cr(II)- and Ni(II)-mediated coupling of aldehyde **12** with each of the β-iodomethacrylates **17** and **18** afforded mixtures of diastereomers [(**24**:**25**=3:2) and (**27**:**28**=1.2:1)] with 65 and 95% isolated yields, respectively. Reaction was fast in DMF, the usual solvent of choice. Furthermore, the reactions were slower in THF and $CH_3CN$ and both solvents afforded similar stereoselectivities but with lower reaction yields: THF, 47% (**24**+**25**) and 40% (**27**+**28**); $CH_3CN$, 48% (**24**+**25**) and 45% (**27**+**28**).

Isolation of isomers was possible by flash chromatography on silica gel.[11] The spectroscopic data obtained for **24** were identical to those previously described for the methyl ester of (+)-massarinolin B.[1] Fluoride-promoted deprotection of **27** yielded the target molecule **2** with quantitative yields. Analogously, deprotection of the silyl derivative **28** afforded 4-*epi*-(+)-massarinolin B (**4**) quantitatively.[12]

Since the absolute stereochemistry of the starting material **8** is known,[13] it is possible now to correlate the stereochemistry of the bicyclo[3.1.1]heptane portion of **2** with that of the side chain, therefore, the absolute stereochemistry of **2** and **4** has been unambiguously established.

For preparative purposes, we attempted to enhance the diastereomeric ratio in favour of **24** by a two-step oxidation–reduction sequence via enone **26**. Among the reagents screened, neither L-Selectride nor zinc borohydride gave acceptable results with respect to either chemo- or stereoselectivity.[14]

The coupling reaction of aldehyde **15** with β-iodomethacrylate **17** gave a mixture of diastereoisomers (**29**:**30**=1.2:1) with 87% yield. Separation of both diastereomers was possible by flash chromatography and the structural elucidation was based on full spectroscopic analysis and comparison with the spectroscopic evidence obtained for **24** and **25**. Hydroxyester **29** is an advanced intermediate in the synthesis of (+)-massarinolin C (**3**).[15]

## 3. Conclusion

The Cr(II)- and Ni(II)-mediated coupling of chiral aldehydes **9**, **12** and **15** with (*E*)-β-iodomethacrylates yielded the corresponding γ-hydroxy-α,β-unsaturated esters with moderate yields but with poor stereoselectivity. Starting from the allylic lactone **8**, application of these transformations to the synthesis of (+)-massarinolin B (**2**), (+)-4-*epi*-massarinolin B (**4**), (+)-pinthunamide (**5**) and the preparation of an advanced intermediate (**29**) in the synthesis of (+)-massarinolin C (**3**) have been described.

## 4. Experimental

### 4.1. General

Melting points are uncorrected. $^1H$ NMR spectra were measured at either 200 or 400 MHz and $^{13}C$ NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS ($^1H$) or solvent ($^{13}C$), except where noted otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise noted. Standard mass spectrometry data were acquired by using GC–MS system in EI mode with the maximum *m*/*z* range of 600. Optical rotations were determined on a digital Perkin–Elmer 241 polarimeter in a 1 dm cell. Tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. Dimethylformamide (DMF) was dried over $CaH_2$, distd under reduced pressure and degassed before use. Acetonitrile is

fractionally distd after refluxing over $CaH_2$. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for handling air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques.[9] $R_f$ values refer to TLC carried out on 0.25 mm silica gel plates, with the same eluant as that indicated for the column chromatography unless otherwise noted. Yields reported are for chromatographically pure isolated products unless mentioned otherwise. Anhydrous $CrCl_2$ and $NiCl_2$ were purchased from Aldrich and Strem Chemicals and were used without purification.

### 4.2. Preparation of intermediates 10, 11, 13 and 14

**4.2.1. (1*R*,2*R*,5*S*,6*S*)-2-Hydroxy-2-methyl-6-(2-propenyl)-bicyclo[3.1.1]hept-6-yl-methanol 10.** To an ice-cooled and stirred solution of crude **8** (2 g, 10.41 mmol) in anhydrous ether (45 mL) $LiAlH_4$ (0.394 g, 10.41 mmol) was added. The mixture was stirred at room temperature for 15 h. To the ice-cooled mixture were added $H_2O$ (0.4 mL), 15% NaOH (0.4 mL) and $H_2O$ (1.2 mL) successively. The mixture was stirred at room temperature for 1 h and filtered through Celite and eluted with ether. The filtrate was concentrated in vacuo and the residue was flash chromatographed on silica gel. Elution with hexane/ethyl acetate 6:4 afforded diol **10** (1.83 g, 91%) as a colourless oil. $[\alpha]_D^{20}$ −24.51 (*c* 1.04, $CHCl_3$). $R_f$ 0.33 (hexane/ethyl acetate 1:1). IR (KBr): $\nu$ 3365, 3081, 2973, 2931, 1637, 1471, 1261, 1121, 1029, 912, 803 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.04 (d, 1H, $J$=10.4 Hz), 1.33 (s, 3H), 1.75–2.10 (m, 5H), 2.16 (m, 1H), 2.25 (m, 1H), 2.4 (dd, 1H, $J_1$=7.5 Hz, $J_2$=14.2 Hz), 2.65 (dd, 1H, $J_1$=7.2 Hz, $J_2$=14.16 Hz), 3.45 (d, 1H, $J$=11.6 Hz), 3.9 (d, 1H, $J$=11.6 Hz), 5.1 (m, 2H), 5.9 (m, 1H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 24.16 (t), 27.61 (t), 31.33 (q), 32.79 (t), 36.34 (d), 37.94 (t), 45.24 (s), 51.20 (d), 63.11 (t), 76.02 (s), 116.98 (t), 135.59 (d) ppm. MS (EI), *m/z* (%): 196 ($M^+$, 2), 178 (10), 137 (35), 110 (35), 94 (100), 79 (85), 67 (55). HRMS-EI ($M^+$) calcd for $C_{12}H_{20}O_2$: 196.1463, found: 196.1457.

**4.2.2. (1*R*,4*S*,6*R*,7*S*)-1-Methyl-9-oxa-7-(2-propenyl)-tricyclo[4.3.0.0$^{4,7}$]nonane 11.** To a solution of diol **10** (0.67 g, 3.42 mmol) in $CH_2Cl_2$ (50 mL) at 0 °C, pyridine (0.82 mL, 10.26 mmol), DMAP (0.084 g, 0.684 mmol) and tosyl chloride (1.3 g, 6.84 mmol) were successively added. The reaction mixture was stirred at room temperature for 48 h. Then, 10% $NaHCO_3$ (10 mL) was added and the reaction mixture was further stirred for 1 h. The crude mixture was extracted with methylene chloride (3×25 mL) and the combined organic layers were successively washed with 1 N HCl (3×10 mL), 10% $NaHCO_3$ (3×10 mL) and brine (3×10 mL). The organic phase was dried with $Na_2SO_4$ and evaporated to yield a crude (1.5 g), which was fractionated by flash chromatography on silica gel (hexane/ethyl acetate 9:1) to afford **11** (0.55 g, 90%) as a colourless oil. $[\alpha]_D^{20}$ +17.9 (*c* 0.8, $CHCl_3$). $R_f$ 0.68 (hexane/ethyl acetate 1:1). IR (neat): $\nu$ 3077, 2926, 2866, 1726, 1642, 1452, 1375, 1032, 912, 849 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.26 (s, 3H), 1.45 (m, 1H), 1.65–1.9 (m, 5H), 2.0–2.2 (m, 2H), 2.3–2.5 (m, 2H), 3.5 (d, 1H, $J$=8.9 Hz), 3.74 (d, 1H, $J$=8.9 Hz), 5.05 (m, 2H), 5.7 (m, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 22.70 (t), 22.96 (t), 25.18 (q), 32.60 (t), 38.05 (t), 39.60 (d), 50.72 (d), 54.96 (s), 70.46 (t), 86.77 (s), 116.62 (t), 134.74 (d) ppm. MS (EI) *m/z* (%): 178 ($M^+$, 13.1), 67 (25), 79 (44), 95 (28.6), 107 (17), 123 (100), 163 (14.3). HRMS-EI ($M^+$) calcd for $C_{12}H_{18}O$: 178.1358, found: 178.1348.

**4.2.3. (1*R*,2*R*,5*S*,6*S*)-2-Hydroxy-2-methyl-6-(2-propenyl)-bicyclo[3.1.1]hept-6-yl-methyl acetate 13.** To a solution of diol **10** (0.205 g, 1.0 mmol) in $CH_2Cl_2$ were successively added pyridine (0.16 mL, 2.2 mmol) and acetic anhydride (0.2 mL, 2.0 mmol). The reaction mixture was stirred for 12 h. Then, ether (5 mL) was added and the reaction mixture was poured on satd $NaHCO_3$ (5 mL) and stirred for 1 h. The organic phase was successively washed with 2 N HCl (3×10 mL), satd $NaHCO_3$ (3×10 mL) and brine (3×10 mL), dried ($Na_2SO_4$) and evaporated to yield a crude product (0.260 g), which was fractionated by flash chromatography on silica gel. By elution with hexane/ethyl acetate 8:2, acetate **13** (0.237 g, 95%) was obtained as a colourless oil. $[\alpha]_D^{20}$ −5.05 (*c* 1.01, $CHCl_3$). $R_f$ 0.48 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): $\nu$ 3480, 3078, 2922, 1716, 1639, 1456, 1237, 1027, 962 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.09 (d, 1H, $J$=10.2 Hz), 1.28 (s, 3H), 1.27–2.35 (m, 7H), 2.04 (s, 3H), 2.45 (d, 2H, $J$=7.52 Hz), 4.21 (dd, 2H, $J_1$=11.8 Hz, $J_2$=36.8 Hz), 5.05 (m, 2H), 5.84 (m, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 15.04 (q), 23.73 (t), 27.44 (t), 31.47 (q), 31.95 (t), 37.47 (t), 37.95 (d), 43.23 (s), 50.75 (d), 65.70 (t), 75.21 (s), 116.97 (t), 134.81 (d), 170.79 (s) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{14}H_{22}O_3Na$: 261.1461, found: 261.1447.

**4.2.4. (1*R*,2*R*,5*S*,6*S*)-2-Methyl-2-(trimethylsilyloxy)-6-(2-propenyl)-bicyclo[3.1.1]hept-6-yl-methyl acetate 14.** To a solution of **13** (0.20 g, 0.84 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C were successively added $Et_3N$ (0.24 mL, 1.7 mmol), DMAP (20.4 mg, 0.17 mmol) and $Me_3SiCl$ (0.16 mL, 1.25 mL). The reaction mixture was stirred for 12 h at room temperature, diluted with ether (20 mL) and poured on satd $NaHCO_3$ (20 mL). The mixture was stirred for 1 h and extracted with ether. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and evaporated to yield a crude product (0.27 g), which was fractionated by flash chromatography on silica gel. Elution with hexane/ethyl acetate 8:2 afforded the silyl acetate **14** (0.22 g, 84%) as a colourless oil. $[\alpha]_D^{20}$ −10.95 (*c* 1.21, $CHCl_3$). $R_f$ 0.62 (hexane/ethyl acetate 7:3). IR ($CHCl_3$): $\nu$ 3075, 2961, 2928, 2873, 1739, 1381, 1250, 1130, 1004, 968, 840 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.11 (s, 9H), 1.5 (d, 1H, $J$=9.7 Hz), 1.28 (s, 3H), 1.15–2.25 (m, 7H), 2.01 (s, 3H), 2.44 (d, 2H, $J$=7.35 Hz), 4.09 (dd, 2H, $J_1$=12.2 Hz, $J_2$=76.6 Hz), 5.04 (m, 2H), 5.80 (m, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 2.53 (q), 20.87 (q), 23.97 (t), 27.06 (t), 30.57 (q), 33.47 (t), 37.65 (t), 38.33 (d), 43.24 (s), 51.66 (d), 66.02 (t), 78.34 (s), 116.76 (t), 135.28 (d), 170.95 (s) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{17}H_{30}O_3$SiNa: 333.1856, found: 333.1821.

### 4.3. Ozonolysis of alkenes 8, 11 and 14. Obtention of aldehydes 9, 12 and 15. General procedure

**4.3.1. (1*R*,4*S*,6*R*,7*S*)-1-Methyl-9-oxa-8-oxo-tricyclo-[4.3.0.0$^{4,7}$]non-7-yl-acetaldehyde 9.** Ozone was bubbled through a solution of **8** (2.5 g, 13.01 mmol) in 75 mL of

$CH_2Cl_2$ at −78 °C until a blue-grey colouration developed. Then, excess ozone was eliminated using argon, and then $SMe_2$ (2.85 mL, 39 mmol) was added. After stirring for 3 h (from –78 °C to room temperature) the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate 6:4) to yield a colourless oil **9** (2.4 g, 95%). $[\alpha]_D^{20}$ +49.06 (*c* 1.35, $CHCl_3$). $R_f$ 0.24 (hexane/ethyl acetate 1:1). IR (neat): *ν* 2972, 2899, 2745, 1759, 1723, 1458, 1383, 1252, 1198, 1082, 939, 893 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 1.49 (s, 3H), 1.72 (d, 1H, *J*=10.7 Hz), 1.92 (s, 4H), 2.19 (m, 1H), 2.45 (m, 1H), 2.64 (t, 1H, *J*=5.4 Hz), 2.83 (dd, 2H, $J_1$=18.2 Hz, $J_2$=30.5 Hz), 9.74 (s, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* 22.88 (t), 24.78 (q), 29.83 (t), 40.81 (d), 43.36 (t), 47.74 (d), 52.87 (s), 88.71 (s), 177.42 (s), 199.12 (d) ppm. HRMS-EI (M+$H^+$) calcd for $C_{11}H_{15}O_3$: 195.1016, found: 195.0998.

**4.3.2. (1*R*,4*S*,6*R*,7*S*)-1-Methyl-9-oxa-tricyclo[4.3.0.0$^{4,7}$]-non-7-yl-acetaldehyde 12.** Ozonolysis of alkene **11** (1.5 g, 8.43 mmol) afforded aldehyde **12** (1.49 g, 98%) as a colourless oil. $[\alpha]_D^{20}$ +40.54 (*c* 1.07, $CHCl_3$). $R_f$ 0.33 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): *ν* 2928, 2870, 2726, 1721, 1452, 1377, 1024, 853 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 1.25 (s, 3H), 1.45 (d, 1H, *J*=10.3 Hz), 1.7–2.25 (m, 7H), 2.75 (dd, 2H, $J_1$=18 Hz, $J_2$=30 Hz), 3.75 (d, 1H, *J*=9.3 Hz), 4.04 (d, 1H, *J*=9.3 Hz), 9.74 (s, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* 22.42 (t), 22.63 (t), 24.92 (q), 32.25 (t), 40.01 (d), 48.36 (t), 51.20 (d), 52.25 (s), 70.58 (t), 86.03 (s), 200.64 (d) ppm. HRMS-EI (M+$H^+$) calcd for $C_{11}H_{17}O_2$: 181.1223, found: 181.1223.

**4.3.3. (1*R*,2*R*,5*S*,6*S*)-2-Methyl-2-(trimethylsilyloxy)-6-(2-oxoethyl)-bicyclo[3.1.1]hept-6-yl-methyl acetate 15.** Ozonolysis of alkene **14** (1 g, 3.22 mmol) yielded aldehyde **15** (0.950 g, 95%) as a colourless oil. $[\alpha]_D^{20}$ −22.32 (*c* 1.257, $CHCl_3$). $R_f$ 0.46 (hexane/ethyl acetate 7:3). IR (KBr): *ν* 2959, 2738, 1730, 1452, 1376, 1233, 1000, 956, 835 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 0.1 (s, 9H), 1.3 (s, 3H), 1.35 (d, 1H, *J*=11.0 Hz), 1.9–2.4 (m, 7H), 2.0 (s, 3H), 2.6–2.8 (m, 2H), 4.15 (d, 1H, *J*=12.2 Hz), 4.58 (d, 1H, *J*=12.1 Hz), 9.85 (s, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* 2.38 (q), 20.71 (q), 23.47 (t), 27.69 (t), 30.28 (q), 33.04 (t), 37.75 (d), 42.89 (s), 47.93 (t), 52.98 (d), 67.33 (t), 77.90 (s), 170.54 (s), 202.07 (d) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{16}H_{28}O_4SiNa$: 335.1649, found: 335.1639.

### 4.4. Coupling reactions between (*E*)-β-halo-acrylates and aldehydes. General procedure

**4.4.1. (*E*)-4-Hydroxy-2-methyl-4-phenyl-2-butenoic acid methyl ester 19.** A mixture of anhydrous $CrCl_2$ (0.60 g, 4.9 mmol) and a catalytic amount of $NiCl_2$ (3.2 mg, 0.02 mmol) in dry oxygen-free dimethylformamide (DMF, 10 mL) was stirred at 25 °C for 10 min under argon atmosphere. To the reagent at 25 °C, solutions of benzaldehyde (0.129 g, 1.02 mmol) in DMF (5 mL) and methyl-(*E*)-3-iodomethacrylate **17** (0.554 g, 2.45 mmol) in DMF (5 mL) were successively added. After stirring at 25 °C for 4 h at room temperature, the reaction mixture was diluted with ether (20 mL), poured into water (20 mL) and extracted with ether repeatedly. The combined extracts were dried ($Na_2SO_4$) and concentrated. Purification by flash column chromatography on silica gel (hexane/ethyl acetate 9:1) afforded 0.16 g (65%) of the desired allylic alcohol **19** as a colourless oil. $R_f$ 0.37 (hexane/ethyl acetate 1:1). IR (neat): *ν* 3445, 3050, 2953, 1715, 1651, 1439, 1128, 1017 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 1.85 (s, 3H), 2.52 (s, 1H), 3.6 (s, 3H), 5.42 (d, 1H, *J*=8.6 Hz), 6.79 (d, 1H, *J*=8.5 Hz), 7.22–7.29 (m, 5H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* 12.93 (q), 51.87 (q), 70.8 (d), 126.2 (d), 128.02 (d), 128.4 (s), 128.75 (d), 142.1 (d), 142.2 (s), 168.3 (s) ppm. MS-EI *m*/*z* (%): 206 ($M^+$, 1.5), 51 (48), 77 (100), 79 (34), 105 (100), 117 (33), 145 (47), 159 (3), 174 (37.5), 188 (19), 191 (3). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.01; H, 6.96.

**4.4.2. (*E*)-4-Hydroxy-2-methyl-4-phenyl-2-butenoic acid 2-(trimethylsilyl)ethyl ester 20.** Coupling of benzaldehyde (0.118 g, 1.12 mmol) and (*E*)-haloester **18** (0.70 g, 2.24 mmol) afforded 0.320 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 9:1) afforded 0.27 g (95%) of the desired alcohol **20** as a colourless oil. $R_f$ 0.27 (hexane/ethyl acetate 8:2). IR ($CHCl_3$): *ν* 3455, 3030, 2955, 2899, 1709, 1649, 1452, 1252, 1036, 936, 856 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 0.35 (s, 9H), 1.01 (dd, 2H, *J*=8.5 Hz), 1.94 (s, 3H), 4.2 (dd, 2H, *J*=8.45 Hz), 5.52 (d, 1H, *J*=8.6 Hz), 6.68 (d, 1H, *J*=8.7 Hz), 7.25–7.4 (m, 5H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* 1.57 (q), 12.85 (q), 17.3 (t), 62.98 (t), 70.73 (d), 126.12 (d), 127.87 (d), 128.6 (d), 128.61 (s), 141.89 (d), 142.16 (s), 167.97 (s) ppm. MS-EI *m*/*z* (%): 275.14 (M+Na, 17.5), 129.1 (100), 169.1 (7.4), 175.1 (10.1), 202.02 (3.7), 247.11 (9.2), 265.13 (5.5). Anal. Calcd for $C_{16}H_{24}O_3Si$: C, 65.71; H, 8.27. Found: C, 65.83; H, 8.37.

**4.4.3. Hydroxyesters 21 and 22.** Coupling of aldehyde **9** (0.110 g, 0.57 mmol) and (*E*)-haloester **18** (0.354 g, 1.14 mmol) afforded 0.25 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 9:1) afforded **21** (0.06 g, 28%) and **22** (0.06 g, 28%).

**4.4.3.1. 2-(Trimethylsilyl)ethyl (1′*R*,4*S*,4′*S*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-8′-oxo-tricyclo[4.3.0.0$^{4,7}$]non-7′-yl)-2-pentenoate 21.** Colourless oil. $[\alpha]_D^{20}$ −0.79 (*c* 1.305, $CHCl_3$). $R_f$ 0.40 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): *ν* 3475, 3057, 2954, 2871, 1761, 1708, 1653, 1458, 1250, 1062, 942, 834 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 0.04 (s, 9H), 1.01 (t, 2H, *J*=8.3 Hz), 1.42–2.80 (m, 3H), 1.46 (s, 3H), 1.85 (s, 3H), 1.9 (m, 4H), 2.5 (m, 2H), 2.61 (m, 1H), 4.22 (t, 2H, *J*=8.3 Hz), 4.69 (ddd, 1H, $J_1$=8.5 Hz, $J_2$=8.5 Hz, $J_3$=4.3 Hz), 6.66 (dq, 1H, $J_1$=8.5 Hz, $J_2$=1.2 Hz) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): *δ* −1.65 (q), 12.62 (q), 17.26 (t), 22.74 (t), 22.75 (t), 24.74 (q), 29.66 (t), 36.46 (t), 42.06 (d), 47.18 (d), 54.33 (s), 62.87 (t), 65.97 (d), 88.40 (s), 128.70 (s), 142.09 (d), 167.76 (s), 179.15 (s) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{20}H_{32}O_5NaSi$: 403.1911, found: 403.1914.

**4.4.3.2. 2-(Trimethylsilyl)ethyl (1′*R*,4*R*,4′*S*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-8′-oxo-tricyclo[4.3.0.0$^{4,7}$]non-7′-yl)-2-pentenoate 22.** Colourless oil. $[\alpha]_D^{20}$ +24.89 (*c* 0.953, $CHCl_3$). $R_f$ 0.46 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): *ν* 3456, 3056, 2954, 2855, 1759, 1709, 1650, 1458, 1250, 1044, 986, 839 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): *δ* 0.04 (s, 9H), 1.02 (t, 2H, *J*=8.3 Hz),

1.48 (s, 3H), 1.74 (m, 1H), 1.85–2.10 (m, 6H), 1.88 (s, 3H), 1.98 (s, 4H), 1.9–2.35 (m, 3H), 2.25 (m, 1H), 2.57 (m, 1H), 2.7 (m, 1H), 4.22 (t, 2H, $J$=8.6 Hz), 4.71 (ddd, 1H, $J_1$=8.1 Hz, $J_2$=8.1 Hz, $J_3$=6.8 Hz), 6.71 (dq, 1H, $J_1$=8.1 Hz, $J_2$=1.2 Hz) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 1.63 (q), 12.62 (q), 17.27 (t), 22.78 (t), 22.99 (t), 24.74 (q), 29.66 (t), 36.25 (t), 40.57 (d), 49.13 (d), 55.33 (s), 62.80 (t), 66.24 (d), 89.28 (s), 128.14 (s), 142.91 (d), 167.90 (s), 179.56 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{20}H_{32}O_5SiNa$: 403.1911, found: 403.1900.

**4.4.4. Hydroxyesters 24 and 25.** Coupling of aldehyde **12** (0.124 g, 0.70 mmol) and (*E*)-haloester **17** (0.312 g, 1.38 mmol) afforded 0.228 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 8:2) afforded **24** (0.075 g, 39%) and **25** (0.050 g, 26%).

**4.4.4.1. Methyl (1′*R*,4′*S*,4*S*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0$^{4,7}$]non-7′-yl)-2-pentenoate 24.** Colourless oil. $[\alpha]_D^{20}$ +8.6 (*c* 1.1, $CHCl_3$). $R_f$ 0.23 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): $\nu$ 3408, 2925, 2855, 1720, 1451, 1122 cm$^{-1}$. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 1.23 (s, 3H), 1.50 (m, 1H), 1.62 (m, 1H), 1.78 (m, 1H), 1.84 (m, 1H), 1.85 (d, 3H, $J$=1.44 Hz), 1.88 (m, 1H), 1.89 (m, 1H), 1.98 (dd, 1H, $J_1$=14.1 Hz, $J_2$=4.0 Hz), 2.13 (m, 1H), 2.14 (m, 1H), 2.30 (m, 1H), 3.60 (d, 1H, $J$=9.45 Hz), 3.74 (s, 3H), 3.89 (d, 1H, $J$=9.45 Hz), 4.46 (ddd, 1H, $J_1$=8.9 Hz, $J_2$=8.9 Hz, $J_3$=3.8 Hz), 6.67 (dq, 1H, $J_1$=8.9 Hz, $J_2$=1.4 Hz) ppm. $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 12.78 (q), 23.53 (t), 23.75 (t), 25.35 (q), 33.41 (t), 40.24 (d), 41.72 (t), 52.45 (q), 53.55 (d), 55.53 (s), 66.94 (d), 72.76 (t), 87.62 (s), 127.95 (s), 145.59 (d), 169.95 (s) ppm. MS-EI *m*/*z* (%): 262 (M$^+$−$H_2O$, 5), 247 (3), 225 (21), 207(46), 203 (10), 187 (8), 175 (21), 151 (37), 147(56), 133(29), 109 (26), 97 (100), 79 (78), 67 (65), 55 (80). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.61; H, 8.68.

**4.4.4.2. Methyl (1′*R*,4′*S*,4*R*,6′*R*,7′*S*)-(*E*)-4-hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0$^{4,7}$]non-7′-yl)-2-pentenoate 25.** Colourless oil. $[\alpha]_D^{20}$ −0.78 (*c* 1.03, $CHCl_3$). $R_f$ 0.28 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): $\nu$ 3407, 2925, 2849, 1717, 1655, 1437, 1265, 1141 cm$^{-1}$. $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 1.23 (s, 3H), 1.50 (m, 1H), 1.61 (m, 1H), 1.78 (m, 1H), 1.84 (m, 1H), 1.85 (d, 3H, $J$=1.49 Hz), 1.88 (m, 1H), 1.89 (m, 1H), 2.09–2.25 (m, 3H), 2.4 (m, 1H), 3.54 (d, 1H, $J$=9.01 Hz), 3.78 (s, 3H), 3.79 (d, 1H, $J$=9.0 Hz), 4.5 (ddd, 1H, $J_1$=8.8 Hz, $J_2$=8.8 Hz, $J_3$=6.4 Hz), 6.65 (dq, 1H, $J_1$=8.8 Hz, $J_2$=1.45 Hz) ppm. $^{13}$C NMR (100 MHz, $CD_3OD$): $\delta$ 12.89 (q), 23.38 (t), 23.60 (t), 25.39 (q), 33.37 (t), 41.35 (d), 41.83 (t), 52.5 (q), 53.43 (d), 55.19 (s), 67.50 (d), 71.93 (t), 88.20 (s), 128.47 (s), 145.23 (d), 169.88 (s) ppm. MS-EI *m*/*z* (%): 262 (M$^+$−$H_2O$, 3), 236 (2), 225 (16), 207 (54), 187 (10), 175 (17), 151 (37), 147 (60), 133 (32), 109 (27), 97 (100), 79 (90), 67 (67), 55 (84). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.65; H, 8.70.

**4.4.5. Hydroxyesters 27 and 28.** Coupling of aldehyde **12** (0.110 g, 0.61 mmol) and (*E*)-haloester **18** (0.38 g, 1.2 mmol) afforded 0.37 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 8:2) afforded **27** (0.12 g, 54%) and **28** (0.092 g, 41%).

**4.4.5.1. (1′*R*,4′*S*,4*S*,6′*R*,7′*S*)-(*E*)-4-Hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0$^{4,7}$]non-7′-yl)-2-pentenoic acid 2-(trimethylsilyl)ethyl ester 27.** Colourless oil. $[\alpha]_D^{20}$ +28.25 (*c* 0.89, $CHCl_3$). $R_f$ 0.37 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): $\nu$ 3398, 2926, 1710, 1650, 1452, 1250, 1034, 935, 838 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.06 (s, 9H), 1.04 (dd, 2H, $J_1$=8.6 Hz, $J_2$=1.8 Hz), 1.27 (s, 3H), 1.47 (d, 1H, $J$=10.2 Hz), 1.65–2.00 (m, 6H), 1.87 (d, 3H, $J$=1.5 Hz), 2.1 (m, 1H), 2.15 (t, 1H, $J$=5.6 Hz), 2.27 (m, 1H), 3.62 (d, 1H, $J$=9.45 Hz), 3.90 (d, 1H, $J$=9.45 Hz), 4.25 (m, 2H), 4.53 (ddd, 1H, $J_1$=8.4 Hz, $J_2$=8.4 Hz, $J_3$=4.4 Hz), 6.69 (dq, 1H, $J_1$=8.4 Hz, $J_2$=1.5 Hz) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −1.52 (q), 12.70 (q), 17.27 (t), 22.65 (t), 22.83 (t), 25.13 (q), 32.44 (t), 39.00 (d), 40.61 (t), 52.12 (d), 54.25 (s), 63.10 (t), 66.67 (d), 71.58 (t), 85.85 (s), 128.04 (s), 142.95 (d), 167.99 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{20}H_{34}O_4SiNa$: 389.2118, found: 389.2127.

**4.4.5.2. (1′*R*,4′*S*,4*R*,6′*R*,7′*S*)-(*E*)-4-Hydroxy-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0$^{4,7}$]non-7′-yl)-2-pentenoic acid 2-(trimethylsilyl)ethyl ester 28.** Colourless oil. $[\alpha]_D^{20}$ −5.08 (*c* 0.47, $CHCl_3$). $R_f$ 0.42 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): $\nu$ 3403, 2925, 2867, 1711, 16490, 1453, 1250, 1038, 936, 839 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.05 (s, 9H), 1.02 (dd, 2H, $J_1$=8.5 Hz, $J_2$=1.8 Hz), 1.25 (s, 3H), 1.47 (d, 1H, $J$=10.1 Hz), 1.2–1.9 (m, 6H), 1.84 (d, 3H, $J$=1.44 Hz), 2.09 (m, 1H), 2.15 (m, 1H), 2.27 (m, 1H), 3.55 (d, 1H, $J$=9.04 Hz), 3.81 (d, 1H, $J$=9.04 Hz), 4.22 (m, 2H), 4.52 (ddd, 1H, $J_1$=7.6 Hz, $J_2$=7.6 Hz, $J_3$=7.2 Hz), 6.63 (dq, 1H, $J_1$=7.6 Hz, $J_2$=1.4 Hz) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −1.52 (q), 12.76 (q), 17.29 (t), 22.67 (t), 22.73 (t), 25.16 (q), 32.38 (t), 40.16 (d), 40.74 (t), 52.08 (d), 53.92 (s), 63.12 (t), 67.45 (d), 70.81 (t), 86.44 (s), 128.52 (s), 142.57 (d), 167.86 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{20}H_{34}O_4SiNa$: 389.2118, found: 389.2108.

**4.4.6. Hydroxyesters 29 and 30.** Coupling of aldehyde **15** (0.18 g, 0.6 mmol) and (*E*)-haloester **17** (0.26 g, 1.15 mmol) afforded 0.230 g of crude product. Fractionation by flash chromatography on silica gel (hexane/ethyl acetate 9:1) afforded **29** (0.11 g, 46%) and **30** (0.1 g, 42%).

**4.4.6.1. Methyl (1′*R*,2′*R*,4*S*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxymethyl-2′-trimethylsilyloxy-2′-methyl-bicyclo[3.1.1]-hept-6′-yl)-4-hydroxy-2-methyl-2-pentenoate 29.** Colourless oil. $[\alpha]_D^{20}$ −40.81 (*c* 1.01, $CHCl_3$). $R_f$ 0.19 (hexane/ethyl acetate 7:3). IR ($CHCl_3$): $\nu$ 3469, 2957, 2955, 2873, 1717, 1651, 1437, 1251, 1043, 1003, 840 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 0.09 (s, 9H), 1.26 (s, 3H), 1.05–2.3 (m, 10H), 1.87 (d, 3H, $J$=1.3 Hz), 2.03 (s, 3H), 3.75 (s, 3H), 4.3 (d, 1H, $J$=12 Hz), 4.5 (d, 1H, $J$=12 Hz), 4.65 (ddd, 1H, $J_1$=8.4 Hz, $J_2$=8.4 Hz, $J_3$=4.4 Hz), 6.70 (dq, 1H, $J_1$=8.4 Hz, $J_2$=1.3 Hz) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 2.48 (q), 12.75 (q), 21.12 (q), 23.68 (t), 26.99 (t), 30.64 (q), 32.97 (t), 39.11 (d), 39.77 (t), 42.45 (s), 51.88 (q), 52.10 (d), 66.40 (d), 66.96 (t), 78.13 (s), 126.97 (s), 144.06 (d), 168.44 (s), 171.36 (s) ppm. HRMS-EI (M+Na$^+$) calcd for $C_{21}H_{36}O_6SiNa$: 435.2173, found: 435.2169.

**4.4.6.2. Methyl (1′*R*,2′*R*,4*R*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxymethyl-2′-trimethylsilyloxy-2′-methyl-bicyclo[3.1.1]hept-6′-yl)-4-hydroxy-2-methyl-2-pentenoate 30.** Colourless oil. $[\alpha]_D^{20}$ −4.26 (*c* 0.59, $CHCl_3$). $R_f$ 0.32 (hexane/ethyl

acetate 7:3). IR ($CHCl_3$): $\nu$ 3501, 2955, 2932, 2873, 1716, 1651, 1437, 1251, 1044, 1003, 840 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.11 (s, 9H), 1.26 (s, 3H), 1.85 (d, 3H, $J$=1.2 Hz), 1.8–1.9 (m, 4H), 1.99 (s, 3H), 2.0–2.2 (m, 4H), 2.21 (m, 1H), 2.4 (m, 1H), 3.74 (s, 3H), 4.03 (d, 1H, $J$=12.5 Hz), 4.62 (d, 1H, $J$=12.4 Hz), 4.67 (ddd, 1H, $J_1$=8.8 Hz, $J_2$=8.8 Hz, $J_3$=3.6 Hz), 6.7 (dq, 1H, $J_1$=8.8 Hz, $J_2$=1.2 Hz) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 2.49 (q), 12.61 (q), 20.92 (q), 23.85 (t), 26.81 (t), 30.48 (q), 32.92 (t), 38.70 (d), 40.02 (t), 42.27 (s), 51.88 (q), 53.25 (d), 66.56 (t), 66.60 (d), 78.28 (s), 126.93 (s), 144.22 (d), 168.39 (s), 170.88 (s) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{21}H_{36}O_6SiNa$: 435.2173, found: 435.2167.

### 4.5. Periodinane oxidations. General procedure

**4.5.1. 2-(Trimethylsilyl)ethyl (1′*R*,4′*S*,6′*R*,7′*S*)-(*E*)-2-methyl-5-(1′-methyl-9′-oxa-8′-oxo-tricyclo[4.3.0.0$^{4,7}$]-non-7′-yl)-4-oxo-2-pentenoate 23.** To a solution of hydroxyester **21** (0.15 g, 0.40 mmol) in $CH_2Cl_2$ (5 mL) Dess–Martin periodinane (0.25 g, 0.6 mmol) was added. The reaction mixture was stirred for 5 h at room temperature. Then, 10% $NaCO_3H$ (5 mL) and 10% $Na_2S_2O_3$ (2.5 mL) were successively added. The reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried ($Na_2SO_4$) and evaporated to give a crude product (0.16 g), which was fractionated by flash chromatography on silica gel. Elution with hexane/ethyl acetate 8:2 afforded ketoester **23** (0.112 g, 75%) as a colourless oil. $[\alpha]_D^{20}$ +52.045 (*c* 0.99, $CHCl_3$). $R_f$ 0.45 (hexane/ethyl acetate 1:1). IR (KBr): $\nu$ 3439, 2960, 2925, 1768, 1709, 1621, 1263, 1091, 1000, 925, 865, 835 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 0.03 (s, 9H), 1.02 (dd, 2H, $J$=8.6 Hz), 1.51 (s, 3H), 1.70 (d, 1H, $J$=10.0 Hz), 1.90 (s, 4H), 2.15 (m, 1H), 2.18 (s, 3H), 2.4 (m, 1H), 2.7 (m, 1H), 2.94 (d, 1H, $J$=19.1 Hz), 3.14 (d, 1H, $J$=19.05 Hz), 4.25 (dd, 2H, $J$=8.6 Hz), 7.04 (s, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ −1.67 (q), 14.31 (q), 17.20 (t), 22.66 (t), 22.84 (t), 24.74 (q), 29.87 (t), 40.44 (d), 43.88 (t), 47.31 (d), 53.57 (s), 63.79 (t), 88.25 (s), 130.99 (d), 141.97 (s), 167.41 (s), 177.47 (s), 198.15 (s) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{20}H_{30}O_5SiNa$: 401.1755, found: 401.1746.

**4.5.2. Unsaturated ketoester 23 (from 22).** Periodinane oxidation of hydroxyester **22** (0.12 g, 0.31 mmol) afforded **23** (0.096 g, 80%).

**4.5.3. Methyl (1′*R*,4′*S*,6′*R*,7′*S*)-(*E*)-2-methyl-5-(1′-methyl-9′-oxa-tricyclo[4.3.0.0$^{4,7}$]non-7′-yl)-4-oxo-2-pentenoate 26.** Periodinane oxidation of hydroxyester **24** (0.175 g, 0.62 mmol) afforded **26** (0.155 g, 89%). Mp 110–112 °C (hexane). $[\alpha]_D^{20}$ +41.7 (*c* 0.505, $CHCl_3$). $R_f$ 0.46 (hexane/ethyl acetate 1:1). IR ($CHCl_3$): $\nu$ 3054, 2920, 2856, 1732, 1626, 1454, 1264, 1122 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.26 (s, 3H), 1.5 (d, 1H, $J$=10.1 Hz), 1.6–1.8 (m, 4H), 1.95–2.15 (m, 3H), 2.21 (s, 3H), 2.9 (dd, 1H, $J_1$=13.3 Hz, $J_2$=66.7 Hz), 3.39 (d, 1H, $J$=9.47 Hz), 3.81 (s, 3H), 4.15 (d, 1H, $J$=9.45 Hz), 7.08 (s, 1H) ppm. $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 14.14 (q), 22.47 (t), 22.76 (t), 24.98 (q), 32.25 (t), 39.67 (d), 49.59 (t), 51.39 (d), 52.39 (q), 52.99 (s), 70.99 (t), 85.74 (s), 131.96 (d), 140.60 (s), 167.80 (s), 200.15 (s) ppm. HRMS-EI (M+$H^+$) calcd for $C_{16}H_{23}O_4$: 279.1591, found: 279.1582.

**4.5.4. Unsaturated ketoester 26 (from 25).** Periodinane oxidation of hydroxyester **25** (0.75 g, 0.26 mmol) afforded **26** (0.6 g, 81%).

### 4.6. Preparation of (+)-massarinolin B (2) and 4-*epi*-(+)-massarinolin B (4)

**4.6.1. (+)-Massarinolin B (2).** To an ice-cooled solution of **27** (0.083 g, 0.23 mmol) in anhydrous THF (1.5 mL) a solution of TBAF (0.180 g, 0.69 mmol) in THF (1 mL) was added. The reaction mixture was stirred for 2 h at room temperature, poured into water (25 mL), acidified with aq HCl and extracted with ethyl acetate (3×25 mL). The combined extracts were dried ($Na_2SO_4$) and concentrated in vacuo to afford (+)-massarinolin B (**2**) (0.06 g, 99%). $[\alpha]_D^{20}$ +49.63 (*c* 0.72, MeOH). IR ($CHCl_3$): $\nu$ 3385, 2926, 1696, 1241, 1142, 1009 $cm^{-1}$. $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 1.23 (s, 3H), 1.51 (m, 1H), 1.61 (m, 1H), 1.77 (m, 1H), 1.83 (m, 1H), 1.84 (d, 3H, $J$=1.2 Hz), 1.87 (m, 1H), 1.89 (m, 1H), 2.00 (dd, 1H, $J_1$=10.8 Hz, $J_2$=4.1 Hz), 2.13 (m, 1H), 2.15 (m, 1H), 2.30 (m, 1H), 3.60 (d, 1H, $J$=9.4 Hz), 3.90 (d, 1H, $J$=9.4 Hz), 4.45 (ddd, 1H, $J_1$=8.9 Hz, $J_2$=8.6 Hz, $J_3$=4.0 Hz), 6.67 (dq, 1H, $J_1$=8.6 Hz, $J_2$=1.2 Hz) ppm. $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ 12.77 (q), 23.55 (t), 23.78 (t), 25.35 (q), 33.44 (t), 40.27 (d), 41.78 (t), 53.59 (d), 55.54 (s), 67.08 (d), 72.77 (t), 87.65 (s), 128.37 (s), 145.44 (d), 171.37 (s) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{15}H_{22}O_4Na$: 289.1410, found: 289.1416.

**4.6.2. 4-*epi*-(+)-Massarinolin B (4).** Fluoride deprotection of **28** (0.081 g, 0.22 mmol) afforded **4** (0.058 g, 99%). $[\alpha]_D^{20}$ +8.71 (*c* 1.51, $CHCl_3$). IR ($CHCl_3$): $\nu$ 3392, 2926, 2866, 1707, 1238, 1195, 1020 $cm^{-1}$. $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 1.22 (s, 3H), 1.47 (d, 1H, $J$=10.2 Hz), 1.59 (m, 1H), 1.73–1.89 (m, 4H), 1.83 (d, 3H, $J$=1.2 Hz), 2.09–2.3 (m, 4H), 2.39 (m, 1H), 3.53 (d, 1H, $J$=9.0 Hz), 3.79 (d, 1H, $J$=9.0 Hz), 4.91 (ddd, 1H, $J_1$=9.2 Hz, $J_2$=9.2 Hz, $J_3$=6.8 Hz), 6.63 (dq, 1H, $J_1$=9.2 Hz, $J_2$=1.2 Hz) ppm. $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ 12.86 (q), 23.41 (t), 23.62 (t), 25.41 (q), 33.39 (t), 41.33 (d), 41.91 (t), 53.45 (d), 55.20 (s), 67.60 (d), 71.98 (t), 88.20 (s), 128.92 (s), 145.06 (d), 171.28 (s) ppm. HRMS-EI (M+$Na^+$) calcd for $C_{15}H_{22}O_4Na$: 289.1410, found: 289.1409.

### 4.7. Methyl (1′*R*,2′*R*,4*S*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxy methyl-2′-trimethylsilyloxy-2′-methyl-bicyclo[3.1.1]hept-6′-yl)-4-*tert*-butyldiphenylsilyloxy-2-methyl-2-pentenoate 31

To a solution of hydroxyester **29** (65 mg, 0.16 mmol) in $CH_2Cl_2$ at 0 °C were successively added $Et_3N$ (0.045 mL, 0.32 mmol), DMAP (4.8 mg, 0.039 mmol) and $^tBuPh_2SiCl$ (0.062 mL, 0.24 mmol). The reaction mixture was stirred for 48 h at room temperature, diluted with ether (5 mL) and poured on satd $NaHCO_3$ (5 mL). The mixture was stirred for 30 min and extracted with ether. The combined organic layers were successively washed with water and brine, dried ($Na_2SO_4$) and evaporated to yield a crude product (0.23 g), which was fractionated by flash chromatography on silica gel. Elution with hexane/ethyl acetate 9:1 afforded **31** (60 mg, 59%) as a colourless oil. $[\alpha]_D^{20}$ −20.10 (*c* 1.25, $CHCl_3$). $R_f$ 0.54 (hexane/ethyl acetate 7:3). IR (film): $\nu$ 2956, 2858, 1737, 1720, 1473, 1251, 859 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 0.05 (s, 9H), 1.03 (s, 9H), 1.05–2.19

(m, 9H), 1.22 (d, 3H, $J$=1.2 Hz), 1.89 (s, 3H), 2.26 (dd, 1H, $J_1$=5.6 Hz, $J_2$=14.4 Hz), 3.63 (s), 3.93 (d, 1H, $J$=12.3 Hz), 4.37 (d, 1H, $J$=12.3 Hz), 4.58 (m, 1H), 6.59 (dq, 1H, $J_1$=1.4 Hz, $J_2$=9.4 Hz), 7.32–7.66 (m, 10H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 2.43 (q), 12.38 (q), 19.19 (s), 20.95 (q), 23.59 (t), 26.93 (q), 30.71 (q), 32.64 (t), 39.13 (d), 40.51 (t), 41.80 (s), 51.61 (q), 52.05 (d), 66.26 (t), 68.24 (d), 78.07 (s), 125.87 (s), 127.33 (d), 127.54 (d), 129.47 (d), 129.62 (d), 133.66 (s), 133.92 (s), 135.85 (d), 143.98 (d), 168.19 (s), 170.96 (s) ppm. HRMS-EI ($M+Na^+$) calcd for $C_{37}H_{54}O_{36}Si_2Na$: 673.3351, found: 673.3370.

### 4.8. Methyl (1′*R*,2′*R*,4*S*,5′*S*,6′*S*)-(*E*)-5-(6′-acetoxy methyl-2′-hydroxy-2′-methyl-bicyclo[3.1.1]-hept-6-yl)-4-*tert*-butyldiphenylsilyloxy-2-methyl-2-pentenoate 32

To a solution of **31** (130 mg, 0.20 mmol) in MeOH (5 mL) PPTS (50.3 mg, 0.2 mmol) was added. The mixture was stirred for 30 min. To the ice-cooled mixture was added satd $NaHCO_3$ (5 mL) and the reaction mixture was further stirred for 30 min. The crude mixture was extracted with ether and the combined organic layers were washed with brine. The organic phase was dried with $Na_2SO_4$ and evaporated to yield a crude (0.13 g), which was fractionated by flash chromatography on silica gel (hexane/ethyl acetate 8:2) to afford **32** (60 mg, 52%). $[\alpha]_D^{20}$ +9.9 ($c$ 0.78, $CHCl_3$). $R_f$ 0.37 (hexane/ethyl acetate 1:1). IR (film): $\nu$ 3350, 2858, 1737, 1720, 1473, 1251, 1050, 859 cm$^{-1}$. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 1.03 (s, 9H), 1.19 (d, 3H, $J$=12 Hz), 1.25–2.30 (m, 10H), 1.91 (s, 3H), 3.63 (s, 3H), 4.24 (s, 2H), 4.58 (q, 1H, $J_1$=6.7 Hz, $J_2$=15.3 Hz), 6.59 (d, 1H, $J$=9 Hz), 7.30–7.66 (m, 10H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 12.32 (q), 19.19 (s), 20.80 (q), 23.58 (t), 27.00 (q), 27.54 (t), 29.63 (t), 31.71 (q), 38.88 (d), 40.33 (t), 42.16 (s), 51.55 (q), 51.55 (d), 66.21 (t), 68.44 (d), 75.18 (s), 125.92 (s), 127.34 (d), 127.60 (d), 129.56 (d), 129.69 (d), 133.68 (s), 133.93 (s), 135.92 (d), 144.18 (d), 168.23 (s), 170.73 (s) ppm. HRMS-EI ($M+Na^+$) calcd for $C_{34}H_{46}O_6Si_2Na$: 601.2956, found: 601.2965.

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## Supplementary data

Spectroscopic data for compounds described in Schemes 1 and 2 and Table 1. HMQC, HMBC, COSY and ROESY experiments for **27**, **28**, **29**, **30**, **2** and **4**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.011.

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10. Satisfactorial spectroscopic data for compounds described in Table 1 and Schemes 1 and 2 have been obtained. See Section 4.
11. Transformation of the mixture of diastereomers **24** and **25** into the corresponding α-*O*-acetyl-mandelic esters gave no results in terms of a more efficient chromatographic separation. The mixture of **24** and **25** was treated with (*S*)-(+)-*O*-acetylmandelic acid, DCC and DMAP in THF at room temperature for 15 h to yield a mixture of (*S*)-(+)-*O*-acetylmandelic esters with 72% yield. See: Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2327–2330.
12. The spectroscopic data obtained for synthetic (+)-(**2**) were superimposable over those described by Gloer for (+)-massarinolin B. $[\alpha]_D^{20}$ +50 ($c$ 0.72 g/dL, $CH_3OH$); lit. $[\alpha]_D^{20}$ +54 ($c$ 0.65 g/dL, $CH_3OH$). Structural assignments of **2** and **4** were based mainly on HMQC, HMBC and ROESY experiments.
13. The absolute stereochemistry of the tricyclic core of synthetic (+)-isoampullicin (**7**) has been correlated with that of R-(−)-carvone through a stereocontrolled multistep synthetic sequence. Furthermore, the X-ray analysis of **7** has been reported (see Ref. 5a).
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# Synthesis and characterization of novel conjugated bisindenocarbazoles

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**Abstract**—We present the synthesis of five new bisindenocarbazoles with different alkyl substituents. The synthesis starts from 2,7-dibromocarbazole and leads to the bisindenocarbazoles **6–10** in five steps with an overall yield of about 50%. By substitution of the core with different alkyl chains in the last step of the synthesis, the morphology of the bisindenocarbazoles can be varied from crystalline materials to molecular glasses. The bisindenocarbazoles are electrochemically stable and exhibit a strong, saturated blue emission with a quantum yield of 63% in solution.


## 1. Introduction

Fused aromatics like pentacene and rubrene are attractive materials for organic electronics. Both pentacene single crystals[1] and thin, polycrystalline pentacene films exhibit carrier mobilities above 1 $cm^2$/Vs in organic field effect transistors (OFETs).[2] Single crystalline rubrene shows carrier mobilities up to 15 $cm^2$/Vs in OFETs.[3] In addition, rubrene has been used as efficient yellow dopant in organic light emitting diodes (OLEDs).[4]

Besides pure hydrocarbons like pentacene, materials containing fused heterocycles have attracted increasing interest as materials for organic electronics during the last years. For example, indolo- and bisindolocarbazoles have been synthesized and successfully tested in OFETs.[5–8]

In this paper, we present the synthesis of five new bisindenocarbazoles, a class of fused heterocycles that has not yet been described in the literature. We have developed a new and versatile strategy for the preparation of these materials, which makes it possible to introduce different alkyl substituents to the core in the very last step of the synthesis. This allows us to tailor the properties of this new class of materials. For example, **6** with four small methyl substituents in the 1- and 1′-positions is highly crystalline, whereas **7** with two butyl and two methyl groups is an amorphous molecular glass.

*Keywords*: Bisindenocarbazole; Carbazole; Suzuki cross coupling.
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## 2. Results and discussion

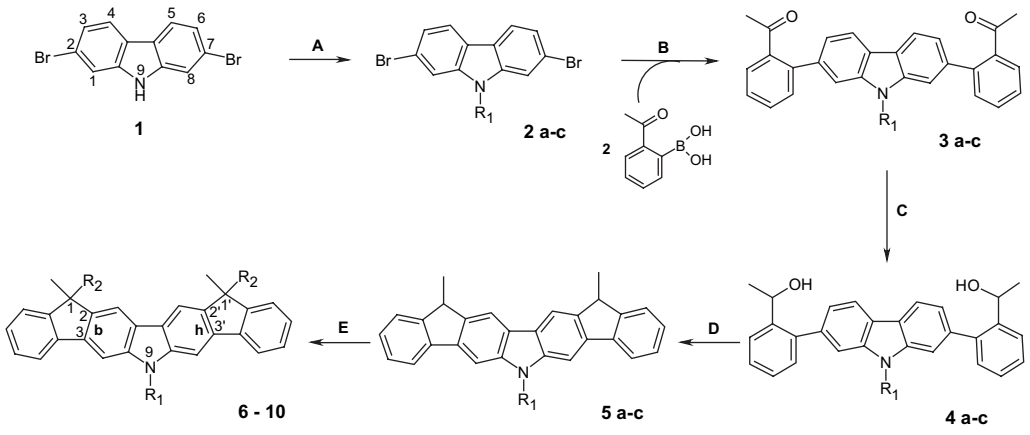
### 2.1. Preparation of the bisindenocarbazoles

Scheme 1 shows the synthetic route to the new bisindenocarbazoles. The preparation of 2,7-dibromocarbazole (**1**) and the *N*-alkylated carbazole monomers (**2a–c**) has been reported elsewhere.[9–13]

For phenylation (**B**) of the *N*-alkyl carbazoles **2a–c** in positions 2 and 7, the Suzuki cross coupling reaction was chosen, as it is an excellent tool for unsymmetrical aryl–aryl couplings.[14] The reactions were carried out in a two-phase system of toluene and aqueous potassium carbonate, with trimethylbenzylammonium chloride as phase-transfer catalyst (PTC). For Suzuki coupling of 2-acetylphenylboronic acid and *N*-alkylated 2,7-dibromocarbazoles **2a–c**, a mixture of $Pd(OAc)_2$ and P(*o*-tol)$_3$ was used as catalyst. Excellent yields of up to 91% of **3a–c** were achieved. In the next step, the keto groups were reduced to the corresponding secondary alcohols **4a–c** by reaction with lithium triethyl borohydride (super-hydride) in abs THF. In the case of bisindenocarbazoles, the reduction with super-hydride solution works fast and quantitatively.

The ring closure reaction of **4a–c** to the bisindenocarbazoles **5a–c** was carried out with boron trifluoride etherate as Lewis-acid catalyst in dichloromethane at room temperature. Ring closure occurs exclusively in the 3- and 6-positions of the carbazole, which are highly activated.

Finally, different alkyl side chains can be introduced to the planar bisindenocarbazole core with *n*-BuLi and the




**2a,b:** A = alkyl bromide, acetone, KOH, PTC, 70 °C, 5 h

**2c:** A = $Me_2SO_4$, acetone, 10N KOH, 50 °C, 30 min

B = $P(otol)_3$, $Pd(OAc)_2$, 2N KOH, toluene, PTC, 90 °C, 2 h

C = lithium triethylborohydride, THF, 0 °C, 1 h

D = $BF_3$*$O(C_2H_5)_2$, $CH_2Cl_2$, RT, 30 min

E = 1.6 M n-BuLi, alkyl bromide, THF, -78 °C, 1 h

| compd | $R_1$ | $R_2$ |
|---|---|---|
| **2-5a** | *sec*-butyl | --- |
| **2-5b** | 2-ethylhexyl | --- |
| **2-5c** | methyl | --- |
| **6** | *sec*-butyl | methyl |
| **7** | *sec*-butyl | n-butyl |
| **8** | *sec*-butyl | ethyl |
| **9** | 2-ethylhexyl | ethyl |
| **10** | methyl | ethyl |

**Scheme 1**. Synthesis of bisindenocarbazoles with different alkyl substituents.

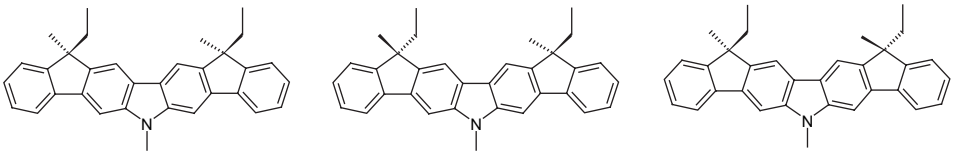
corresponding alkyl halide. The alkylation of bisindenocarbazoles in the very last step is a big advantage of this synthetic approach. As we will show in the next paragraphs, the morphology and the thermal properties of the target molecules can be tailored by adding alkyl groups of different lengths without changing the optical and electrical properties.

The bisindenocarbazoles **6–10** are mixtures of stereoisomers. Compound **6** is a mixture of two enantiomers, **7–9** have three stereocenters and hence eight enantiomers and four diastereomers. Compound **10** with two stereocenters in the 1- and 1′-positions is a mixture of two enantiomers and two diastereomers. Only in the case of **10** we were able to separate the two diastereomers by medium pressure liquid chromatography (MPLC). The first fraction is the *meso* form with (*R*,*S*)-configuration. The second fraction consists of the (*R*,*R*)- and (*S*,*S*)-enantiomers (Scheme 2). The (*R*,*R*/*S*,*S*)- and (*R*,*S*)-isomers are formed in a ratio of 2:1. The melting points of the two isomers differ by 19 °C. The (*R*,*S*)-isomer melts at 292 °C and the (*R*,*R*/*S*,*S*) racemate melts at 273 °C. In contrast, it was not possible to separate the bisindenocarbazoles **7–9**, which are a mixture of four diastereomers. Therefore, the NMR and thermal data refer to the isomeric mixtures.

All bisindenocarbazoles show good solubility in common organic solvents (e.g., THF, toluene, chloroform). The structures of the bisindenocarbazoles were confirmed by IR, $^1H$ and $^{13}C$ NMR, mass spectrometry, and elemental analysis. The synthetic procedures and the analytical data of all compounds are given in Section 4.

## 2.2. Thermal properties

The thermal properties of the bisindenocarbazoles were determined by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and are summarized in Table 1. TGA experiments in nitrogen showed that the bisindenocarbazoles **6–10** start to sublime at temperatures above 260 °C. Between 300 and 350 °C, quantitative weight



*(R,S)*-isomer of **10** *(S,S)*-isomer of **10** *(R,R)*-isomer of **10**

**Scheme 2**. Different isomers and configurations of **10**.

**Table 1**. Thermal properties of the bisindenocarbazoles **6–9**

| Compd | $T_g$ [°C][a] | $T_m$ [°C][a] | $T_{subl}$ [°C][b] |
|---|---|---|---|
| **6** | — | 265 | 310 |
| **7** | 106[c] | — | 320 |
| **8** | 103[c] | 250[c,d] | 305 |
| **9** | 74[c] | 164[c] | 330 |
| **10** (*R*,*S*) | — | 292 | 260 |
| **10** (*R*,*R*/*S*,*S*) | — | 273 | 260 |

[a] Determined by DSC, scan rate 10 K/min, second run, $N_2$ atmosphere.
[b] Onset of sublimation determined by TGA, heating rate 10 K/min, $N_2$ atmosphere.
[c] $T_g$ and $T_m$ refer to mixtures of four diastereomers.
[d] Melting point only detected in the first heating cycle.

loss was detected in all cases. The fact that the molecules can be sublimed quantitatively at ≈320 °C at normal pressure allows to prepare high quality films of the materials by vapor deposition.

DSC measurements clearly show how the morphology of the molecules can be tailored by changing the alkyl side groups. Compound **6** with four methyl substituents in the 1- and 1′-positions is crystalline ($T_m$=265 °C), whereas **7** with two butyl and two methyl side chains is amorphous and exhibits only a glass transition at 106 °C. In contrast to **6**, which recrystallizes upon cooling, the ethyl/methyl-substituted molecule **8** can be transferred into a glassy state upon cooling in the DSC experiment. Melting point of **8** is only observed in the first heating cycle at 250 °C. In the second and third run only the glass transition at 103 °C is detected. In the bisindenocarbazole **9**, the *N*-*sec*-butyl substituent of the central carbazole unit is replaced by a longer 2-ethylhexyl chain. This leads to a low glass transition temperature of 74 °C and melting point at 164 °C.

In the case of **10**, we were able to separate the two diastereomers. Both the (*R*,*R*/*S*,*S*)- and (*R*,*S*)-isomers of **10** are crystalline and melt at 273 and 292 °C, respectively. Upon cooling, both compounds show recrystallization in the DSC experiment. The mixture of the two diastereomers is also crystalline. In contrast to the two pure isomers, the mixture does not recrystallize upon cooling but forms a glass, which recrystallizes during the subsequent heating cycle. This shows that the mixture has a higher tendency to form a molecular glass than the pure diastereomers.

### 2.3. Optical properties

As expected, identical UV–vis spectra are obtained from the bisindenocarbazoles. The change of the alkyl side chains has no influence on the absorption of the bisindenocarbazole chromophore. The absorption and fluorescence spectra of **6** (Fig. 1) are representative for the bisindenocarbazoles **6–10**. The absorption maximum is at 380 nm. The bisindenocarbazoles exhibit a strong, saturated blue fluorescence with an emission maximum at 410 nm. The small Stokes shift of 6 nm is typical for the rigid structure of the bisindenocarbazoles.[15]

The fluorescence spectrum of **6** shows characteristic vibronic structures. The separation between the peaks at 388 and 410 nm is 1382 $cm^{-1}$, and between 410 and the shoulder at 435 nm is 1461 $cm^{-1}$. These values correspond

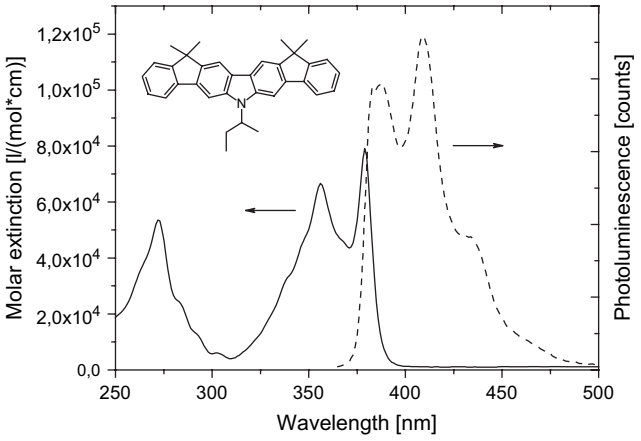



**Figure 1**. Absorption and fluorescence spectra of the bisindenocarbazole **6**. The absorption spectra were taken from $10^{-5}$ M cyclohexane solutions and the fluorescence spectra from $10^{-6}$ M cyclohexane solutions with an excitation wavelength of 350 nm.

to two discrete carbazole skeleton vibrations in the IR-spectrum.

In order to estimate the fluorescence quantum yield ($\Phi_f$) of the bisindenocarbazoles, the fluorescence of **6** was compared with the well known blue laser dye Exalite 428 [7,7″-bis(4-*tert*-amylphenyl)-9,9,9′,9′,9″,9″-hexapropyl-2,2′:7′,2″-terfluorene]. Exalite 428 has a quantum efficiency of 90% in cyclohexane solution.[16] Solutions ($10^{-5}$ M) of **6** and Exalite 428 in cyclohexane were prepared and diluted to an optical density of ≈0.1 in order to minimize self-absorption.[17] From these solutions, fluorescence spectra were taken and by integration, a fluorescence quantum yield of 63% was calculated for **6**.

### 2.4. Electrochemical properties

The electrochemical stability of the bisindenocarbazoles was examined by cyclic voltammetry (CV). All measurements were carried out at 25 °C in $CH_2Cl_2$ solution containing 0.1 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as supporting electrolyte with a glassy carbon working electrode. The oxidation potentials were measured versus Ag/AgCl as the reference electrode.[18] The CV curve of **6** (Fig. 2) shows one oxidation peak at 0.60 V, which is fully reversible. Repeated oxidation and reduction cycles had no influence on the CV curve. The same results are obtained for other bisindenocarbazoles **7–10**. This is a proof for the electrochemical stability of the new bisindenocarbazoles. It has been reported that the electrochemical oxidation of compounds based on 2,7-linked carbazoles is not fully reversible and that such materials undergo dimerization reactions in the activated 3- and 6-positions of the carbazole rings.[6,10] The high electrochemical stability of the bisindenocarbazoles **6–10**, in which these positions are blocked by ring closure, strongly supports this argument and shows that the activated 3- and 6-positions in 2,7-linked carbazole compounds have to be blocked in order to obtain electrochemically stable materials.

The HOMO levels of the bisindenocarbazoles **6–10** can be estimated from the CV measurement. For this purpose, the CV was calibrated with the standard ferrocene/ferrocenium

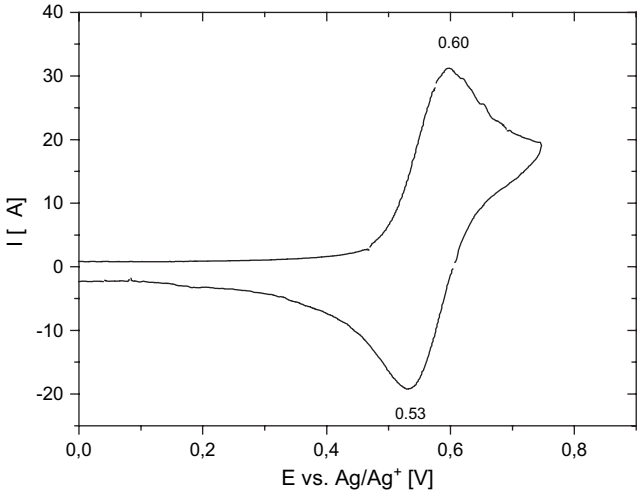



**Figure 2**. CV measurement of **6**, measured at 25 °C at a scan rate of 50 mV/s versus $Ag/Ag^+$ in acetonitrile with $TBAPF_6$ as supporting electrolyte.

redox system. Taking −4.8 eV as HOMO level for the ferrocene redox system,[19] HOMO values of −5.3 eV were obtained. With an optical band gap of 3.2 eV, calculated from the absorption edge at 391 nm, LUMO values of −2.1 eV are calculated for compounds **6–10**.

## 3. Conclusions

In conclusion, we have developed a new versatile synthetic route to conjugated bisindenocarbazoles. The title compounds **6–10** are obtained in five steps from 2,7-dibromocarbazole **1** with an overall yield of 50%. By substitution with a variety of alkyl substituents in the very last step of the synthesis, their morphology can be varied from highly crystalline materials (**6**) to amorphous molecular glasses (**7**). The compounds sublime quantitatively at temperatures around 320 °C and excellent films can be prepared by evaporation. In CV experiments, the bisindenocarbazoles showed a high electrochemical stability. This is in contrast to the 2,7-carbazole trimers, which have been reported before.[10] These trimers show irreversible electrochemical oxidation due to dimerization reactions in the highly activated 3- and 6-positions of the carbazole ring. In the bisindenocarbazoles **6–10**, the reactive 3- and 6-positions in the central carbazole unit are blocked by the ring closure. From CV measurements and optical band gap, HOMO levels of −5.3 eV and LUMO values of −2.1 eV were calculated. All bisindenocarbazoles **6–10** exhibit a strong, saturated blue emission with a quantum yield of 63% in solution and will be tested as blue dopants in organic light emitting diodes in the near future.

## 4. Experimental

### 4.1. General

$^1$H NMR spectra were recorded with a Bruker AC 250 (250 MHz) apparatus. All data are given as chemical shifts $\delta$ [ppm] downfield from $Si(CH_3)_4$. The IR spectra were recorded using a Bio-Rad Digilab FTS-40. The UV–vis spectra were recorded with a Hitachi U-3000 spectrophotometer. Emission spectra were obtained from a Shimadzu spectrofluorophotometer RF-5301PC. Conventional mass spectra (MS) were recorded with a Finnigan MAT 8500 (70 eV) with a MAT 112S Varian. Thermogravimetric analysis (TGA) was performed on a Perkin–Elmer TAS-409 at a heating rate of 10 K/min under $N_2$. For differential scanning calorimetry measurements (DSC), Perkin–Elmer DSC-7 apparatus was used (heating/cooling rate: 10 K/min). Cyclic voltammetry measurements (CV) were performed with a glassy carbon working electrode (0.2 mm) in a three-electrode potentiostat configuration from EG&G Princeton Applied Research.

All chemicals and reagents were used as received from Aldrich. Tetrahydrofuran (THF) was distilled over potassium before use. The synthesis of 2,7-dibromocarbazole (**1**) and *N*-alkylated 2,7-dibromocarbazoles (**2a–c**) has been reported elsewhere.[9–13]

### 4.2. 2,7-Bis-(2-acetylphenyl)-9-*sec*-butyl-carbazole (3a)

2,7-Dibromo-9-*sec*-butyl-carbazole (**2a**) (1.3 g, 3.5 mmol) and 2-acetylphenylboronic acid (1.3 g, 7.7 mmol) were dissolved in 45 ml of toluene. A 2 M solution of $K_2CO_3$ (25 ml) and 0.2 g of trimethylbenzylammonium chloride was added. The reaction mixture was degassed by three freeze/thaw cycles before 31.3 mg (0.14 mmol) $Pd(OAc)_2$ and 127.0 mg (0.42 mmol) tri-*o*-tolylphosphine ($P(o\text{-tol})_3$) were added under argon. The mixture was stirred for 15 h at 90 °C before it was poured into ice water and extracted with diethyl ether. After evaporation of the solvent, the product was purified by column chromatography on silica gel with hexane/THF (6:1) as eluent yielding 1.42 g (89%) of **3a** as a colorless solid. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.71(t, 3H), 1.58 (d, 3H), 1.86 (s, 6H), 1.95 (m, 1H), 2.21 (m, 1H), 4.53–4.67 (m, 1H), 7.20 (m, 2H), 7.37 (m, 4H), 7.52 (m, 6H), 8.13 (d, 2H). MS (70 eV): $m/z$=459 ($M^+$).

### 4.3. 2,7-Bis-(2-acetylphenyl)-9-(2-ethylhexyl)-carbazole (3b)

Compound **3b** was prepared according to the procedure described above (yield: 91%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.78–0.87 (m, 6H), 1.12–1.40 (m, 8H), 1.48 (s, 6H), 2.07 (m, 1H), 4.16 (m, 2H), 7.17 (d, 2H), 7.34 (m, 6H), 7.36 (m, 2H), 7.70 (d, 2H), 8.14 (d, 2H). MS (70 eV): $m/z$=515 ($M^+$).

### 4.4. 2,7-Bis-(2-acetylphenyl)-9-methyl-carbazole (3c)

Compound **3c** was prepared according to the procedure described above (yield: 83%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 1.99 (s, 6H), 3.88 (s, 3H), 7.24 (d, 1H), 7.27 (d, 1H), 7.40 (m, 2H), 7.39–7.48 (m, 2H), 7.54–7.58 (m, 6H), 8.16 (d, 2H). MS (70 eV): $m/z$=417 ($M^+$).

### 4.5. 2,7-Bis-[2-(2-hydroxyethylphenyl)-9-*sec*-butyl]-carbazole (4a)

Compound **3a** (0.37 g, 0.80 mmol) was dissolved in 25 ml abs THF. The solution was flushed with argon and cooled to 0 °C before 2.3 ml (2.40 mmol) of 1 M lithium triethyl borohydride solution in THF (super-hydride) was added

slowly. The reaction mixture was stirred at 0 °C for 1 h and 15 ml of an aqueous $NH_4Cl$ solution was added. Thereafter, the reaction batch was poured into 150 ml water and extracted with diethyl ether. The organic layer was washed with water and the solvent was removed. The product was purified by column chromatography on silica gel with hexane/ethyl acetate (1.5:1) as eluent yielding 0.35 g (95%) of **4a** as a colorless solid. $^1$H NMR (250 MHz, DMSO): $\delta$ (ppm) 0.74 (t, 3H), 1.29–1.33 (m, 6H), 1.67 (m, 3H), 2.01 (m, 1H), 2.24 (m, 1H), 4.93 (m, 3H), 5.14 (m, 2H), 7.20 (d, 2H), 7.35–7.51 (m, 6H), 7.68 (d, 2H), 7.73 (d, 2H), 8.29 (d, 2H). MS (70 eV): $m/z$=463 ($M^+$).

### 4.6. 2,7-Bis-[2-(2-hydroxyethylphenyl)-9-(2-ethylhexyl)]-carbazole (4b)

Compound **4b** was prepared according to the procedure described above (yield: 96%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.71–0.88 (m, 6H), 1.14–1.46 (m, 11H), 1.49 (d, 3H), 2.07 (m, 1H), 4.16 (d, 2H), 5.09 (m, 2H), 7.17 (d, 2H), 7.36–7.49 (m, 8H), 7.71 (d, 2H), 8.12 (d, 2H). MS (70 eV): $m/z$=519 ($M^+$).

### 4.7. 2,7-Bis-[2-(2-hydroxyethylphenyl)-9-methyl]-carbazole (4c)

Compound **4c** was prepared according to the procedure described above (yield: 98%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 1.45 (d, 6H), 3.90 (s, 3H), 5.10 (q, 2H), 7.18 (d, 1H), 7.35–7.40 (m, 6H), 7.43–7.51 (m, 3H), 7.73 (d, 2H), 8.15 (d, 2H). MS (70 eV): $m/z$=421 ($M^+$).

### 4.8. 1,1′-Dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-*sec*-butyl-carbazole (5a)

To a solution of 0.1 g (0.22 mmol) **4a** in 10 ml dichloromethane, 0.1 ml (0.65 mmol) boron trifluoride etherate was added. The mixture was stirred for 30 min at room temperature before 15 ml ethanol and 20 ml water were added. The reaction batch was extracted with dichloromethane, washed with water, and dried with $Na_2SO_4$ before the solvent was evaporated. Purification by column chromatography on silica gel with hexane/THF (3:1) as eluent yielded 83 mg (92%) of **5a** as colorless solid. $^1$H NMR (250 MHz, DMSO): $\delta$ (ppm) 0.81 (t, 3H), 1.64 (d, 6H), 1.80 (d, 3H), 2.12 (m, 1H), 2.49 (m, 1H), 4.10 (q, 2H), 5.05 (m, 1H), 7.35–7.46 (m, 4H), 7.64 (d, 2H), 8.12 (d, 2H), 8.21 (s, 2H), 8.39 (d, 2H). MS (70 eV): $m/z$=427 ($M^+$).

### 4.9. 1,1′-Dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-(2-ethylhexyl)-carbazole (5b)

Compound **5b** was prepared as described above (yield: 90%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.84 (m, 6H), 1.51–1.46 (m, 8H), 1.49 (d, 6H), 2.05 (m, 1H), 3.96 (q, 2H), 4.86 (m, 2H), 7.33–7.44 (m, 4H), 7.60 (d, 2H), 8.10 (d, 2H), 8.19 (s, 2H), 8.35 (d, 2H). MS (70 eV): $m/z$=483 ($M^+$).

### 4.10. 1,1′-Dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-methyl-carbazole (5c)

Compound **5c** was prepared as described above (yield: 88%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 1.56 (d, 6H), 4.13 (q, 2H), 4.51 (s, 3H), 7.32–7.40 (m, 4H), 7.55 (d, 2H), 7.72 (s, 2H), 7.86 (d, 2H), 8.20 (s, 2H). MS (70 eV): $m/z$=385 ($M^+$).

### 4.11. 1,1′-Di-*n*-butyl-1,1′-dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-*sec*-butyl-carbazole (7)

Compound **5a** (60 mg, 0.14 mmol) was dissolved in 15 ml THF (abs) under argon. The solution was cooled to −78 °C before 0.19 ml (0.3 mmol) *n*-BuLi (1.6 M solution in hexane) was added slowly. After 15 min stirring, 0.2 ml (0.4 mmol) 1-bromobutane was added. The solution was allowed to warm to room temperature and stirred for another hour before it was poured into 50 ml ice water. The reaction batch was extracted with diethyl ether, the organic phase was washed with water, and the solvent was evaporated. Purification was carried out by column chromatography on silica gel with hexane/THF (10:1) as eluent. In addition, **7** was purified by MPLC with hexane/THF (15:1) at a pressure of 18 bar. The reaction yielded 51 mg (75%) of **7** as white solid. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.62 (m, 9H), 0.87 (t, 4H), 1.01–1.10 (m, 4H), 1.51 (m, 6H), 1.74 (d, 3H), 1.96–2.17 (m, 5H), 2.28–2.47 (m, 1H), 4.76 (m, 1H), 7.27–7.37 (m, 6H), 7.69 (s, 2H), 7.76 (d, 2H), 8.01 (s, 2H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm) 12.2, 14.3, 19.6, 23.5, 26.9, 28.1, 28.6, 41.8, 50.4, 53.6, 114.1, 119.9, 123.2, 123.3, 123.6, 127.1, 127.3, 128.5, 141.2, 143.7, 153.4. IR (Si-wafer): $\tilde{\nu}$ ($cm^{-1}$) 3011, 2958, 2972, 1488, 1452, 1378, 1342, 1240, 740. MS (70 eV): $m/z$=539 ($M^+$). Anal. Calcd for $C_{40}H_{45}N$ (539.8): C, 89.00; H, 8.40; N, 2.59. Found: C, 89.09; H, 8.31; N, 2.58.

### 4.12. 1,1-Dimethyl-1′,1′-dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-*sec*-butyl-carbazole (6)

Compound **6** was prepared according to the procedure described for **7**. For alkylation, iodomethane was used (yield: 70%). Compound **6** was purified by MPLC with hexane/THF (10:1) at a pressure of 18 bar. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.90 (t, 3H), 1.61 (m, 12H), 1.78 (d, 3H), 2.05–2.21 (m, 1H), 2.35–2.53 (m, 1H), 4.81 (m, 1H), 7.28–7.49 (m, 6H), 7.82 (s, 2H), 7.89 (d, 2H), 8.15 (s, 2H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm) 12.2, 19.6, 26.8, 28.5, 46.5, 53.6, 101.4, 114.0, 120.8, 123.1, 123.7, 127.4, 132.1, 137.6, 140.3, 145.3, 154.9. IR (Si-wafer): $\tilde{\nu}$ ($cm^{-1}$) 3014, 2961, 2926, 1489, 1452, 1377, 1342, 1241, 740. MS (70 eV): $m/z$=455 ($M^+$). Anal. Calcd for $C_{34}H_{33}N$ (455.7): C, 89.63; H, 7.30; N, 3.07. Found: C, 89.56; H, 7.33; N, 3.12.

### 4.13. 1,1′-Diethyl-1,1′-dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-*sec*-butyl-carbazole (8)

Compound **8** was prepared according to the procedure described for **7**. For alkylation, bromoethane was used. Compound **8** was purified by MPLC with hexane/THF (15:1) at a pressure of 18 bar (yield: 80%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.41 (m, 6H), 0.90 (m, 3H), 1.58 (s, 6H), 1.78 (d, 3H), 2.05–2.22 (m, 5H), 2.34–2.41 (m, 1H), 4.78 (m, 1H), 7.26–7.41 (m, 6H), 7.78 (s, 2H), 7.82 (d, 2H), 8.05 (s, 2H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm) 9.0, 11.8, 19.2, 27.3, 28.2, 34.1, 50.4, 53.2, 113.7, 115.0, 119.4, 122.9, 124.1, 126.4, 138.3, 141.0, 142.9, 152.6. IR (Si-wafer): $\tilde{\nu}$ ($cm^{-1}$) 3049, 2963, 2929, 1488, 1452, 1378,

1342, 1240, 741. MS (70 eV): $m/z$=483 ($M^+$). Anal. Calcd for $C_{36}H_{37}N$ (483.7): C, 89.39; H, 7.71; N, 2.90. Found: C, 89.54; H, 7.69; N, 2.85.

### 4.14. 1,1′-Diethyl-1,1′-dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-(2-ethylhexyl)-carbazole (9)

Compound **9** was prepared according to the procedure described for **7**. For alkylation, **5b** was treated with bromoethane. Compound **9** was purified by MPLC with hexane/THF (20:1) at a pressure of 18 bar (yield: 76%). $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.33 (m, 6H), 0.80–0.96 (m, 6H), 1.18–1.48 (m, 8H), 1.52 (s, 6H), 1.98–2.16 (m, 5H), 4.20 (m, 2H), 7.21–7.39 (m, 6H), 7.58 (s, 2H), 7.75 (d, 2H), 7.98 (s, 2H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm) 7.8, 9.8, 12.9, 21.8, 23.4, 26.0, 27.6, 29.8, 32.9, 38.2, 46.5, 49.2, 98.6, 112.5, 118.2, 121.6, 125.6, 125.7, 137.3, 139.7, 141.8, 151.4. IR (Si-wafer): $\tilde{\nu}$ ($cm^{-1}$) 3046, 2960, 2928, 1491, 1460, 1354, 1330, 1265, 739. MS (70 eV): $m/z$=539 ($M^+$). Anal. Calcd for $C_{40}H_{45}N$ (539.8): C, 89.00; H, 8.40; N, 2.59. Found: C, 89.03; H, 8.46; N, 2.59.

### 4.15. 1,1′-Diethyl-1,1′-dimethyl-bisindeno[3,2-*b*:2′3′-*h*]-9-methyl-carbazole (10)

Compound **10** was prepared according to the procedure described for **7**. For alkylation, **5c** was treated with bromoethane. Compound **10** was purified by MPLC with hexane/THF (25:1) at a pressure of 18 bar (yield: 76%). In case of **10**, it was possible to separate the two isomers by this technique. The (*R*,*S*)-isomer (200 mg) and (*S*,*S*/*R*,*R*)-isomer (400 mg) were obtained after vacuum freeze drying.

*(R,S)-isomer*: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.28–0.45 (m, 6H), 1.59 (s, 3H), 1.88 (s, 3H), 2.15 (q, 2H), 2.29–2.45 (m, 1H), 2.51–2.68 (m, 1H), 4.32 (s, 3H), 7.28–7.44 (m, 6H), 7.71–7.76 (m, 2H), 7.78 (d, 1H), 7.86 (d, 1H), 8.05 (s, 1H), 8.17 (d, 1H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm) 9.41, 27.74, 27.83, 28.04, 34.19, 34.48, 50.96, 52.91, 100.29, 112.33, 113.82, 119.56, 119.80, 119.94, 122.35, 123.30, 123.994, 124.64, 127.21, 127.30, 127.35, 127.39, 132.41, 139.34, 139.64, 140.47, 141.22, 141.29, 142.38, 144.25, 152.96. IR (Si-wafer): $\tilde{\nu}$ ($cm^{-1}$) 3049, 2962, 2923, 1495, 1457, 1378, 1307, 1225, 743. MS (70 eV): $m/z$=441 ($M^+$). Anal. Calcd for $C_{33}H_{31}N$ (441.6): C, 89.75; H, 7.08; N, 3.17. Found: C, 89.54; H, 6.95; N, 3.20.

*(S,S/R,R)-isomer*: $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ (ppm) 0.37–0.40 (m, 6H), 1.63 (s, 6H), 2.08–2.16 (m, 4H), 4.00 (s, 3H), 7.30–7.45 (m, 6H), 7.69 (s, 2H), 7.85 (d, 2H), 8.06 (s, 2H). $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ (ppm) 9.42, 27.79, 29.82, 34.56, 50.50, 99.81, 114.22, 119.94, 123.20, 123.26, 127.34, 139.08, 141.36, 142.07, 143.59, 152.96. IR (Si-wafer): $\tilde{\nu}$ ($cm^{-1}$) 3050, 2961, 2920, 1494, 1458, 1349, 1307, 1264, 739. MS (70 eV): $m/z$=441 ($M^+$). Anal. Calcd for $C_{33}H_{31}N$ (441.6): C, 89.75; H, 7.08; N, 3.17. Found: C, 89.73; H, 7.09; N, 3.09.

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# Stereoselective synthesis of trifluoromethyl-substituted 1,2-diamines by aza-Michael reaction with *trans*-3,3,3-trifluoro-1-nitropropene

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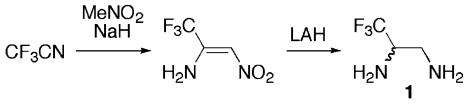
**Abstract**—Aza-Michael addition of optically pure 4-phenyl-2-oxazolidinone to 3,3,3-trifluoro-1-nitropropene proceeds smoothly at low temperature with a high yield. Diastereoselectivity of the addition depends on the base used and lithiated species proved to be highly efficient affording 92% de. Optically pure 1,2-diamino-3,3,3-trifluoropropane is prepared in 58% yield from the aza-Michael addition product through a three-step procedure.


## 1. Introduction

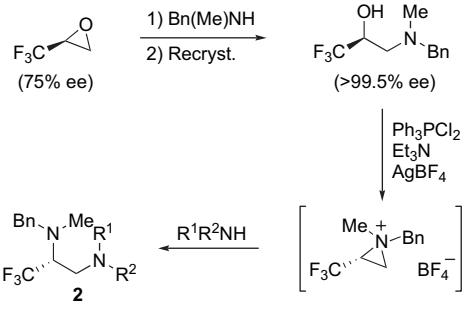
For more than 50 years fluorinated compounds receive tremendous interest as candidates for new pharmaceuticals and agrochemicals.[1] Today 16–17% of pharmaceuticals do incorporate fluorine and half of agrochemicals are fluorinated molecules. During the past decade, the number of fluorinated compounds developed by companies increased by a 2-fold factor and more and more investigations are now focusing toward chiral and optically pure fluorinated molecules.[2]

The synthesis of selectively fluorinated non-racemic chiral compounds having sophisticated structures is generally realized by fluorinating the final intermediate during the synthetic sequence. The synthesis of organofluorine compounds using fluorine-containing 'building blocks' is an efficient alternative to the direct introduction of fluorine. Although there has been recent general interest in the preparation and utilization of optically enriched and/or pure building blocks, there are, however, very few optically active and synthetically usable fluorinated compounds that are commercially available. Thus efforts, more than ever, are required to develop efficient methodologies to produce such compounds.

1,2-Ethylenediamines are key starting materials in the synthesis of nitrogen-containing heterocyclic compounds[3] (piperazines, imidazolines, imidazolidines, etc.) as well as aliphatic amines[4] (amino acids, amino alcohols, etc.). Chiral 1-trifluoromethyl-substituted 1,2-ethylenediamines especially gained our attention as promising building blocks for the synthesis of optically active trifluoromethylated nitrogen compounds. The synthesis of racemic 1,2-diamino-3,3,3-trifluoropropane **1** has been reported only very recently by Sosnovskikh et al.[5] The authors prepared the compound according to Scheme 1 by reduction of 2-amino-3,3,3-trifluoro-1-nitropropene with lithium aluminum hydride, and characterized **1** as bis-tosyl derivative.[6] At the same time




**Scheme 1**.




**Scheme 2**.

*Keywords*: Perfluoroalkyl nitroalkene; Diastereoselective aza-Michael addition; 3,3,3-Trifluoro-1-nitropropene; 4-Phenyl-2-oxazolidinone.
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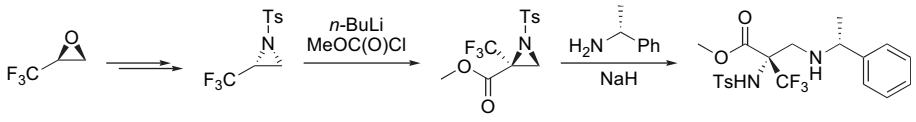
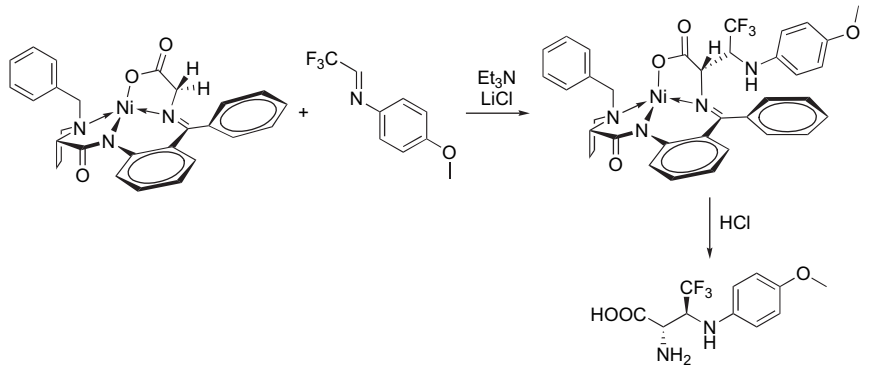
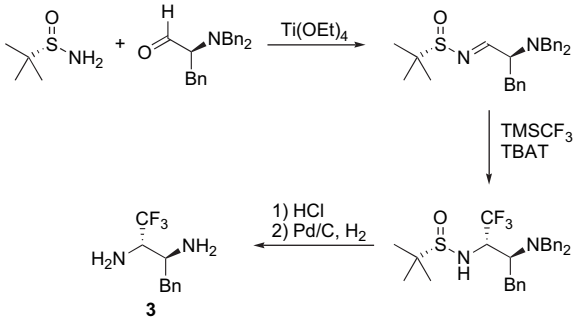


**Scheme 3**.

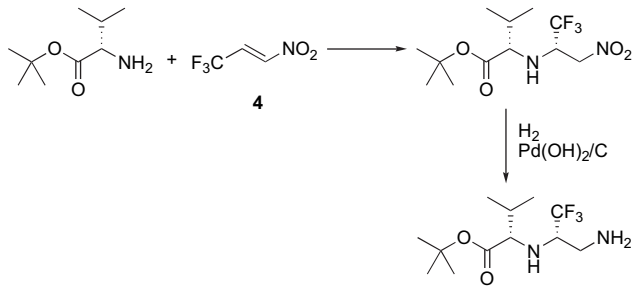


**Scheme 4**.

Katagiri et al. described the synthesis of optically active *N*,*N*′-substituted 1,2-diamino-3,3,3-trifluoropropanes **2** starting from optically pure 2,3-epoxy-1,1,1-trifluoropropane (Scheme 2).[7] In 2003, Uneyama's group developed an alternate strategy involving *N*-tosylaziridines (Scheme 3).[8] That has to be paralleled with a work by Soloshonok, who described aza-aldol reactions of chiral Ni(II) complex of glycine with imines (Scheme 4).[9] Prakash and Mandal developed a different route to access trifluoromethyl vicinal ethylenediamine involving nucleophilic trifluoromethylation of optically active (*R*)-*N*-*tert*-butanesulfinimines (Scheme 5).[10] Last, Zanda et al. described the diastereoselective addition of α-amino esters to 3,3,3-trifluoro-1-nitropropene (Scheme 6).[11] The diastereoselectivity observed by Zanda is in the range 23–84% depending on experimental conditions.



**Scheme 5**.



**Scheme 6**.

To the best of our knowledge, the literature do not disclose any other report on the synthesis, either stereoselective or not, of 1,2-diamino-2-perfluoroalkyl compounds. Herein we report our results concerning the stereoselective synthesis of 1,2-diamino-3,3,3-trifluoropropane **1** by Michael addition of amino compounds on prochiral *trans*-3,3,3-trifluoro-1-nitropropene **4**.

## 2. Results and discussion

The use of nitroalkenes as Michael acceptors has received much attention due to the number of efficient methods for converting nitro groups into amines, carbonyls, etc.[12] Aza-Michael reactions somewhat remained in the background as β-aminonitroalkanes are reported as unstable compounds.[13,14] Nevertheless, some remarkable results have been obtained concerning the addition of achiral, prochiral, or chiral nitrogen nucleophiles to either achiral, prochiral, or chiral nitroalkenes. Restricting our analysis to those diastereocontrolled addition reactions we can only find some 15 examples.[15–28] *trans*-3,3,3-Trifluoro-1-nitropropene **4** is a highly reactive Michael acceptor and is regioselectively attacked at the C2 position (Fig. 1).[29] To the best of our knowledge, the only aza-Michael reactions with **4** reported so far in the literature concern pyrazole **5** and triazoles **6**, adducts being obtained as pairs of enantiomers,[30] and α-amino esters as reported by Zanda et al.[11]

Intrigued by the diastereoselective potential of the aza-Michael reaction with 2-perfluoroalkyl-1-nitroalkenes we investigated the addition of a series of various chiral nitrogen

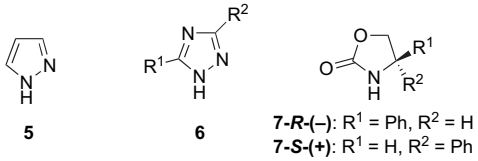
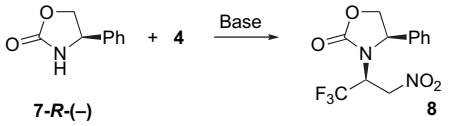


**Figure 1**.

nucleophiles to **4** to set up an access to enantiopure 1,2-diamino-2-perfluoroalkyl compounds.[31] Remarkable results were obtained with 4-phenyl-2-oxazolidinone **7** that is commercially available as both *R*-(−) and *S*-(+) isomers (Scheme 7). We studied the scope and the diastereoselectivity of the reaction as a function of experimental conditions such as temperature, base used for nitrogen deprotonation (or addition promoter), or solvent composition (Table 1).




**Scheme 7**.

The conjugate addition of 4-phenyl-2-oxazolidinone lithium or potassium salt to *trans*-3,3,3-trifluoro-1-nitropropene **4** proceeds smoothly and gets to completion within 15–30 min at −78 °C. Higher yields were invariably obtained using *n*-butyllithium as a base instead of potassium *tert*-butoxide. That is likely related to the size of the alkaline counter-ion, which is consistent with the intermediate result obtained with sodium hydride (Entry 14). Indeed *trans*-3,3,3-trifluoro-1-nitropropene **4** is unstable under basic conditions even at low temperature. Consequently the quicker the anion from **7** adds to the nitroalkene precluding its degradation, the better. That is equally consistent with the lower yield obtained when no phase transfer catalyst is used (Entry 3, 42% yield after 30 min). Due to the higher solubility of *n*-butyllithium in the reaction mixture, lack of 18-crown-6 in that case does not have drastic effects on conversion and yield (Entry 11). Alternative addition conditions have been tested. In the conditions described by Rawal et al., for the addition of oxazolidinones to 3-butyn-2-one (*N*-methylmorpholine, NMM)[32] no reaction occurs (Entry 15). Bis(acetonitrile)palladium(II) chloride has been recently described to promote the intramolecular addition of oxazolidinones to double bonds in a high yield.[33] However, in the conditions described by Hirai et al. 4-phenyl-2-oxazolidinone does not add to **4** and is integrally recovered after work up of the reaction mixture (Entry 16). The same negative results are obtained using potassium fluoride on alumina as described by Blass et al. for the addition of oxazolidinone to a series of various electrophiles.[34]

In all the experiments described herein a major diastereomer formed as expected from earlier results obtained with non-fluorinated nitroalkenes.[21] As fluorinated substituents may modify the stereochemical issue of diastereoselective reactions,[2] we were bent on determining the absolute configuration of the reaction adduct. A single-crystal X-ray analysis of compound **8** derived from (*R*)-(−)-4-phenyl-2-oxazolidinone showed that the chiral center that is created has an *S* absolute configuration (Fig. 2). That result is in agreement with those in the non-fluorinated series. The high level of asymmetric induction can be explained by a metal-chelated eight-membered transition state model (Fig. 3). Thus transition state TS-*re* suffers from steric repulsion between phenyl and trifluoromethyl groups, which does not exist in TS-*si*. Quite surprisingly the metal cation reveals extremely important for the diastereoselectivity of the reaction. While $K^+$

**Table 1**. Conjugate addition of *R*-(−)-4-phenyl-2-oxazolidinone **7** on *trans*-3,3,3-trifluoro-1-nitropropene **4**

| Entry[a] | Compound **7** | *T* (°C) | Base | Conversion[b] (%) | Yield[c] (%) | de[d] (%) |
|---|---|---|---|---|---|---|
| 1 | *R*-(−) | −100 | *t*-BuOK | 66 | 55 | 64 |
| 2 | *R*-(−) | −78 | *t*-BuOK | 68 | 54 | 58 |
| 3[e] | *R*-(−) | −78 | *t*-BuOK | 64 | 42 | 56 |
| 4 | *R*-(−) | −40 | *t*-BuOK | 65 | 45 | 52 |
| 5 | *R*-(−) | +25 | *t*-BuOK | 44 | 28 | 50 |
| 6 | *R*-(−) | +50 | *t*-BuOK | 28 | 8 | 50 |
| 7[f] | *R*-(−) | −78 | *t*-BuOK | 60 | 48 | 50 |
| 8 | *R*-(−) | −100 | *n*-BuLi | 80 | 74 | 92 |
| 9 | *R*-(−) | −78 | *n*-BuLi | 100 | 83 | 92 |
| 10[g] | *R*-(−) | −78 | *n*-BuLi | 100 | 91 | 92 |
| 11[e] | *R*-(−) | −78 | *n*-BuLi | 100 | 83 | 92 |
| 12 | *R*-(−) | −30 | *n*-BuLi | 100 | 85 | 86 |
| 13[h] | *R*-(−) | −78 | *n*-BuLi | 100 | 84 | 92 |
| 14[e,i] | *R*-(−) | −78 | NaH | 71 | 54 | 70 |
| 15[j] | *R*-(−) | +25 | NMM | 0 | — | — |
| 16[k] | *R*-(−) | +25 | $PdCl_2(MeCN)_2$ | 0 | — | — |
| 17[l] | *R*-(−) | +25 | $KF/Al_2O_3$ | 0 | — | — |
| 18[e] | *R*-(−) | −78 | *t*-BuOLi | 100 | 86 | 92 |
| 19 | *R*-(−) | −78 | PhMgCl | 32 | 0 | — |
| 20 | *S*-(+) | −78 | *n*-BuLi | 100 | 86 | 92 |

[a] Unless otherwise stated, stoichiometric amounts of **4**, **7**, and 18-crown-6 were allowed to react in THF for 15 min before addition of aqueous ammonium chloride and standard work up.
[b] Conversion of oxazolidinone **7**, evaluated by $^1H$ NMR spectroscopy.
[c] Based on isolated diastereomerically pure **8**.
[d] Evaluated by $^1H$ and $^{19}F$ NMR spectroscopies in the crude reaction mixture.
[e] No 18-crown-6 was used and reaction time was extended to 30 min.
[f] The reaction was carried out in DMF.
[g] Nitroalkene **4** (1.5 equiv) was used.
[h] The reaction was carried out in diethyl ether.
[i] Anion was prepared for 1 h at 50 °C.
[j] Experimental conditions are as described elsewhere.[32]
[k] Experimental conditions are as described elsewhere.[33]
[l] Experimental conditions are as described elsewhere.[34]

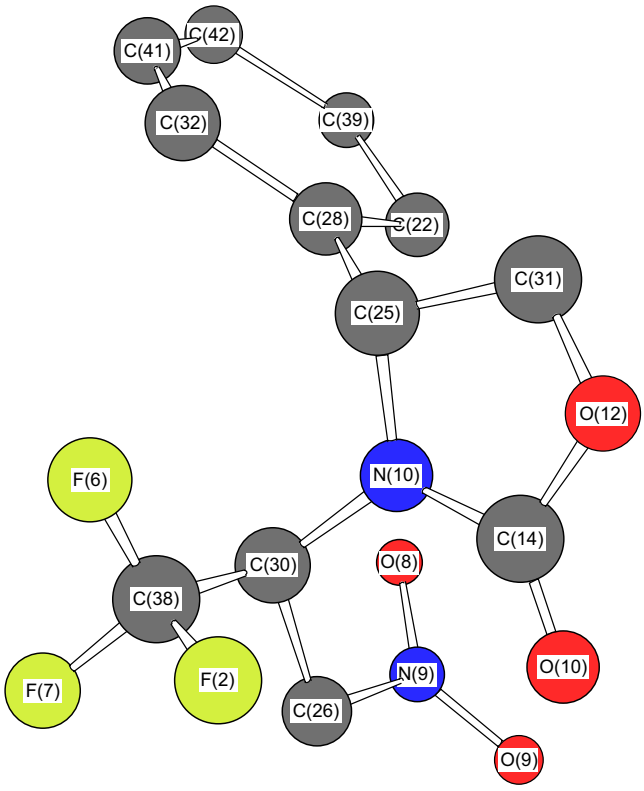



**Figure 2**. Structure of compound **8** resulting from the conjugate addition of **7**-*R*-(−) on **4** as determined by X-ray crystal analysis.

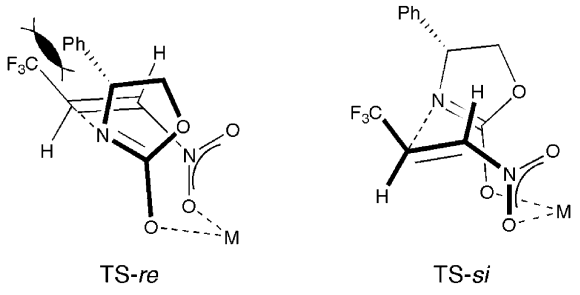
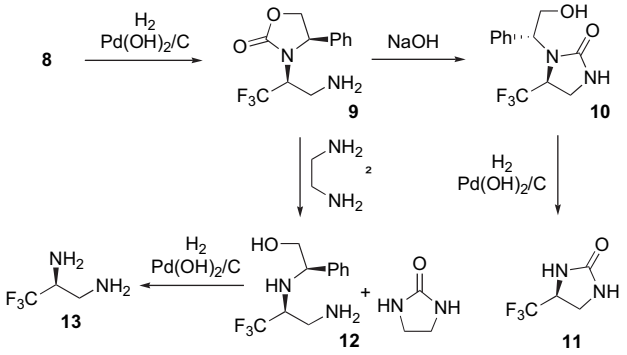



**Figure 3**.

yields medium diastereomeric excess (58% de, Entry 2), $Na^+$ and especially $Li^+$ give much better results (70% de and 92% de, respectively; Entry14 and Entries 8–11, 13, respectively). An additional experiment carried out with lithium *tert*-butoxide also gave 92% de indicating that the higher diastereoselectivity presumably results from a better fit between the geometry of the eight-membered ring transition state and the cation size (Entry 18). Diastereomeric excess obtained with potassium *tert*-butoxide is roughly the same when the reaction is carried out at +50 or −40 °C (50–52% de, Entries 4–6). A slight improvement, however, is observed at lower temperature and at −100 °C, 68% de is obtained (Entry 1). We tried to carry out the reaction at a temperature below −100 °C using a pentane/THF mixture. In that case, however, oxazolidine **7** proves only poorly soluble and does not allow synthetically useful conversion.

The transformation of **8** into 1,2-diamino-3,3,3-trifluoropropane **13** using the procedure described for non-fluorinated analogue compounds[21] revealed troublesome and inefficient (Scheme 8). Indeed catalytic reduction of the nitro group in **8** followed by a treatment of **9** with lithium in ammonia or sodium hydroxide did not afford diamine **13** as expected from results in the non-fluorinated series. Instead was obtained imidazolidone **10** that was then debenzylated to afford 4-trifluoromethyl-2-imidazolidone **11**. Further attempts to hydrolyze **11** for getting 1,2-diamino-3,3,3-trifluoropropane **13** invariably failed and complex mixtures of polar compounds were obtained that could not be separated even after treatment with acetyl chloride. To prevent the intramolecular rearrangement of aminocarbamate **9** into hydroxyurea **10**, the former was refluxed with ethylene diamine. We were then able to obtain diamine **12** nearly quantitatively together with 2-imidazolidone. Compound **12** was submitted to hydrogenolysis and optically pure *S*-(−)-1,2-diamino-3,3,3-trifluoropropane **13** was obtained. Debenzylation of **12**, however, proved difficult and despite many efforts for optimizing the experimental conditions (varying the nature and amount of catalyst used, hydrogen pressure, hydrogen source, temperature, solvent, and pH), compound **13** was never obtained in a yield better than 51%. About 40–45% of starting material was recovered unchanged and could be engaged in another hydrogenolysis cycle. Another debenzylation procedure using ammonium persulfate[35] proved inefficient to form compound **13**.




**Scheme 8**.

## 3. Conclusion

We have described the first diastereoselective synthesis of 1,2-diamino-3,3,3-trifluoropropane **13**. The title compound is prepared in four steps starting from readily available optically pure 4-phenyl-2-oxazolidinone **7** and *trans*-3,3,3-trifluoro-1-nitropropene **4**. The synthetic route is versatile and allows several intermediate function installations, especially on compounds **9** and **12**. Consequently unambiguous derivatization of one amino group or the other can be easily achieved and makes these compounds valuable intermediates for the elaboration of chiral non-racemic sophisticated fluorinated compounds.

## 4. Experimental

### 4.1. General procedure

$^1H$, $^{13}C$, and $^{19}F$ NMR chemical shifts $\delta$ are reported in parts per million relative to their standard reference ($^1H$: $CHCl_3$ at

7.27 ppm, HDO at 4.63 ppm, $CD_2HOD$ at 3.31 ppm; $^{13}C$: $CDCl_3$ at 77.0 ppm, $CD_3OD$ at 49.0 ppm; $^{19}F$: $CFCl_3$ external at 0.00 ppm). IR spectra were recorded in wave numbers ($cm^{-1}$). Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded at chemical ionization (CI) or in the electro spray (ESI) mode. Mass data are reported in mass units (*m/z*). Abbreviations: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; b, broad. *trans*-3,3,3-Trifluoro-1-nitropropene was prepared according to the literature.[36]

**4.1.1. Synthesis of (−)-3-[2-(*S*)-(1-nitro-3,3,3-trifluoropropyl)]-[4-(*R*)-phenyl]-oxazolidin-2-one 8.** A 1.6 M solution of *n*-butyllithium in hexane (370 μL, 0.61 mmol) is added dropwise to (*R*)-4-phenyloxazolidin-2-one (100 mg, 0.61 mmol) in anhydrous THF (5 mL) at −78 °C. Deprotonation is allowed to occur for 1 h before *trans*-3,3,3-trifluoro-1-nitropropene **4** (112 mg, 0.79 mmol) in THF (2 mL) is slowly added. The reaction mixture is stirred for 30 min at −78 °C, saturated aqueous $NH_4Cl$ (3 mL) is added, and the temperature is allowed to rise to room temperature. The mixture is extracted with ether. The organic layer is washed with water, brine, dried over $Na_2SO_4$, and reduced under vacuum. The crude residue is purified by chromatography over silica gel (hexane/ethyl acetate 7:3) to yield **8** (169 mg, 91%) as a white solid. TLC $R_f$ 0.5 (hexane/ethyl acetate 7:3). mp 108 °C. $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 7.57–7.31 (m, 5H); 5.49 (dd, $J$=8.6, 14.4 Hz, 1H); 4.99 (t, $J$=8.3 Hz, 1H); 4.78 (dd, $J$=4.7, 14.4 Hz, 1H); 4.73 (t, $J$=8.5 Hz, 1H); 4.40 (m, 1H); 4.29 (t, $J$=7.2 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 156.9; 135.1; 130.7; 130.1; 128.3; 124.2 (q, $J$=284.0 Hz); 71.0; 70.1; 61.8; 53.8 (q, $J$=31.9 Hz). $^{19}F$ NMR ($CDCl_3$, 188 MHz) $\delta$ −71.2. IR (KBr) $\nu$ 2924; 1766; 1567; 1416; 1378; 1252; 1184; 1138. MS (CI/$NH_3$) *m/z* 322 $[M+NH_4]^+$; 339 $[M+NH_3+NH_4]^+$; 626 $[2M+NH_4]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{11}F_3N_2NaO_4$ 327.0569, found 327.0574. $[\alpha]_D^{20}$ −61 (*c* 0.88, $CHCl_3$).

**4.1.2. Synthesis of (−)-3-[2-(*S*)-(1-amino-3,3,3-trifluoropropyl)]-[4-(*R*)-phenyl]-oxazolidin-2-one 9.** Compound **8** (570 mg, 1.88 mmol) and palladium hydroxide 20% (53 mg) in dry methanol (20 mL) are vigorously stirred under hydrogen pressure (30 bar) for 14 h at room temperature. The catalyst is removed by filtration over a Celite pad and washed with methanol. The filtrate is reduced in vacuo and the residue is dried in the presence of $P_2O_5$ to yield compound **9** (458 mg, 88%) as a colorless oil. $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.41–7.27 (m, 5H); 4.98 (dd, $J$=7.3, 8.9 Hz, 1H); 4.69 (t, $J$=8.9 Hz, 1H); 4.22 (dd, $J$=7.5, 8.7 Hz, 1H); 3.85 (m, 1H); 3.64 (s, 2H); 3.36 (dd, $J$=10.6, 13.7 Hz, 1H); 3.08 (dd, $J$=4.7, 13.4 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 158.3; 137.4; 129.4; 129.0; 127.9; 124.6 (q, $J$=283.0 Hz); 70.9; 59.9; 58.2 (q, $J$=29.3 Hz); 36.8. $^{19}F$ NMR ($CDCl_3$, 188 MHz) $\delta$ −71.3. IR (film, CsI) $\nu$ 3369; 2923; 1755; 1534; 1416; 1363; 1245; 1177; 1131. MS (CI/$NH_3$) *m/z* 275 $[M+H]^+$; 549 $[2M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{14}F_3N_2O_2$ 275.1007, found 275.1012. $[\alpha]_D^{20}$ −40 (*c* 1.25, $CHCl_3$).

**4.1.3. Synthesis of (−)-1-[2-hydroxy-1-(*R*)-phenylethyl]-5-(*S*)-trifluoromethylimidazolidin-2-one 10.** Compound **9** (400 mg, 1.46 mmol) and sodium hydroxide (400 mg, 9.76 mmol) are stirred in refluxing methanol (8 mL) for 2 h. The reaction mixture is neutralized at 0 °C with HCl 3 M and extracted with ether. The organic layer is washed with brine, dried over $MgSO_4$, and reduced in vacuo to yield imidazolidone **10** (241 mg, 60%) as a slightly yellow oil. TLC $R_f$ 0.65 (AcOEt). $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.41–7.27 (m, 5H); 6.30 (s, 1H); 4.63 (dd, $J$=3.7, 8.1 Hz, 1H); 4.27 (dd, $J$=8.1, 12.5 Hz, 1H); 4.04 (dd, $J$=3.7, 12.5 Hz, 1H); 3.92 (m, 1H); 3.60 (t, $J$=10.0 Hz, 1H); 3.50 (dd, $J$=3.7, 10.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 163.3; 137.7; 129.3; 128.6; 127.6; 125.3 (q, $J$=281.2 Hz); 64.3; 63.6; 57.3 (q, $J$=31.8 Hz); 39.4. $^{19}F$ NMR ($CDCl_3$, 188 MHz) $\delta$ −76.3. IR (film, CsI) $\nu$ 3317; 2924; 1706; 1497; 1451; 1392; 1280; 1172; 1143. MS (CI/$NH_3$) *m/z* 275 $[M+H]^+$; 292 $[M+NH_4]^+$. HRMS (ESI) *m/z* calcd for $C_{12}H_{13}F_3N_2NaO_2$ 297.0821, found 297.0836. $[\alpha]_D^{20}$ −10 (*c* 7.5, $CHCl_3$).

**4.1.4. Synthesis of (+)-4-(*S*)-trifluoromethylimidazolidin-2-one 11.** Compound **10** (100 mg, 0.36 mmol) and palladium hydroxide 20% (100 mg) in dry methanol (8 mL) are vigorously stirred under hydrogen pressure (60 bar) for 46 h at room temperature. The catalyst is removed by filtration over a Celite pad and washed with methanol. The filtrate is reduced in vacuo and the residue is purified by silica gel chromatography (AcOEt/MeOH 9:1) to yield compound **11** (11 mg, 21%) as a white powder. TLC $R_f$ 0.45 (AcOEt/MeOH 9:1). $^1H$ NMR ($CD_3OD$, 200 MHz) $\delta$ 4.40 (m, 1H); 3.79 (t, $J$=10.0 Hz, 1H); 3.55 (dd, $J$=4.6, 10.0 Hz, 1H). $^{13}C$ NMR ($CD_3OD$, 75 MHz) $\delta$ 165.8; 126.8 (q, $J$=278.0 Hz); 54.9 (q, $J$=32.6 Hz); 41.7. $^{19}F$ NMR ($CD_3OD$, 188 MHz) $\delta$ −81.8. IR (KBr) $\nu$ 3233; 1724; 1494; 1457; 1273; 1176; 1143. MS (CI/$NH_3$) *m/z* 172 $[M+NH_4]^+$; 189 $[M+NH_3+NH_4]^+$. HRMS (ESI) *m/z* calcd for $C_4H_5F_3N_2NaO$ 177.0252, found 177.0278. $[\alpha]_D^{20}$ +5 (*c* 0.83, MeOH).

**4.1.5. Synthesis of 2-(1-aminomethyl-2,2,2-trifluoroethylamino)-2-phenyl-ethanol 12.** Oxazolidinone **9** (250 mg, 0.91 mmol) is stirred in refluxing freshly distilled ethylene diamine for 18 h. Ethylene diamine is removed under vacuum and the residue is dissolved in HCl 1 M (15 mL), and washed with ether. The pH of the aqueous phase is brought to 14 with NaOH 6 M, and the solution is washed with ether. The organic phase is then washed with brine and dried over $MgSO_4$ to yield compound **12** (169 mg, 75%) as a slightly yellow oil. $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 7.37–7.33 (m, 5H); 4.10 (dd, $J$=4.2, 8.8 Hz, 1H); 3.73 (dd, $J$=4.4, 10.8 Hz, 1H); 3.63 (dd, $J$=8.6, 10.8 Hz, 1H); 2.93 (m, 1H); 2.89 (dd, $J$=4.1, 13.9 Hz, 1H); 2.72 (dd, $J$ =5.1, 13.0 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 140.1; 129.1; 128.4; 128.0; 67.8; 63.6; 57.7 (q, $J$=25.6 Hz); 41.0. $^{19}F$ NMR ($CDCl_3$, 188 MHz) $\delta$ −73.6. IR (film, CsI) $\nu$ 3344; 2926; 1670; 1602; 1454; 1358; 1264; 1134; 1071. MS (CI/$NH_3$) *m/z* 249 $[M+H]^+$. HRMS (ESI) *m/z* calcd for $C_{11}H_{16}F_3N_2O$ 249.1209, found 249.215. $[\alpha]_D^{20}$ −20 (*c* 0.50, $CHCl_3$).

**4.1.6. Synthesis of (+)-2-(*S*)-1,2-diamino-3,3,3-trifluoropropane 13.** Compound **12** (1.20 g, 4.83 mmol) and palladium hydroxide 20% (0.60 g) in THF/methanol 1:1 (80 mL) are vigorously stirred under hydrogen pressure (60 bar) for 48 h at room temperature. The catalyst is removed by filtration over a Celite pad and washed with methanol. The filtrate is reduced in vacuo and the residue is purified by column chromatography ($CHCl_3$/MeOH/concd $NH_4OH$ 12:4:1) to yield residual starting material (504 mg)

and compound **13** (316 mg, 88% based on recovered starting material) as a brown liquid. TLC $R_f$ 0.6 ($CHCl_3$/MeOH/concd $NH_4OH$ 12:4:1). $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 3.39 (m, 1H); 3.16 (dd, $J$=3.7, 12.8 Hz, 1H); 2.83 (dd, $J$=9.5, 12.9 Hz, 1H). $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 126.3 (q, $J$=280.0 Hz); 54.8 (q, $J$=28.6 Hz); 40.6. $^{19}F$ NMR ($CDCl_3$, 188 MHz) $\delta$ −78.3. IR (film, CsI) $\nu$ 3373; 1558; 1411; 1269; 1161; 1016. MS (CI/$NH_3$) $m/z$ 129 $[M+H]^+$; 146 $[M+NH_4]^+$. HRMS (ESI) $m/z$ calcd for $C_3H_8F_3N_2$ 129.0640, found 129.0640. $[\alpha]_D^{20}$ +4 ($c$ 6.00, $CDCl_3$).

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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.2006.06.013.

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# Synthetic utility of glycosyl triazoles in carbohydrate chemistry

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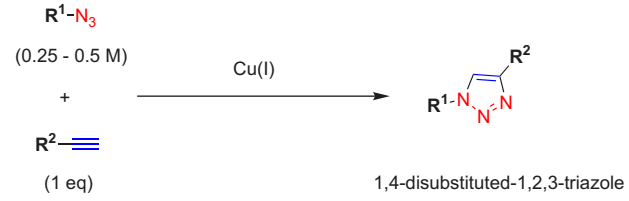
**Abstract**—We report herein a study of the synthetic utility of the glucosyl triazole moiety in carbohydrate chemistry. A model glucosyl triazole was prepared by a modified Huisgen 1,3-dipolar cycloaddition reaction. The relative rate of cycloaddition was investigated using a variety of alcohol co-solvents and reaction temperatures. It was found that the reaction proceeded with similar efficiency irrespective of co-solvent, however mildly elevated temperatures (40 °C cf. rt) increased the speed of reaction significantly (2 h cf. 8 h). The robustness of the triazole moiety was then interrogated under conditions typically encountered in carbohydrate chemistry reaction sequences—alcohol group protection/deprotection, nucleophilic displacement, and *O*-glycosylation. The triazole integrity was retained in all cases studied as evidenced from full compound characterization. Finally, a diverse set of triazole-linked glycoconjugates was synthesized. Collectively, our results demonstrated that the glucosyl triazole moiety was indeed a robust entity for carbohydrate chemistry.


## 1. Introduction

Oligosaccharides linked to proteins and lipids via *N*- or *O*-glycosidic linkages (glycoconjugates) have been shown to govern crucial life processes and disease states.[1–7] Glycosylation patterns for proteins and lipids are exquisitely controlled via mechanisms independent from that of the genomic transcription and as a result glycoconjugates from natural sources often exist as heterogeneous isoforms (glycoforms). The isolation of homogeneous material from crude biological extracts in sufficient quantities for study can, therefore, be difficult. Medicinal chemistry, through provision of an impressive array of synthetic methodologies, offers a potentially more reliable route to homogeneous glycoconjugates leading to either exact copies of naturally occurring glycoconjugates or, alternatively, incorporating unnatural glycosidic linkages. An appreciable benefit of the latter approach is that the 'artificial' glycoconjugate may retain the geometric and spatial characteristics of the native glycoform[8,9] yet exhibit stability toward *N*- and *O*-glycosyl hydrolase activity and inhibit these enzymes to some extent,[10] so increasing the potential for a wide array of in vivo applications. In addition, the artificial linkage may be fine tuned as an inert functionality toward subsequent synthetic transformations necessary elsewhere within the target molecule synthesis.

In the past three years, there has been a flourish of activity in the literature concerning the 1,3-dipolar cycloaddition reaction (1,3-DCR) of organic azides with terminal acetylenes (Huisgen reaction).[11] This interest stems largely from the optimization of 1,3-DCR by Sharpless[12] and Meldal[13] with respect to ease and efficiency of catalysis and regioselectivity of the triazole product. The reaction involves a step-wise Cu(I)-catalyzed dipolar cycloaddition of a terminal acetylene to an organic azide to form, exclusively, the 1,4-disubstituted-1,2,3-triazole (Scheme 1).[12,13] The highly exothermic and kinetically controlled reaction is conducted favorably in water and is also tolerant to a wide variety of organic co-solvents and as such has become a premier component of 'click chemistry'.[12b]




**Scheme 1**. Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of azides and terminal alkynes.

The modified 1,3-DCR has shown great versatility and utility on non-saccharide substrates in medicinal chemistry, chemical biology, and materials science.[14,15] The application to 'traditional' carbohydrate chemistry[16] has been somewhat slower, but presents as an attractive reaction for several reasons. Glycosyl azides are generally stable crystalline solids, inert toward a wide range of reaction conditions and are available diastereomerically pure.[17] In traditional

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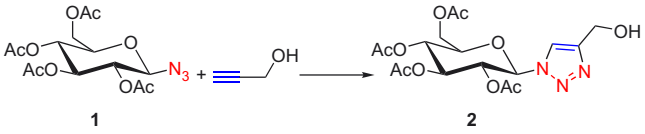
carbohydrate synthesis they serve primarily as stable precursors of glycosylamines (for glycopeptide synthesis) and are also less commonly precursors to glycosylfluoride donors.[18] Glycosyl azides are readily synthesized through the stereoselective bimolecular displacement of a glycosyl halide with an azide nucleophile[17] and 2-azido sugars are obtained through the triflyl azide-mediated diazotransfer of amino sugars.[19] Preparation of carbohydrates containing a terminal acetylene moiety is also readily achieved either by the alkylation of carbohydrates (to synthesize propargyl ethers) or Lewis-acid-catalyzed glycosylation (to synthesize *O*-propargyl glycosides).[20] The 1,3-DCR utilizes low cost and relative non-toxic reagents and solvents so alleviating the need to use often expensive and highly toxic glycosylation and peptide coupling reagents, the risk and costs of which are acute on bulk scales. Finally, product purification is simple; in many cases, chromatography is not necessary with either precipitation[21] or liquid–liquid extraction sufficient to obtain pure product.

The incorporation of an azide and/or an alkyne moiety on a carbohydrate scaffold unleashes the potential to access a new dimension of structural diversity to complement the vast structural diversity already inherent to carbohydrates and so it is anticipated that interest in the 1,3-DCR with carbohydrate substrates will grow. A detailed synthetic analysis concerning the utility of this reaction and the stability of the formed glycosyl triazole linkage toward typical carbohydrate reaction sequences would be beneficial to assess the viability of the glycosyl triazole linker as a tool for carbohydrate chemistry, and was the inspiration for the study described herein. Specifically, we report (i) an investigation of the rate of formation of the glycosyl triazole linkage with variable solvent and temperature parameters, (ii) the stability of this linkage toward conditions commonly used in carbohydrate reaction sequences, including hydroxyl group protection/deprotection, *O*-glycosylations, and nucleophilic displacement, (iii) an examination of the retention of anomeric stereochemistry and the rates of triazole formation with respect to the glycosyl azide precursor configuration (α/β), and (iv) the versatility of the 1,3-DCR of various sugar azides with a diverse array of acetylene partners.

## 2. Results and discussion

The model glycosyl triazole employed to investigate the study of rate of triazole formation was the glucosyl triazole compound **2**.[16f] Compound **2** was prepared by 1,3-DCR of propargyl alcohol with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**1**) using a procedure adapted from the literature.[12,13] Reaction of propargyl alcohol with the azide partner **1** in the presence of a $CuSO_4$/ascorbate mixture in aqueous alcohol, affords exclusively the 1,4-disubstituted β-D-glucosyl triazole **2** with complete retention of anomeric stereochemistry and in high yield. This configuration has been confirmed by X-ray crystallography.[22] The effect of alcohol co-solvents methanol, ethanol, isopropanol, *tert*-butanol, and propargyl alcohol on reaction completion time is presented in Table 1. Irrespective of the co-solvent employed, the reaction to form **2** was complete within 2 h (as evidenced by TLC) when the reaction was carried out at a slightly elevated temperature (40 °C) (Table 1, entries 1–5).

**Table 1**. Study of formation of glycosyl triazole **2**[a]

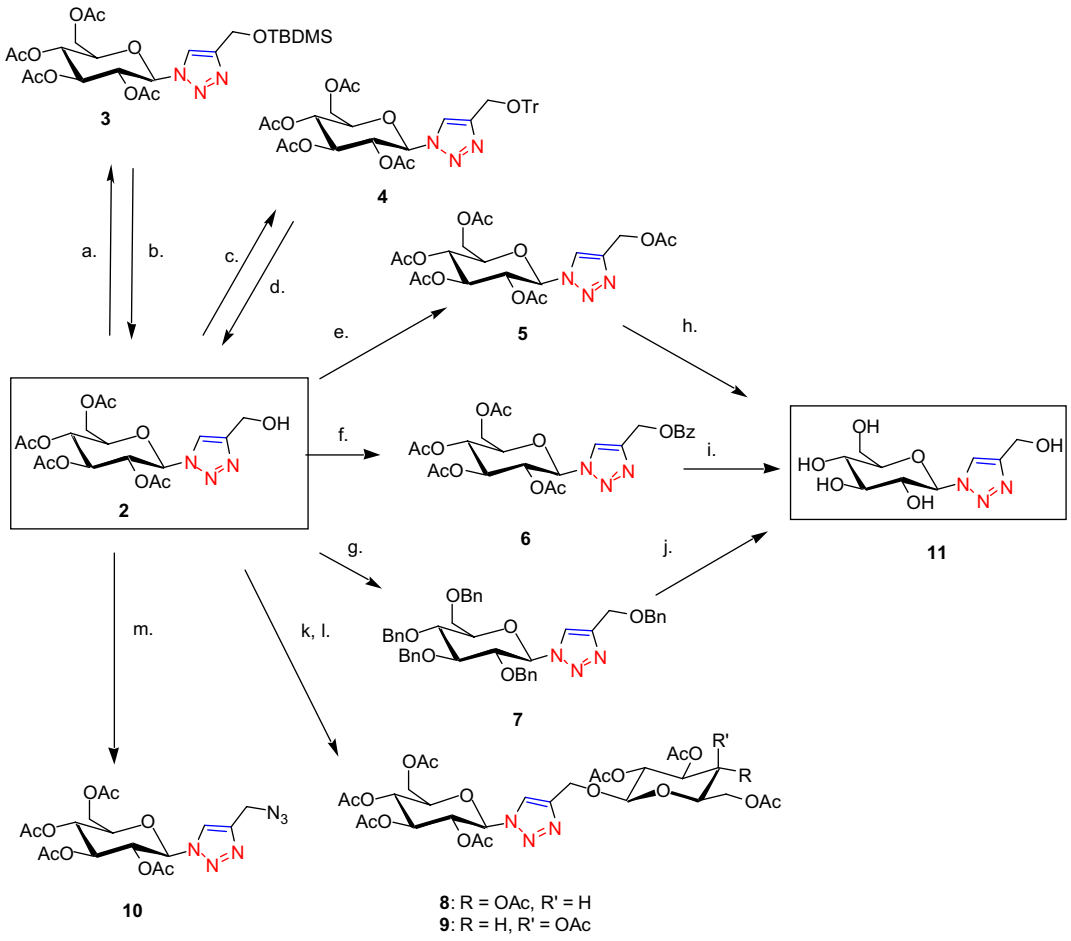



| Entry | Co-solvent | Temp (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Methanol | 40 | 2 | 79 |
| 2 | Ethanol | 40 | 2 | 88 |
| 3 | Isopropanol | 40 | 2 | 91 |
| 4 | *tert*-Butanol | 40 | 2 | 92 |
| 5 | Propargyl alcohol | 40 | 2 | 85 |
| 6 | *tert*-Butanol | 25 | 8 | 90 |

[a] All reactions were carried out using **1** (0.5 M), propargyl alcohol (0.5 M), 20 mol % $CuSO_4$, 40 mol % sodium ascorbate (relative to substrate) in 1:1 water/alcohol (with the exception of entry 5).
[b] Yield calculated following liquid–liquid extraction into $CH_2Cl_2$.

Noteworthy is that when the coupling partner propargyl alcohol was employed also as bulk co-solvent this did not substantially increase the rate of reaction. An increased reaction time (8 h) was necessary to afford complete conversion when the reaction was conducted at room temperature (Table 1, compare entries 4 and 6), although the yields were similar (90 cf. 92%). The reactants were initially insoluble in all solvent media, but as the reaction progressed, a deep yellow, homogeneous mixture was observed. In all cases, the yield (following liquid–liquid extraction into $CH_2Cl_2$) was high and exhibited minimal variability (79–92%). This simple work up provided material sufficiently pure for most ensuing synthetic purposes, however a final solid-phase extraction (SPE) purification step was employed to remove trace paramagnetic Cu(II) salts for the purpose of NMR analysis and the provision of analytically pure material. Reaction conditions were simple, requiring only vigorous stirring at the designated temperature within capped scintillation vials under air.

Next, the stability of the glycosyl triazole linkage toward commonly used carbohydrate chemistry reaction conditions was investigated (Scheme 2). Silyl, trityl, acetyl, benzoyl, and benzyl alcohol protecting groups were all incorporated smoothly on to the alcohol moiety of **2** to generate compounds **3**–**7**, respectively, with the triazole linkage remaining intact. Reaction conditions to remove these protecting groups were also compatible with the triazole linkage, either regenerating **2** or the globally deprotected analogue **11**. Protection and deprotection yields were excellent with no baseline decomposition observed by TLC. Interestingly, the hydrogenation of the benzylated compound **7** was sluggish using typical conditions ($H_2$, 5% Pd/C), necessitating basic hydrogenation conditions (i.e., $H_2$, 30% $Pd(OH_2)$/C). Removal of the benzyl ether in the 2-position of the sugar was potentially problematic, quite possibly due to steric hindrance imposed by the glucosyl triazole. Despite this, the free glucosyl triazole **11** was recovered in good yield (78%) after 24 h. Glycosylation of the triazole acceptor **2** using either typical Lewis acid catalysis ($BF_3 \cdot Et_2O$) or Koenigs–Knorr conditions (AgOTf) successfully generated **8** and **9**, respectively, although yields were not high (53% and 41%, respectively). This was possibly due to the weak glycosyl acceptor nature of the triazole alcohol. Alternatively, the triazole may interfere with activation of the glycosyl donor through interaction with the Lewis



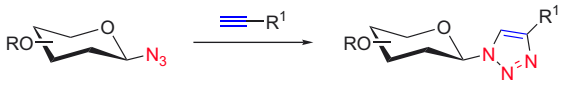

**Scheme 2**. Protecting group and glycosylation chemistry on model glucosyl triazole **2**. Conditions: (a) TBDMSCl, imidazole, DCM, rt, 1 h, 88%; (b) TBAF, THF, rt, 15 min, 82%; (c) TrCl, pyridine, 40 °C, o/n, 90%; (d) camphor sulfonic acid, DCM, rt, 4 h, 85%; (e) $Ac_2O$/pyridine, rt, 2 h, 90%; (f) BzCl, $Et_3N$, DCM, o/n, 82%; (g) (i) $NaOCH_3$, $CH_3OH$, rt, 2 h; then (ii) NaH, BnBr, DMF, rt, o/n, 68%; (h) $NaOCH_3$, $CH_3OH$, rt, 30 min, 90%; (i) $NaOCH_3$, $CH_3OH$, rt, 12 h, 92%; (j) $H_2$, 30% $Pd(OH)_2$/C, $CH_3OH$/DCM, rt, 24 h, 78%; (k) 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1.0 equiv), AgOTf, DCM, 52% of **8**; (l) β-D-galactose pentaacetate (1.0 equiv), $BF_3{\cdot}Et_2O$, DCM, rt, o/n, 43% of **9**; (m) (i) MsCl, $Et_3N$, DCM, rt, 30 min; then (ii) $NaN_3$, DMF, o/n, rt, 53%.

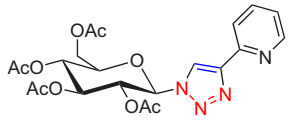
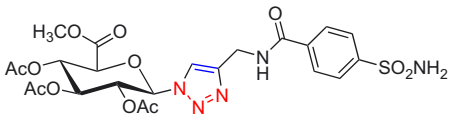
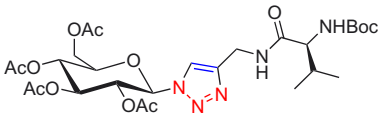
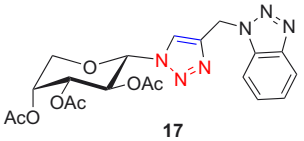
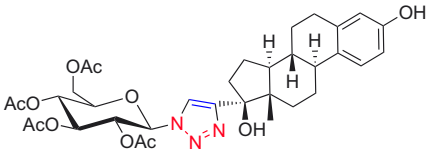
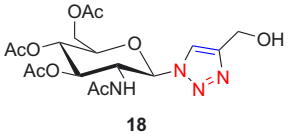
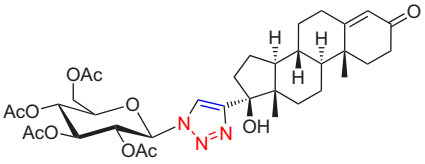
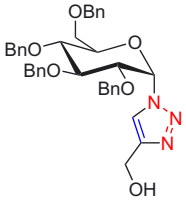
acid; nonetheless, this provides rapid entry into disaccharide mimics. Finally, the azide displacement of the crude mesylated intermediate from **2** to form triazole azide **10** provides a system for carrying out iterative click reactions.

Having established some of the chemical modifications available, we set out to synthesize a variety of glycoconjugates with diversity in both the carbohydrate and aglycone moieties. Derivatives of hydrophobic bioactive compounds and synthetic precursors to more complex glycoconjugates were sought as part of our general focus on carbohydrate-based therapeutics. Table 2 shows compounds synthesized from our model glucosyl azide **1** (compounds **12**–**15**), methyl 2,3,4-tri-*O*-acetyl-1-azido-1-deoxy-β-D-glucopyranuronate[23] (compound **16**), 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl azide (compound **17**), 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl azide (compound **18**[16f]), and 2,3,4,6-tetra-*O*-benzyl-α-D-glucosyl azide (compound **19**). Minimal or no chromatography was required in all cases to obtain samples of sufficient purity for further synthetic transformation. Reaction rates and yields varied somewhat depending on the acetylene dipolarophilicity and solubility. While the reaction is reported as reasonably insensitive to substrate solubility, more hydrophobic substrates generally took longer to react, as is shown for the steroidal glucosyl triazole **15**. Interestingly, while the reaction for **15** took 20 h to reach completion, the estradiol analogue **14** required only 30 min for completion under identical reaction conditions. Furthermore, both compounds were isolated by precipitation from cold water, although a final chromatographic purification step was required for these two compounds in order to remove traces of starting materials and Cu salts.

Our attention then shifted to examining the rate dependence on anomeric configuration and the nature of the saccharide protecting groups. The reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucosyl azide to α-glucosyl triazole **19** proceeded with complete α-retention of anomeric stereochemistry. The reaction was slow, requiring a total of ca. 48 h at 60 °C to reach completion. Doubling of the Cu(II) and ascorbate catalyst load (i.e., 0.4 equiv Cu(II), 0.8 equiv ascorbate) was also required since gradual oxidation of the Cu(I)-complex intermediate was observed using standard conditions and no conversion was observed after 8 h by either TLC or ESI-MS. The sluggish nature of this reaction was rationalized as resulting from increased steric bulk surrounding the anomeric center upon transformation from the linear azide to the triazole, increased hydrophobicity imparted by the benzyl groups, and stabilization of the azide dipole by the anomeric effect.

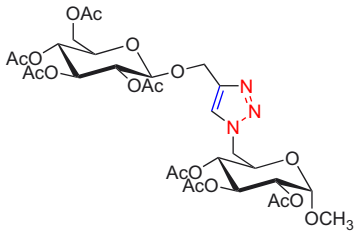
**Table 2**. Examples of glycosyl triazoles



| Compound[a] | Time (yield)[b] | Compound[a] | Time (yield)[b] |
|---|---|---|---|
|  **12** | 30 min (92%) |  **16** | 30 min (85%)[c] |
|  **13** | 20 min (77%) |  **17** | 10 min (94%) |
|  **14** | 30 min (71%) |  **18** | 3 h (62%) |
|  **15** | 20 h (64%) |  **19** | 48 h (73%) |

[a] General reaction conditions: azide (0.5 M), acetylene (0.5 M), $CuSO_4 \cdot 5H_2O$ (0.2 equiv), sodium ascorbate (0.4 equiv), 1:1 *t*-BuOH/$H_2O$, 40 °C, with the exception of **19**, which used acetylene (4.2 equiv), $CuSO_4 \cdot 5H_2O$ (0.4 equiv), sodium ascorbate (0.8 equiv) at 60 °C.
[b] Standard purification as described in Section 4.
[c] Molar yield calculated after precipitation and filtration.

The scope of the reaction can be expanded further by installing the azide/acetylene functionality into other positions on the carbohydrate ring and/or on to different carbohydrate partners to serve as a convenient and direct route to triazole-tethered disaccharide mimics. The triazole-tethered disaccharide **20** was formed in 78% yield from the 1,3-DCR of a 6-azido glucose analogue and a glucose-derived propargyl ether. This yield is an improvement over the glycosylations on **2** to synthesize the structurally related triazole-tethered disaccharides **8** (52%) and **9** (43%). 1,3-DCR can therefore serve as a useful means of rapidly generating artificial cyclodextrins,[24] glycodendrimers,[25] and glycopolymers[26] under kinetically controlled conditions.



**20**

## 3. Conclusions

The facile Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction has emerged of late as a potent tool in accessing diverse molecular architectures. Its versatility and potential is now starting to be realized in glycochemistry, providing expedient access to an interesting and relatively new family of pharmacologically relevant heterocyclic carbohydrates. Owing to the inherent complex nature of carbohydrate chemistry, especially concerning anomeric stereochemistry and stability, the reaction has not been sufficiently scrutinized as a viable alternative or addition to classical methods. We have successfully explored the utility of the reaction by examining the compatibility and tolerance of the conditions to pre-installed saccharide protecting groups, but also the stability of the installed triazole linkage under protection/deprotection sequences and glycosylations. The reaction is forgiving, mild, high yielding, simple to purify, and stereo- and regiospecific. Owing to such impressive versatility, we envisage the reaction to be useful addition to the arsenal of traditional solution-based reactions within carbohydrate chemistry. Further exploration of the scope of this chemistry will also include modification of other

hydrophobic drug molecules to improve their water solubility.[27] Furthermore, due to the inherent robustness of the glycosyl triazole linkage, it is reasonable to expect the reaction to be compatible with existing solution- and solid-phase, convergent (block) and linear glycoprotein/peptide strategies. Finally, recent regioselective access to the 1,5-disubstituted triazole from azide and alkyne precursors will expand the structural diversity available from the chemistry presented here.[28]

## 4. Experimental

### 4.1. General

Glycosyl azide precursors were prepared by phase transfer nucleophilic displacement of corresponding peracetylated α-glycosylbromide.[17] All reagents were purchased from commercial sources and were used without further purification. All solvents were available commercially dried or freshly dried and distilled prior to use. $^1$H NMR (400 MHz), $^{13}$C NMR (100 MHz), 2D gCOSY, and gHSQC spectra were recorded on a 400 MHz spectrometer with chemical shift values given in parts per million ($\delta$) relative to TMS (0.00 ppm) using $CDCl_3$ solvent unless otherwise stated. Melting points are reported as uncorrected. High resolution electrospray ionization mass spectra (HRESIMS) were recorded on a 4.7T Fourier transform mass spectrometer in positive ion mode unless otherwise stated. Reaction progress was monitored by TLC using Silica gel-60 $F_{254}$ plates with detection by short wave UV fluorescence ($\lambda$=254 nm) and staining with 10% (v/v) $H_2SO_4$ in ethanol char. Flash chromatography was conducted using flash silica gel (60–240 mesh). Solid-phase extraction (SPE) was conducted using cartridges prepacked with silica sorbent.

**4.1.1. 4-Hydroxymethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (2).** To a vigorously stirring suspension of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (2.0 g, 5.35 mmol) in *tert*-butyl alcohol (11 mL) was added propargyl alcohol (1.3 mL, 22.43 mmol, 4.2 equiv). The reaction was initiated by the addition of a solution of $CuSO_4\cdot 5H_2O$ (270 mg, 1.08 mmol, 0.2 equiv) and sodium ascorbate (424.5 mg, 2.14 mmol, 0.4 equiv) in distilled $H_2O$ (11 mL). The deep yellow suspension was stirred vigorously at 40 °C for 2 h. At this time, TLC indicated reaction completion (1:1 ethyl acetate/hexanes). Distilled $H_2O$ (20 mL) was added and the aqueous layer extracted twice with $CH_2Cl_2$ (2×50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford a crude yellow solid residue, which was recrystallized from hot absolute ethanol to afford triazole **1** as off-white crystalline solid (2.1 g, 92%). Mp: 150–151 °C (lit. mp: 148–150 °C as a mixture of 4- and 5-hydroxymethyl regioisomers[16f]). $R_f$=0.22 (8:2 ethyl acetate/hexanes). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.87 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.06 (s, 3H, OAc), 3.99 (ddd, $^3J_{5-4}$=10.2 Hz, $^3J_{5-6'}$=5.2 Hz, $^3J_{5-6}$=2.4 Hz, 1H, H-5′), 4.13 (dd, $^2J_{6-6'}$= 12.4 Hz, $^3J_{6-5}$=2.4 Hz, 1H, H-6′), 4.28 (dd, $^2J_{6'-6}$= 12.4 Hz, $^3J_{6'-5}$=5.2 Hz, 1H, H-6″), 4.79 (s, 2H, C$H_2$OH), 5.20–5.25 (m, 1H, H-4′), 5.38–5.45 (m, 2H, H-3′/H-2′), 5.86–5.88 (m, 1H, H-1′), 7.78 (s, 1H, triazole H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.4 (OAc), 20.7 (OAc), 20.75 (OAc), 20.9 (OAc), 56.6 (*C*$H_2$OH), 61.8 (C-6), 67.9 (C-2), 70.6 (C-3), 72.9 (C-4), 75.3 (C-5), 86.1 (C-1), 120.9 (triazole CH), 148.5 (triazole C), 169.3 (OAc), 169.6 (OAc), 170.2 (OAc), 170.7 (OAc). HRESIMS calcd for $C_{17}H_{23}N_3O_{10}Na^+$: 452.127565. Found: 452.126953. Anal. Calcd for $C_{17}H_{23}N_3O_{10}$: C, 47.55; H, 5.40; N, 9.79. Found: C, 47.33; H, 5.39; N, 9.51.

**4.1.2. 4-*tert*-Butyldimethylsilyloxymethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (3).** A solution of alcohol **2** (200 mg, 0.47 mmol) and imidazole (95 mg, 1.40 mmol, 3 equiv) was prepared in dry $CH_2Cl_2$ (5 mL) under nitrogen and *tert*-butyldimethylsilyl chloride (85 mg, 0.56 mmol, 1.2 equiv) was added in a single portion. The solution was stirred at rt under nitrogen for 2 h at which time, TLC indicated reaction completion (8:2 ethyl acetate/hexanes). $CH_2Cl_2$ (5 mL) was then added and the solution was washed with 1 N HCl (5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to a crude oil, which was purified by flash silica chromatography (4:6 ethyl acetate/hexanes) to afford a white solid (225 mg, 0.41 mmol, 88%). Mp: 100–101 °C. $R_f$=0.74 (8:2 ethyl acetate/hexanes). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.08 (s, 6H, 2×Si$CH_3$), 0.90 (s, 9H, *t*-Bu), 1.85 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.06 (s, 3H, OAc), 3.98 (ddd, $^3J_{5-4}$=10.4 Hz, $^3J_{5-6'}$=5.2 Hz, $^3J_{5-6}$=2.4 Hz, 1H, H-5′), 4.14 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6-5}$=2.4 Hz, 1H, H-6′), 4.23 (dd, $^2J_{6'-6}$=12.8 Hz, $^3J_{6'-5}$=5.2 Hz, 1H, H-6″), 4.82 (s, 2H, C$H_2$OSi), 5.21–5.26 (m, 1H, H-4′), 5.37–5.41 (m, 1H, H-3′), 5.44–5.48 (m, 1H, H-2′), 5.85 (d, $^3J_{1-2}$=9.2 Hz, 1H, H-1′), 7.67 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ −5.2 (Si$CH_3$), −5.1 (Si$CH_3$), 18.5 (TBDMS quart C), 20.4 (OAc), 20.71 (OAc), 20.74 (OAc), 20.9 (OAc), 26.1 (*t*-Bu), 57.9 (*C*$H_2$OTBDMS), 61.8 (C-6), 67.9 (C-4), 70.4 (C-3), 73.0 (C-2), 75.3 (C-5), 85.8 (C-1), 120.1 (triazole CH), 149.6 (triazole C), 169.1 (OAc), 169.6 (OAc), 170.1 (OAc), 170.7 (OAc). HRESIMS calcd for $C_{23}H_{37}N_3O_{10}SiNa^+$: 566.214042. Found: 566.215711. Anal. Calcd for $C_{23}H_{37}N_3O_{10}Si$: C, 50.81; H, 6.86; N, 7.73. Found: C, 50.89; H, 7.07; N, 7.61.

**4.1.3. Deprotection of silyl ether 3→2.** A portion of silyl ether **3** (25 mg, 0.05 mmol) was then dissolved in dry THF (1.0 mL) and a 1.0 M solution of tetrabutylammonium fluoride (500 μL, 0.5 mmol, 10 equiv) was added. The solution was stirred for 15 min at rt when found complete by TLC (8:2 ethyl acetate/hexanes). Evaporation and purification by flash silica chromatography (8:2 ethyl acetate/hexanes) afforded alcohol **2** as white solid (13 mg, 61%).

**4.1.4. 4-Trityloxymethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (4).** To a solution of alcohol **2** (200 mg, 0.47 mmol) and dry pyridine (5 mL) was added trityl chloride (230 mg, 0.84 mmol, 1.8 equiv). The solution was warmed to 40 °C and stirred for 24 h. The solvent was evaporated under reduced pressure and the remaining crude yellow solid was purified by flash silica chromatography (1:9 ethyl acetate/petroleum ether) to afford a crude white solid. A final recrystallization from hot absolute ethanol to remove trace trityl alcohol afforded a white crystalline solid (283 mg, 90%). Mp: 192–193 °C. $R_f$=0.63 (7:3 ethyl acetate/hexanes). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.87 (s, 3H,

OAc $CH_3$), 2.02 (s, 3H, OAc $CH_3$), 2.06 (s, 3H, OAc $CH_3$), 2.09 (s, 3H, OAc $CH_3$), 4.00 (ddd, $^3J_{5-4}$=10 Hz, $^3J_{5-6'}$=4.8 Hz, $^3J_{5-6}$=2 Hz, 1H, H-5′), 4.16 (dd, $^2J_{6-6'}$= 12.8 Hz, $^3J_{6-5}$=2.4 Hz, 1H, H-6′), 4.28 (s, 2H, C$H_2$OTr), 4.31 (dd, $^2J_{6'-6}$=12.8 Hz, $^3J_{6'-5}$=5.2 Hz, 1H, H-6″), 5.23–5.28 (m, 1H, H-4′), 5.39–5.44 (m, 1H, H-3′), 5.47–5.51 (m, 1H, H-2′), 5.87 (d, $^3J_{1-2}$=9.6 Hz, 1H, H-1′), 7.22–7.32 (m, 10H, Ar H), 7.46–7.49 (m, 5H, Ar H), 7.75 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.4 (OAc), 20.76 (OAc), 20.77 (OAc), 20.9 (OAc), 58.8 (C-5), 61.8 (C-6), 68.0 (C-4), 70.4 (C-2), 73.0 (C-3), 75.4 (*C*$H_2$OTr), 85.9 (C-1), 87.6 (C$Ph_3$), 120.5 (triazole CH), 127.4 (Ar CH), 128.2 (Ar CH), 128.9 (Ar CH), 143.8 (triazole C), 147.1 (Ar C), 169.1 (OAc), 169.6 (OAc), 170.2 (OAc), 170.7 (OAc). HRESIMS calcd for $C_{36}H_{37}N_3O_{10}Na^+$: 694.237116. Found 694.237058. Anal. Calcd for $C_{36}H_{37}N_3O_{10}$: C, 64.37; H, 5.55; N, 6.26; O, 23.82. Found: C, 64.12; H, 5.38; N, 6.35.

**4.1.5. Deprotection of trityl ether 4→2.** A portion of trityl ether **4** (42 mg, 0.06 mmol) was dissolved in 1:1 $CH_2Cl_2$/methanol (3 mL). A catalytic amount of camphor sulfonic acid was then added and the solution was stirred vigorously at 40 °C for 1 h, at which time TLC indicated reaction completion (7:3 ethyl acetate/hexanes). The solution was neutralized by the addition of $Et_3N$ (10 μL, 0.07 mmol) and extracted twice with $CH_2Cl_2$ (2×2 mL). The combined organic extracts were washed with distilled $H_2O$ (4 mL) and the organic layer was dried ($MgSO_4$), filtered, and evaporated. The resulting crude residue was purified by gradient flash silica chromatography (2:8 ethyl acetate/hexanes to neat ethyl acetate gradient) to afford alcohol **2** as white solid (25 mg, 95%).

**4.1.6. 4-Acetoxymethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (5).** Alcohol **2** (200 mg, 0.47 mmol) was dissolved in dry pyridine (2 mL) and acetic anhydride (1 mL) and a catalytic amount of DMAP was added. The solution was stirred at rt for 1 h when TLC indicated reaction completion (1:1 ethyl acetate/hexanes). Removal of the solvent under reduced pressure afforded a crude off-white solid, which was recrystallized from hot absolute ethanol to afford peracetate **5** as an off-white amorphous solid (185 mg, 84%). Mp: 143–144 °C. $R_f$=0.48 (7:3 ethyl acetate/hexanes). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.86 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.08 (s, 3H, OAc), 3.98 (ddd, $^3J_{5-4}$=10.0 Hz, $^3J_{5-6}$=4.8 Hz, $^3J_{5-6'}$=2 Hz, 1H, H-5′), 4.14 (dd, $^2J_{6'-6}$= 12.8 Hz, $^3J_{6'-5}$=2 Hz, 1H, H-6″), 4.29 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6-5}$=5.2 Hz, 1H, H-6′), 5.20 (s, 2H, C$H_2$OAc), 5.21–5.24 (m, 1H, H-4′), 5.39–5.41 (m, 2H, H-2′, H-3′), 5.84–5.86 (m, 1H, H-1′), 7.82 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.3 (OAc), 20.69 (OAc), 20.72 (OAc), 20.9 (OAc), 21.0 (OAc), 57.6 (C-5), 61.7 (C-6), 67.9 (C-4), 70.5 (*C*$H_2$OAc), 72.8 (C-3), 75.4 (C-2), 86.0 (C-1), 122.3 (triazole CH), 143.9 (triazole C), 169.1 (OAc), 169.5 (OAc), 170.1 (OAc), 170.7 (OAc), 171.0 (OAc). HRESIMS calcd for $C_{19}H_{25}N_3O_{11}Na^+$: 494.13810. Found: 494.137458. Anal. Calcd for $C_{19}H_{25}N_3O_{11}$: C, 54.03; H, 5.10; N, 7.88. Found: C, 53.91; H, 5.12; N, 7.74.

**4.1.7. Deprotection of peracetate 5→11.** A portion of the peracetate (100 mg) was suspended in dry methanol (3 mL) and a 1.0 M solution of sodium methoxide in dry methanol (30 μL, 0.03 mmol) was added. The resulting pale yellow solution was stirred at rt for 15 min before reaction completion. The solution was neutralized by the addition of dry Amberlite IR-120 acidic ion-exchange resin, filtered, and evaporated to dryness under reduced pressure to afford pentol **11** as white solid (53 mg, 96%). See compound **11** for analytical details.

**4.1.8. 4-Benzyloxymethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (6).** To a solution of alcohol **2** (200 mg, 0.47 mmol) in dry $CH_2Cl_2$ (5 ml) and $Et_3N$ (195 μL, 1.41 mmol, 3 equiv) was added benzoyl chloride (52 μL, 0.71 mmol, 1.5 equiv) dropwise. The reaction stirred at rt for 2 h when found complete by TLC. $CH_2Cl_2$ (5 mL) was then added and the organic layer washed consecutively with 1 N HCl (2×5 mL), saturated $NaHCO_3$ (2×5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford crude off-white solid, which was recrystallized from hot absolute ethanol to afford benzoyl ester **5** as an off-white, amorphous solid (220 mg, 88%). Mp: 180–181 °C. $R_f$=0.53 (7:3 ethyl acetate/hexanes). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.82 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.06 (s, 3H, OAc), 3.99 (ddd, $^3J_{5-4}$,=10.2 Hz, $^3J_{5-6}$=5.2 Hz, $^3J_{5-6'}$= 2 Hz, 1H, H-5′), 4.13 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6'-5}$=2.0 Hz, 1H, H-6″), 4.28 (dd, $^2$H$_{6-6'}$=12.8 Hz, $^3J_{6-5}$=4.8 Hz, 1H, H-6′), 5.20–5.25 (m, 1H, H-4′), 5.37–5.41 (m, 1H, H-3′), 5.41–5.50 (m, 3H, H-2′, C$H_2$OBz), 5.87 (d, $^3J_{1-2}$=9.2 Hz, 1H, H-1′), 7.39 (m, 2H, Ar H), 7.52 (m, 1H, Ar H), 7.91 (s, 1H, triazole H), 8.02–8.04 (m, 2H, Ar H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.3 (OAc), 20.70 (OAc), 20.73 (OAc), 20.9 (OAc), 58.1 (C-5), 61.7 (C-6), 67.9 (C-4), 70.5 (*C*$H_2$OBz), 72.8 (C-3), 75.4 (C-2), 86.0 (C-1), 122.6 (triazole CH), 128.6 (Ar CH), 129.9 (Ar CH), 130.0 (Ar CH), 133.5 (Ar C), 143.9 (triazole C), 166.5 (OBz C=O), 169.0 (OAc C=O), 169.5 (OAc C=O), 170.1 (OAc C=O), 170.7 (OAc C=O). HRESIMS calcd for $C_{24}H_{27}N_3O_{11}Na^+$: 556.15378. Found: 556.153103. Anal. Calcd for $C_{24}H_{27}N_3O_{11}$: C, 54.03; H, 5.10; N, 7.88. Found: C, 53.91; H, 5.12; N, 7.74.

**4.1.9. Deprotection of benzoyl ester 6→11.** A portion of benzoyl ester **6** (25 mg, 0.047 mmol) was suspended in dry methanol (2 mL) and a 1.0 M solution of sodium methoxide (10 μL, 0.01 mmol) in dry methanol was added. The pale yellow solution was stirred o/n at 40 °C to effect complete benzoyl deprotection. TLC indicated reaction completion after 12 h (8:2 ethyl acetate/hexanes and 1:9 water/acetonitrile) and the solution was neutralized by the addition of Amberlite IR-120 acidic ion-exchange resin. Filtration and evaporation to dryness under reduced pressure afforded pentol **11** as white solid (10 mg, 82%).

**4.1.10. 4-Benzyloxymethyl-1-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-1,2,3-triazole (7).** To a solution of pentol **11** (140 mg, 0.54 mmol) in dry DMF (5 mL) under nitrogen was added at 0 °C a 60% sodium hydride mineral oil dispersion (130 mg, 3.24 mmol, 6 equiv). The heterogeneous mixture was allowed to warm to room temperature and stirred for an additional 30 min before benzyl bromide (380 μL, 3.24 mmol, 6 equiv) was added. The deep yellow solution was stirred at rt for 8 h. The solution was then

cooled again to 0 °C and methanol was added gradually. Bulk solvent was then removed and $CH_2Cl_2$ (20 mL) was added. The organic extract was washed consecutively with 1 N HCl (2×5 mL), saturated $NaHCO_3$ (2×5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford a pale yellow oil, which was purified by flash silica chromatography (2:8 ethyl acetate/hexanes) to afford pentabenzyl ether **7** as white crystalline solid (330 mg, 86%). Mp=98–99 °C. $R_f$=0.43 (6:4 ethyl acetate/hexanes). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.65–3.76 (m, 3H, H-5′, H-6′, H-6″), 3.78–3.89 (m, 2H, H-3′, H-4′), 4.02–4.06 (m, 2H, H-2′), 4.07–4.09 (m, 2H, C$H_2$OBn), 4.47–4.56 (m, 4H, $CH_2$Ph), 4.59–4.67 (m, 2H, $CH_2$Ph), 4.67–4.73 (m, 2H, $CH_2$Ph), 4.88–4.95 (m, 2H, $CH_2$Ph), 5.96 (d, $^3J_{1-2}$=9.6 Hz, 1H, H-1′), 6.93–6.97 (m, 2H, Ar CH), 7.16–7.19 (m, 4H, Ar CH), 7.27–7.34 (m, 19H, Ar CH), 7.66 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 63.8 ($CH_2$Ph), 68.6 (C-6), 72.2 ($CH_2$Ph), 73.8 ($CH_2$Ph), 75.1 (C$H_2$OBn), 75.4 ($CH_2$Ph), 76.0 ($CH_2$Ph), 77.5 (C-3 or C-4), 78.2 (C-5), 81.0 (C-2), 85.7 (C-3 or C-4), 87.8 (C-1), 122.2 (triazole CH), 127.94 (*Ar* C), 127.99 (*Ar* C), 128.01 (*Ar* C), 128.03 (*Ar* C), 128.06 (*Ar* C), 128.09 (*Ar* C), 128.17 (*Ar* C), 128.18 (*Ar* C), 128.23 (*Ar* C), 128.46 (*Ar* C), 128.59 (*Ar* C), 128.64 (*Ar* C), 128.67 (*Ar* C), 128.72 (*Ar* C), 137.2 (Ar C), 137.9 (Ar C), 138.0 (2×Ar C), 138.4 (Ar C), 145.7 (triazole C). HRESIMS calcd for $C_{44}H_{45}N_3O_6Na^+$: 734.320057. Found=734.320207. Anal. Calcd for $C_{44}H_{45}N_3O_6$: C, 74.24; H, 6.37; N, 5.90; O, 13.49. Found: C, 74.64; H, 6.49; N, 5.71.

**4.1.11. Deprotection of perbenzyl ether 7 → 11.** Perbenzyl ether **6** (20 mg, 0.03 mmol) was dissolved in dry 1:2 $CH_2Cl_2$/methanol (~2 mL) and a catalytic amount of activated 30% $Pd(OH)_2$/C was added. The vessel was placed under nitrogen, evacuated and then placed under an atmosphere of hydrogen and stirred at rt for 24 h. TLC indicated near reaction completion after ca. 24 h (8:2 ethyl acetate/hexanes and 1:9 water/acetonitrile). The mixture was filtered on Celite and eluted several times with methanol. Evaporation of the filtrate afforded pentol **11** as clear gum (6 mg, 78%).

**4.1.12. [1-(2,3,4,6-Tetra-*O*-acetylglucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl-2,3,4,6-tetra-*O*-acetyl glucopyranoside (8).** A solution of alcohol **2** (100 mg, 0.23 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide (172 mg, 0.42 mmol, 1.8 equiv) in dry $CH_2Cl_2$ (5 mL) was prepared under nitrogen. Silver trifluoromethanesulfonate (66 mg, 0.26 mmol, 1.1 equiv) was then added and the mixture stirred at rt for 4 h when found complete by TLC (7:3 ethyl acetate/hexanes). The solution was neutralized by the addition of diisopropylethylamine (100 μL, 0.57 mmol). Insoluble silver salts were removed by filtration on Celite and the crude product was eluted with $CH_2Cl_2$ (~20 mL). Concentration of the filtrate under reduced pressure and flash silica chromatography of the crude residue (4:6 ethyl acetate/hexanes) afforded glucoside **8** as a white foam (98 mg, 56%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.88 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.97 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.74 (ddd, 1H, $^3J_{5-4}$=10.2 Hz, $^3J_{5-6}$=4.4 Hz, $^3J_{5-6'}$=2.4 Hz, 1H, GlcO H-5′); 3.99 (ddd, $^3J_{5-4}$=10.4 Hz, $^3J_{5-6}$=4.8 Hz, $^3J_{5-6'}$=2 Hz, 1H, GlcN H-5′), 4.13 (dd, $^2J_{6'-6}$=12.4 Hz, $^3J_{6'-5}$=2.0 Hz, 1H, GlcN H-6″), 4.18 (dd, $^2J_{6'-6}$=12.4 Hz, $^3J_{6'-5}$=2.4 Hz, 1H, GlcO H-6″), 4.26–4.32 (m, 2H, GlcN H-6′, GlcO H-6′), 4.54 (d, $^3J_{1-2}$=8 Hz, 1H, GlcO H-1′), 4.78–4.92 (m, 2H, C$H_2$O), 4.98 (dd, $^3J_{2-3}$=9.6 Hz, $^3J_{2-1}$=8.4 Hz, 1H, GlcO H-2′), 5.06–5.11 (m, 1H, GlcO H-4′), 5.15–5.20 (m, 1H, GlcO H-3′), 5.21–5.26 (m, 1H, GlcN H-4′), 5.39–5.42 (m, 2H, GlcN H-2′, H-3′), 5.84–5.86 (m, 1H, GlcN H-1′), 7.80 (s, 1H, triazole H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.3 (OAc), 20.72 (2×OAc), 20.79 (3×OAc), 20.86 (OAc), 20.89 (OAc), 61.7 (GlcN or GlcO C-6), 62.0 (GlcN or GlcO C-6), 62.1 (C$H_2$O), 67.9 (GlcN C-4), 68.6 (GlcO C-4), 70.6 (GlcN C-2 or C-3), 71.3 (GlcO C-2), 72.0 (GlcO C-5), 72.6 (GlcN C-2 or C-3), 72.8 (GlcO C-3), 75.5 (GlcN C-5), 86.1 (GlcN C-1), 99.0 (GlcO C-1), 122.3 (triazole CH), 169.55 (OAc), 169.57 (OAc), 169.62 (OAc), 170.05 (OAc), 170.1 (OAc), 170.4 (OAc), 170.6 (OAc), 170.9 (OAc). HRESIMS calcd for $C_{31}H_{41}N_3O_{19}Na^+$: 782.22267. Found: 782.223136. Anal. Calcd for $C_{31}H_{41}N_3O_{19}$: C, 49.01; H, 5.44; N, 5.53; O, 40.02. Found: C, 48.93; H, 5.61; N, 5.17.

**4.1.13. [1-(2,3,4,6-Tetra-*O*-acetylglucopyranosyl)-1*H*-1,2,3-triazol-4-yl]methyl-2,3,4,6-tetra-*O*-acetyl galactopyranoside (9).** A solution of alcohol **2** (157 mg, 0.37 mmol) and β-D-galactose pentaacetate (143 mg, 0.37 mmol, 1 equiv) in dry $CH_2Cl_2$ (5 mL) was prepared under nitrogen and cooled to 0 °C. Boron trifluoride etherate (113 μL, 0.92 mmol, 2.5 equiv) was then added dropwise and the reaction was allowed to warm to rt. The reaction was found complete by TLC (8:2 ethyl acetate/hexanes) after stirring under nitrogen o/n. $CH_2Cl_2$ (5 ml) was added and washed with saturated $NaHCO_3$ (2×5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to a pale yellow oil, which was purified by flash silica chromatography to afford the galactoside **10** as a clear gum, which slowly crystallized on standing in the refrigerator (165 mg, 59%). Mp: 106–107 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.85 (s, 3H, OAc), 1.92 (s, 3H, OAc), 1.93 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.12 (s, 3H, OAc), 3.92–3.96 (m, 1H, Gal H-5′), 4.00 (ddd, $^3J_{5-4}$=7.2 Hz, $^3J_{5-6}$=5.2 Hz, $^3J_{5-6'}$= 2 Hz, 1H, Glc H-5′), 4.07–4.13 (m, 2H, Glc H-6″, Gal H-6″), 4.21 (dd, $^2J_{6-6'}$=11.6 Hz, $^3J_{6-5}$=6.4 Hz, 1H, Gal H-6′), 4.27 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6-5}$=5.2 Hz, 1H, Glc H-6′), 4.46 (d, $^3J_{1-2}$=8 Hz, 1H, Gal H-1′), 4.76–4.92 (m, 2H, C$H_2$O), 5.17 (dd, $^3J_{2-3}$=10.8 Hz, $^3J_{2-1}$=8 Hz, 1H, Gal H-2′), 4.98 (dd, $^3J_{3-2}$=10.4 Hz, $^3J_{3-4}$=3.2 Hz, 1H, Gal H-3′), 5.21–5.26 (m, 1H, Glc H-4′), 5.35–5.43 (m, 3H, Glc H-2′, Glc H-3′, Gal H-4′), 5.85 (d, $^3J_{1-2}$=8.8 Hz, 1H, Glc H-1′), 7.80 (s, 1H, triazole H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.3 (OAc), 20.69 (OAc), 20.71 (OAc), 20.75 (OAc), 20.83 (2×OAc), 20.87 (OAc), 20.9 (OAc), 61.5 (C$H_2$O), 61.6 (Gal C-6), 61.7 (Glc C-6), 67.3 (Gal C-4), 67.9 (Gal C-2), 68.8 (Glc C-4), 70.7 (Gal C-5), 70.8 (Glc C-3), 71.0 (Gal C-3), 72.6 (Glc C-2), 75.4 (Glc C-5), 86.0 (Glc C-1), 99.1 (Gal C-1), 122.2 (triazole CH), 144.3 (triazole C), 169.3 (OAc), 169.6 (OAc), 169.7 (OAc), 170.0 (OAc), 170.2 (OAc), 170.5 (OAc), 170.6 (OAc), 170.7 (OAc). HRESIMS calcd for $C_{31}H_{41}N_3O_{19}Na^+$: 782.222647. Found: 782.223784. Anal. Calcd for $C_{31}H_{43}N_3O_{20}$ (monohydrate): C, 47.88; H, 5.57; N, 5.40. Found: C, 47.62; H, 5.26; N, 5.07.

**4.1.14. 4-Azidomethyl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (10).** To a solution of alcohol **2** (200 mg, 0.47 mmol) in dry $CH_2Cl_2$ (5 mL) was added $Et_3N$ (195 μL, 1.41 mmol, 3 equiv) and methanesulfonyl chloride (55 μL, 0.71 mmol, 1.5 equiv). The solution was stirred at rt under nitrogen for 30 min, at which time, TLC indicated reaction completion (7:3 ethyl acetate/hexanes). $CH_2Cl_2$ (5 mL) was then added and the solution was washed consecutively with 1 N HCl (2×5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford the mesylate as a pale yellow oil, which was used in the subsequent step without further purification. The crude mesylate was dissolved in dry DMF (2 mL) and $NaN_3$ (153 mg, 2.35 mmol, 5 equiv) was added. The mixture was warmed to 40 °C and stirred for 24 h. The bulk solvent was then removed under reduced pressure and $CH_2Cl_2$ (5 mL) was added. The extract was washed with distilled $H_2O$ (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to afford a crude off-white solid. Recrystallization from hot absolute ethanol afforded azide **10** as amorphous white solid (102 mg, 48%). Mp: 110–111 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.87 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.07 (s, 3H, OAc), 4.00 (ddd, $^3J_{5-4}$=10.4 Hz, $^3J_{5-6}$=5.2 Hz, $^3J_{5-6'}$=2.4 Hz, 1H, H-5′), 4.14 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6'-5}$=2.4 Hz, 1H, H-6″), 4.30 (dd, $^2J_{6-6'}$=12.4 Hz, $^3J_{6-5}$=5.2 Hz, 1H, H-6′), 4.48 (s, 2H, $CH_2N_3$), 5.20–5.25 (m, 1H, H-4′), 5.38–5.44 (m, 2H, H-2′, H-3′), 5.84–5.90 (m, 1H, H-1′), 7.79 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.3 (OAc), 20.7 (OAc), 20.8 (OAc), 20.9 (OAc), 45.7 ($N_3CH_2$), 61.7 (C-6), 67.9 (C-4), 70.5 (C-3), 72.7 (C-2), 75.5 (C-5), 86.1 (C-1), 121.0 (triazole CH), 169.2 (OAc), 169.6 (OAc), 170.1 (OAc), 170.7 (OAc). HRESIMS calcd for $C_{17}H_{22}N_6O_9Na^+$: 477.134047. Found 477.134673. Anal. Calcd for $C_{17}H_{22}N_6O_9$: C, 44.94; H, 4.88; N, 18.50. Found: C, 44.72; H, 4.90; N, 18.27.

**4.1.15. 1-(β-D-Glucopyranosyl)-4-hydroxymethyl-1,2,3-triazole (11).** White solid (various yields: see text). Mp: 162–163 °C. $R_f$=0.15 (1:9 water/acetonitrile). $^1$H NMR (400 MHz, $D_2O$): $\delta$ 3.46–3.50 (m, 1H), 3.55–3.67 (m, 3H, H-3′, H-5′, H-6′), 3.75–3.78 (m, 1H, H-6″), 3.84–3.89 (m, 1H, H-2′), 4.60 (s, 2H, C$H_2$OH), 5.61 (d, $^3J_{1-2}$=9.2 Hz, 1H, H-1′), 8.06 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $D_2O$): $\delta$ 54.7 (C$H_2$OH), 60.6 (C-6), 69.1 (C-4), 72.4 (C-2), 76.1 (C-3), 79.0 (C-5), 87.6 (C-1), 123.5 (triazole CH). HRESIMS calcd for $C_9H_{15}N_3O_6Na^+$: 284.085310. Found: 284.085457.

**4.1.16. Preparation of compounds 12–18, 20.** To a vigorously stirring suspension or solution of the azide (0.5 M) and acetylene (0.5 M) in the selected co-solvent, was added a solution of $CuSO_4\cdot5H_2O$ (0.2 equiv) and sodium ascorbate (0.4 equiv) in deionized $H_2O$. The deep yellow mixture was stirred vigorously at 40 °C and the reaction progress was monitored by TLC. Once complete, the crude mixture was extracted with three equal amounts of $CH_2Cl_2$, combined, dried ($MgSO_4$), filtered, and evaporated to afford the glycosyl triazole as off-white to white solid. A portion or the entire crude solid was purified by SPE, flash chromatography or recrystallization from hot absolute ethanol to afford analytically pure compound.

**4.1.17. 4-Pyridin-2-yl-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (12).** White amorphous solid (92%). Mp: 195–196 °C. $R_f$=0.42 (8:2 ethyl acetate/hexane). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.87 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.08 (s, 3H, OAc), 4.01 (ddd, $^3J_{5-4}$=10.4 Hz, $^3J_{5-6'}$=4.8 Hz, $^3J_{5-6}$=2.0 Hz, 1H, H-5′), 4.15 (dd, $^2J_{6-6'}$=12.8 Hz, $J_{6-5}$=2.0 Hz, 1H, H6), 4.29 (dd, $^2J_{6'-6}$=12.4 Hz, $^3J_{6'-5}$=4.8 Hz, H-6″), 5.23–5.28 (m, 1H, H-4′), 5.40–5.45 (m, 1H, H-3′), 5.50–5.55 (m, 1H, H-2′), 5.90 (d, $^3J_{1-2}$=9.2 Hz, 1H, H-1′), 7.30–7.33 (m, 1H, Ar H), 7.85–7.88 (m, 1H, Ar H), 8.21–8.23 (m, 1H, Ar H), 8.65 (br s, 1H, triazole H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.4 (OAc), 20.73 (s, 3H, OAc), 20.74 (s, 3H, OAc), 20.9 (s, OAc), 61.7 (C-6), 67.9 (C-4), 70.7 (C-3), 72.9 (C-2), 75.3 (C-5), 86.1 (C-1), 120.7 (triazole CH), 121.0 (Ar C), 123.5 (Ar CH), 137.3 (Ar CH), 148.9 (triazole C), 149.5 (Ar CH), 149.6 (Ar C), 169.0 (OAc), 169.5 (OAc), 170.2 (OAc), 170.7 (OAc). HRESIMS calcd for $C_{21}H_{24}N_4O_9Na^+$: 499.143549. Found: 499.142640. Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.44; H, 5.08; N, 11.76; O, 30.22. Found: C, 52.17; H, 5.04; N, 11.36.

**4.1.18. 4-Amidomethyl-L-*N*BocVal-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (13).** White foam (77%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.85 (d, $^3J$=6.4 Hz, 3H, Val *i*-pr $CH_3$); 0.91 (d, $^3J$=7.2 Hz, Val *i*-pr $CH_3$); 1.41 (s, 9H, Boc $CH_3$), 1.84 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.06 (s, OAc), 2.13 (m, 1H, Val *i*-pr CH), 3.92 (m, 1H, BocNH), 3.98 (ddd, $^3J_{5-4}$=10.2 Hz, $^3J_{5-6}$=4.4, $^3J_{5-6'}$=2.0 Hz, 1H, H-5′), 4.12 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6-5}$=2.4 Hz, 1H, H-6′), 4.27 (dd, $^2J_{6'-6}$=12.4 Hz, $^3J_{6'-5}$=4.8 Hz, 1H, H-6″), 4.26 (br s, 2H, C$H_2$CONH), 5.06–5.1 (m, 1H, Val α-CH), 5.20–5.25 (m, 1H, H-4′), 5.37–5.43 (m, 1H, H-2′), 5.83–5.85 (m, 1H, H-1′), 6.73 (br s, 1H, CONH), 7.78 (s, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 17.8 (Val $CH_3$), 19.5 (Val $CH_3$), 20.3 (OAc), 20.7 (OAc), 20.7 (OAc), 20.9 (OAc), 28.5 (*t*-Bu), 31.0 (Val *i*-pr CH), 35.0 (C$H_2$CONH), 60.0 (Val α-C), 61.70 (C-5), 67.9 (C-6), 70.5 (C-2), 72.8 (C-3), 75.3 (C-4), 86.0 (C-1), 156.1 (Boc C═O), 169.0 (OAc C═O), 169.5 (OAc C═O), 170.2 (OAc C═O), 170.7 (OAc C═O), 170.6 (CONH C═O). HRESIMS calcd for $C_{27}H_{41}N_5O_{12}Na^+$: 650.264393. Found: 650.26406.

**4.1.19. 4-(17α-Estradiol)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (14).** Pale yellow solid (71%). Mp: 133–134 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.45–0.60 (m, 1H, CH), 1.02 (s, 3H, estradiol $CH_3$), 1.20–1.60 (m, 6H, estradiol), 1.83 (s, 3H, OAc), 1.85–1.91 (m, 2H, estradiol $CH_2$), 1.96–2.12 (m, 6H, estradiol H), 2.02 (s, 3H, OAc), 2.05 (s, 6H, 2×OAc), 2.46–2.54 (m, 2H, estradiol $CH_2$), 2.70 (br s, 1H, OH), 2.72–2.81 (m, 2H, estradiol), 3.99 (ddd, $^3J_{5-4}$=10 Hz, $^3J_{5-6'}$=4.8, $^3J_{5-6}$=2.0 Hz, 1H, H-5′), 4.14 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6-5}$=2.0 Hz, 1H, H-6′), 4.30 (dd, $^2J_{6'-6}$=12.4 Hz, $^3J_{6'-5}$=4.8 Hz, 1H, H-6″), 5.22–5.27 (m, 1H, H-4′), 5.37–5.42 (m, 1H, H-3′), 5.44–5.48 (m, 1H, H-2′), 5.86 (d, $^3J_{1-2}$=8 Hz, 1H, H-1′), 6.52–6.58 (m, 2H, 2×Ar CH), 7.02–7.04 (m, 1H, Ar CH), 7.70 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.4 (C-18), 20.3 (OAc), 20.7 (OAc), 20.8 (OAc), 20.9 (OAc), 23.9 (estradiol), 26.5 (estradiol), 27.5 (estradiol), 29.8 (estradiol), 33.0 (estradiol), 38.20 (estradiol), 39.6 (estradiol), 43.6 (estradiol), 47.6 (estradiol), 48.6 (estradiol),

61.8 (C-6′), 68.0 (C-4′), 70.5 (C-2′), 72.9 (C-3′), 75.3 (C-5′), 82.8 (estradiol C-17), 85.9 (C-1), 112.9 (Ar CH), 115.5 (Ar CH), 120.3 (triazole CH), 126.5 (Ar CH), 132.5 (Ar C), 138.4 (Ar C), 153.9 (triazole C), 154.8 (phenol C), 169.1 (OAc), 169.7 (OAc), 170.2 (OAc), 170.9 (OAc). HRESIMS calcd for $C_{34}H_{43}N_3O_{11}Na^+$: 692.27898. Found: 692.279186.

**4.1.20. 4-Ethisterone-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1,2,3-triazole (15).** White crystalline solid (64%). Mp: 124 -125 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 0.32–0.396 (m, 1H, ethisterone CH), 0.65–0.71 (m, 1H, ethisterone CH), 1.04 (s, 3H, ethisterone $CH_3$), 1.16 (s, 3H, ethisterone $CH_3$), 1.33–1.66 (m, 7H, ethisterone), 2.01 (s, 3H, OAc), 2.02–2.04 (m, 4H, ethisterone), 2.05 (s, 3H, OAc), 2.06 (s, 6H, 2×OAc), 2.22–2.41 (m, 5H, ethisterone), 2.44–2.52 (m, 1H, ethisterone CH), 3.99 (ddd, $^3J_{5-4}$=10 Hz, $^3J_{5-6'}$=4.8 Hz, $^3J_{5-6}$=2.0 Hz, 1H, H-5′), 4.14 (dd, $^2J_{6-6'}$=12.8 Hz, $^3J_{6-5}$=2.0 Hz, 1H, H-6′), 4.30 (dd, $^2J_{6-6}$=12.8 Hz, $^3J_{6'-5}$=4.8 Hz, 1H, H-6″), 5.20–5.25 (m, 1H, H-4′), 5.36–5.44 (m, 2H, H-2′, H-3′), 5.68 (s, 1H, ethisterone C=CH), 5.83–5.85 (m, 1H, H-1′), 7.66 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.4 (ethisterone $CH_3$), 17.6 (ethisterone $CH_3$), 20.3 (OAc), 20.7 (OAc), 20.8 (OAc), 20.9 (OAc), 24.1 (ethisterone), 31.8 (ethisterone), 32.7 (ethisterone), 33.0 (ethisterone), 34.1 (ethisterone), 35.9 (ethisterone), 36.5 (ethisterone), 38.0 (ethisterone), 38.8 (ethisterone), 47.1 (ethisterone), 49.0 (ethisterone), 53.6 (ethisterone), 61.3 (C-6), 68.0 (C-4), 70.5 (C-2 or C-3), 72.8 (C-2 or C-3), 75.4 (C-5), 82.5 (ethisterone C-17), 86.0 (C-1), 119.9 (triazole CH), 124.0 (ethisterone C=*C*H), 154.5 (triazole C), 168.9 (OAc), 169.6 (OAc), 170.1 (OAc), 170.7 (ethisterone *C*=CH), 171.4 (OAc), 199.7 (ethisterone C=O). HRESIMS calcd for $C_{35}H_{47}N_3O_{11}Na^+$: 708.31028. Found: 708.310775. Anal. Calcd for $C_{35}H_{47}N_3O_{11}$: C, 61.30; H, 6.91; N, 6.13; O, 25.66. Found: C, 61.31; H, 6.99; N, 5.98.

**4.1.21. 4-(4-Sulfamoylamidomethyl)-1-(methyl 2′,3′,4′-tri-*O*-acetyl-β-D-glucuronate)-1,2,3-triazole (16).** Off-white amorphous solid (85%). Mp (decomp): 221–222 °C. $R_f$=0.08 (8:2 ethyl acetate/hexanes). $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 1.76 (s, 3H, OAc), 1.95 (s, 3H, OAc), 1.98 (s, 3H, OAc), 3.59 (s, 3H, $CO_2CH_3$), 4.51 (d, $^3J_{CH_2-NH}$=5.2 Hz, 2H, NHC$H_2$), 4.76 (d, $^3J_{5-4}$=10 Hz, 1H, H-5′), 5.19–5.24 (m, 1H, H-4′), 5.44–5.59 (m, 1H, H-3′), 5.72–5.76 (m, 1H, H-2′), 6.34 (d, $^3J_{1-2}$=9.6 Hz, 1H, H-1′), 7.45 (br s, 2H, $SO_2NH_2$), 7.86–8.01 (m, 4H, Ar H), 8.35 (s, 1H, triazole H), 9.23 (t, $^3J_{NH-CH_2}$=5.6 Hz, 1H, ArCON*H*); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): 20.6 (OAc $CH_3$), 20.9 (OAc $CH_3$), 21.0 (OAc $CH_3$), 35.5 ($CH_2$NH), 53.3 ($CO_2CH_3$), 69.0 (C-4), 70.4 (C-2), 72.3 (C-3), 73.5 (C-5), 84.4 (C-1), 122.9 (triazole CH), 126.3 (Ar CH), 128.7 (Ar CH), 137.6 (Ar C), 146.4 (Ar C), 147.1 (triazole C), 165.9 (C=O), 167.3 (C=O), 169.1 (C=O), 170.0 (C=O), 170.2 (C=O). HRESIMS (−ve ion) calcd for $C_{23}H_{26}N_5O_{12}S^-$: 596.130416. Found: 596.132499. Anal. Calcd for $C_{23}H_{27}N_5O_{12}S$: C, 46.23; H, 4.55; N, 11.72; O, 32.13; S, 5.37. Found: C, 46.10; H, 4.66; N, 11.51.

**4.1.22. 4-Methylenebenzotriazole-1-(2′,3′,4′-tri-*O*-acetyl-α-D-arabinosyl)-1,2,3-triazole (17).** White solid (94%). Mp: 215–216 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.80 (s, 3H, OAc), 1.98 (s, 3H, OAc), 2.17 (s, 3H, OAc), 3.87 (dd, $^2J_{5-5'}$=13.6, $^3J_{5-4}$=1.2 Hz, 1H, H-5′), 4.11 (dd, $^2J_{5'-5}$=13.6 Hz, $^3J_{5'-4}$=2 Hz, 1H, H-5″), 5.19 (dd, $^3J_{3-2}$=10 Hz, $^3J_{3-4}$=3.2 Hz, 1H, H-3′), 3.58 (ddd, $^3J_{4-3}$=3.6 Hz, $^3J_{4-5'}$=2 Hz, $^3J_{4-5}$=1.2 Hz, 1H, H-4′), 5.43–5.48 (m, 1H, H-2′), 5.66 (d, $^3J_{1-2}$=11.2 Hz, 1H, H-1′), 5.92–6.03 (m, 2H, Bt-$CH_2$), 7.33–7.37 (m, 1H, Ar H), 7.43–7.47 (m, 1H, Ar H), 7.64–7.66 (m, 1H, Ar H), 7.81 (s, triazole CH), 8.03–8.05 (m, 1H, Ar H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 20.3 (OAc), 20.7 (OAc), 21.1 (OAc), 43.9 (Bt-$CH_2$), 67.5 (C-5), 67.8 (C-4), 68.4 (C-2), 70.5 (C-3), 87.0 (C-1), 110.2 (Ar CH), 120.1 (Ar CH), 121.9 (triazole CH), 124.3 (Ar CH), 127.9 (Ar CH), 169.1 (OAc), 170.0 (OAc), 170.3 (OAc); HRESIMS calcd for $C_{20}H_{22}N_6O_7Na^+$: 481.144218. Found: 481.14411. Anal. Calcd for $C_{20}H_{22}N_6O_7$: C, 52.40; H, 4.84; N, 18.33; O, 24.43. Found: C, 52.39; H, 4.94; N, 18.05; O, 24.62.

**4.1.23. 1-(2′-Deoxy-2′-acetamido-3′,4′,6′-tri-*O*-acetyl-β-D-glucopyranosyl)-4-(hydroxymethyl)-1,2,3-triazole (18).**[16f] Off-white foam (62%). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.57 (s, 3H, NHAc), 1.92 (s, 3H, OAc), 1.97 (s, 3H, OAc), 1.98 (s, 3H, OAc), 3.99–4.03 (dd, $^2J_{6-6'}$=12.4 Hz, $^3J_{6-5}$=2.4 Hz, 1H, H-6′), 4.09–4.13 (dd, $^2J_{6'-6}$=12.4 Hz, $^3J_{6'-5}$=5.2 Hz, 1H, H-6″), 4.19 (ddd, $^3J_{5-4}$=10 Hz, $^3J_{5-6'}$=4.8 Hz, $^3J_{5-6}$=2.4 Hz, 1H, H-5′), 4.47 (d, $^3J_{CH_2-OH}$=4.4 Hz, 2H, C$H_2$OH), 5.04–5.09 (m, 1H, H-3′), 5.20–5.21 (m, 1H, $CH_2O$*H*), 5.29–5.34 (m, 1H, H-4′), 6.06 (d, $^3J_{1-2}$=10 Hz, 1H, H-1′), 8.04 (d, $^3J_{NH-H_2}$=9.6 Hz, 1H, NHAc N*H*), 8.09 (s, 1H, triazole CH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 25.7 (OAc), 25.9 (OAc), 26.0 (OAc), 27.8 (NHAc), 57.4 (C-2), 60.0 ($CH_2$OH), 67.3 (C-4), 73.4 (C-5), 77.9 (C-3), 78.7 (C-6), 90.0 (C-1), 126.8 (triazole CH), 153.6 (triazole C), 174.8 (C=O), 174.9 (C=O), 175.0 (C=O), 175.5 (C=O). HRESIMS calcd for $C_{17}H_{24}N_4O_9Na^+$: 541.143549. Found: 451.142863.

**4.1.24. 4-Hydroxymethyl-1-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)-1,2,3-triazole (19).** To a vigorously stirring solution of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl azide (100 mg, 0.18 mmol) in hot *tert*-butyl alcohol (500 μL at ca. 60 °C), was added propargyl alcohol (45 μL, 0.74 mmol, 4.2 equiv) and a solution of $CuSO_4\cdot 5H_2O$ (18 mg, 0.08 mmol, 0.4 equiv) and sodium ascorbate (30 mg, 0.15 mmol, 0.8 equiv) in distilled $H_2O$ (500 μL). The deep yellow suspension was stirred at 60 °C for approx. 2 d, at which time TLC indicated reaction completion (1:1 ethyl acetate/hexanes). The aqueous phase was then extracted with $CH_2Cl_2$ (2×10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to afford a pale yellow syrup, which crystallized on standing to afford a white amorphous solid. (79 mg, 73%), Mp: 82–83 °C. $R_f$=0.19. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.51 (dd, $^2J_{6-6'}$=10.8 Hz, $^3J_{6-6}$=2.0 Hz, 1H, H-6′), 3.67 (dd, $^2J_{6'-6}$=10.8 Hz, $^3J_{6'-5}$=2.8 Hz, 1H, H-6″), 3.81 (dd, $^3J$=10 Hz, $^3J$=8.4 Hz, 1H, H-4′), 3.89–3.93 (m, 1H, H-5′), 4.02 (dd, $^3J_{2-3}$=9.6 Hz, $^3J_{2-1}$=6 Hz, 1H, H-2′), 4.39–4.53 (m, 2H, OBn $CH_2$), 4.49–4.73 (m, 2H, OBn $CH_2$), 4.52–4.85 (m, 2H, OBn $CH_2$), 4.60–4.64 (m, 1H, H-3′), 4.80 (s, 2H, $OCH_2$), 4.84–4.94 (m, 2H, OBn $CH_2$), 5.80 (d, $^3J_{1-2}$=5.6 Hz, 1H, H-1′), 7.13–7.16 (m, 4H, OBn CH), 7.25–7.33 (m, 16H, OBn CH), 7.51 (s, triazole CH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 56.8 (O$CH_2$), 68.3 (C-6), 73.7 (C-5), 73.9 (OBn $CH_2$), 74.4 (OBn $CH_2$), 75.0 (OBn $CH_2$), 75.8 (OBn $CH_2$), 77.4 (C-4), 78.8 (C-2), 82.0 (C-3), 84.3 (C-1),

124.0 (triazole *C*H), 127.9 (OBn CH), 127.93 (OBn *C*H), 127.97 (OBn *C*H), 128.1 (OBn CH), 128.2 (OBn CH), 128.4 (OBn CH), 128.5 (OBn CH), 128.59 (OBn *C*H), 128.62 (OBn *C*H), 128.7 (OBn CH), 128.9 (OBn *C*H), 137.7 (OBn C), 137.8 (OBn C), 138.3 (OBn C), 138.7 (OBn C). HRESIMS calcd for $C_{37}H_{39}N_3O_6Na^+$: 644.273116. Found: 644.272986.

**4.1.25. Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(4-{[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy]methyl}-1*H*-1,2,3-triazol-1-yl)-α-D-glucopyranoside (20).** White foam (78%). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.96 (s, 3H, OAc), 1.99 (s, 6H, 2×OAc), 2.00 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.08 (s, 6H, 2×OAc), 3.14 (s, 3H, $OCH_3$), 3.72 (ddd, $^3J_{5-4}$=10 Hz, $^3J_{5-6}$=5.2 Hz, $^3J_{5-6'}$=2.8 Hz, 1H, βGlc H-5′), 4.14 (dd, $^2J_{6-6'}$=12.4 Hz, $^3J_{6-5}$=2.4 Hz, 1H, βGlc H-6′), 4.17–4.20 (m, 1H, αGlc H-5′), 4.26 (dd, $^2J_{6'-6}$=12.4 Hz, $^3J_{6'-5}$=4.62, 1H, βGlc H-6″), 4.39 (dd, $^2J_{6-6'}$=14.4 Hz, $^3J_{6-5}$=8.4 Hz, 1H, αGlc H-6′), 4.56 (dd, $^2J_{6'-6}$=14.6 Hz, $^3J_{6'-5}$=2.4 Hz, 1H, αGlc H-6″), 4.52 (d, $^3J_{1-2}$=8.4 Hz, 1H, βGlc H-1′), 4.73–4.82 (m, 3H, αGlc H-2′, αGlc H-4′, C$H_2$O), 4.89 (d, $^3J_{1-2}$=3.6 Hz, 1H, αGlc H-1′), 4.99 (dd, $^3J$=9.2 Hz, $^3J_{2-1}$=8 Hz, 1H, βGlc H-2′), 5.05–5.09 (m, 1H, βGlc H-4′), 5.14–5.19 (m, 1H, αGlc H-3′), 7.16 (s, 1H, triazole H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 50.9 (βGlc C-5), 55.8 ($OCH_3$), 62.0 (βGlc C-6), 62.9 (*C*$H_2$O), 67.8 (αGlc C-5), 68.5 (βGlc C-4), 69.9 (αGlc C-3), 70.0 (αGlc C-2), 70.9 (αGlc C-4), 71.3 (βGlc C-2), 72.1 (βGlc H-5), 72.9 (αGlc C-3), 96.9 (αGlc C-1), 99.7 (βGlc C-1), 124.6 (triazole CH), 144.4 (triazole C), 169.5 (OAc), 169.6 (OAc), 170.0 (OAc), 170.2 (OAc), 170.4 (OAc), 170.5 (OAc), 170.9 (OAc). HRESIMS calcd for $C_{30}H_{41}N_3O_{18}Na^+$: 754.227733. Found 754.226711. Anal. Calcd for $C_{30}H_{41}N_3O_{18}$: C, 49.25; H, 5.65; N, 5.74; O, 39.36. Found: C, 48.92; H, 5.71; N, 5.49.

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## Supplementary data

$^1$H NMR (400 MHz) spectra for compounds **2**–**20** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.001.

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# Synthesis of substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*]-[1,2]diazepine-8-carboxylates

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Dedicated to Professor Dr. Miha Tišler, Professor Emeritus of the University of Ljubljana, on the occasion of his 80th birthday

**Abstract**—Substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates were prepared in good to excellent yields from ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate with 1,2-disubstituted hydrazines by heating in an alcohol.


## 1. Introduction

There are many methods described in the literature for the synthesis of the pyrazole ring. Two of the most important methods for practical purposes are the reaction between hydrazines and β-difunctional compounds, and 1,3-dipolar cycloadditions. Other methods are alkylation at the 4-position of 1-substituted pyrazoles, and alkylation at the 5-position. Only a few reports describe introduction of an aryl or heteroaryl group into the pyrazole ring under Pd(0) catalysis.[1–8] *N*-Substituted pyrazole dicarboxylate and bicyclic derivatives such as pyrazolo-oxazine, pyrazolo-pyrazine, pyrazolo-oxazepine and pyrazolo-diazepine[9,10] and other fused pyrazoles[11,12] are prospective pharmaceuticals and agrochemicals.

In connection with our interest in alkyl 3-dimethylaminopropenoates and related enaminones as building blocks for the preparation of various heterocyclic systems and functionalised heterocycles, such as heteroaryl-substituted α-amino- and α-hydroxy acid derivatives, fused pyridinones, pyrimidones, pyranones and related systems,[13–15] including some naturally occurring alkaloids,[16–21] we reported recently some transformations of alkyl [(*Z*)-4-dimethylaminomethylidene-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl]acetate with *N*-nucleophiles into 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylates[22,23] and (substituted pyrazol-3-yl)pyrimidinones and (pyrazol-3-yl)pyranones.[24]

While pyrazolo[3,4-*d*][1,2]diazepines have been obtained by cycloaddition of 2-diazopropane to 1,2-diazepine derivatives,[25–30] isomeric pyrazolo[4,3-*d*][1,2]diazepines are mentioned in the literature only once. In the heterocyclisation of 5-acetylenylpyrazole-4-carboxylic acid hydrazides under the influence of CuCl an unexpected formation of a diazepinone and dehydrodimerisation into the corresponding bis(pyrazolo[4,3-*d*][1,2]diazepinone) have been described.[31]

## 2. Results and discussion

Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}-propenoate (**1**) was prepared from ethyl (5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)acetate according to the procedure described in the literature.[23] In the reaction of **1** with hydrazine or monosubstituted hydrazines the corresponding 5-amino-substituted pyrazolo[4,3-*c*]pyridine-7-carboxylates were formed.[23]

When compound **1** was reacted with 1,2-disubstituted hydrazines **2** in acetonitrile cyclisation did not take place to give compound **3**. However, when the reaction was carried out in an alcohol, compounds **4** were formed (Scheme 1). The mechanism of the formation of **4** is unknown so far. However, since the cyclisation in non-hydroxylic solvent did not produce the pyrazolo[4,3-*d*][1,2]diazepine derivatives **3**, the addition of alcohol to the $C_7{=}C_8$ double bond in compound **3** seems to be very unlikely. The possible explanation is therefore that either an aminal **5** or enol ether **6** are formed as intermediates in the presence of an alcohol. In the

*Keywords*: Pyrazolo[4,3-d][1,2]diazepines; 3-(Dimethylamino)propenoates; Heterocycles.
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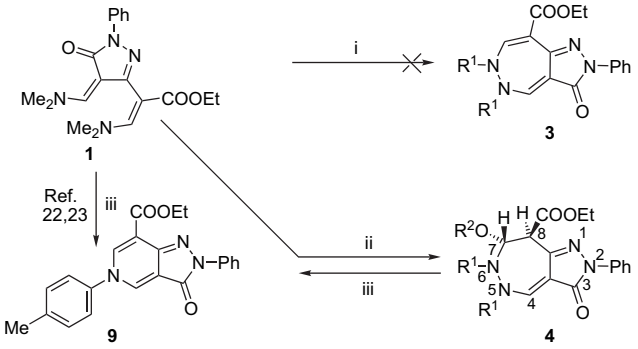
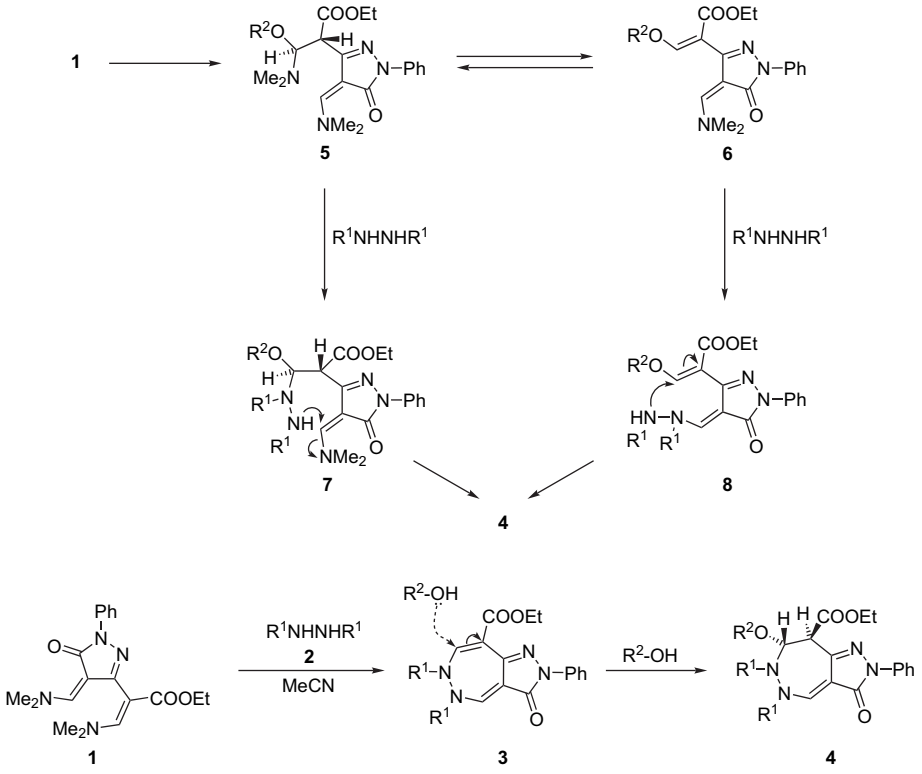


| Compound | $R^1$ | $R^2$ | Reaction time [h] | Yield [%] |
|---|---|---|---|---|
| **4a** | Me | Me | 1.5 | 74 |
| **4b** | Me | Et | 1.5 | 81 |
| **4c** | Me | *n*-Pr | 4 | 83 |
| **4d** | Me | *i*-Pr | 4 | 41 |
| **4e** | Me | *n*-Bu | 2 | 67 |
| **4f** | Me | *t*-Bu | 3 | 89 |
| **4g** | Me | Allyl | 7.5 | 59 |
| **4h** | Et | Me | 7 | 51 |
| **4i** | Et | Et | 7 | 61 |
| **4j** | Et | *n*-Pr | 7 | 40 |
| **4k** | Et | *i*-Pr | 7 | 47 |

**Scheme 1**. Reagents and reaction conditions: (i) $R^1NHNHR^1$ (**2a** $R^1$=Me; **2b** $R^1$=Et), MeCN, reflux; (ii) $R^1NHNHR^1$ (**2a** $R^1$=Me; **2b** $R^1$=Et), $R^2OH$, reflux; (iii) 4-Me-$C_6H_4$-$NH_2\times$HCl, MeOH, reflux.



**Scheme 2**.

reaction with 1,2-disubstituted hydrazine the corresponding intermediates **7** or **8** are formed, which cyclise to give the final products **4** (Scheme 2).

Compound **4a** was transformed using 4-methylaniline into 2*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylate derivative **9** identical with the compound prepared previously.[22,23]

## 3. Structure determination

The structures of all new compounds were determined by spectroscopic methods (IR, $^1$H NMR; in the case of **4b** also by $^{13}$C and HMBC) and by elemental analyses. Physical and spectral data for compound **5** were in agreement with the literature data.[22,23] Compounds **4** were obtained as pure

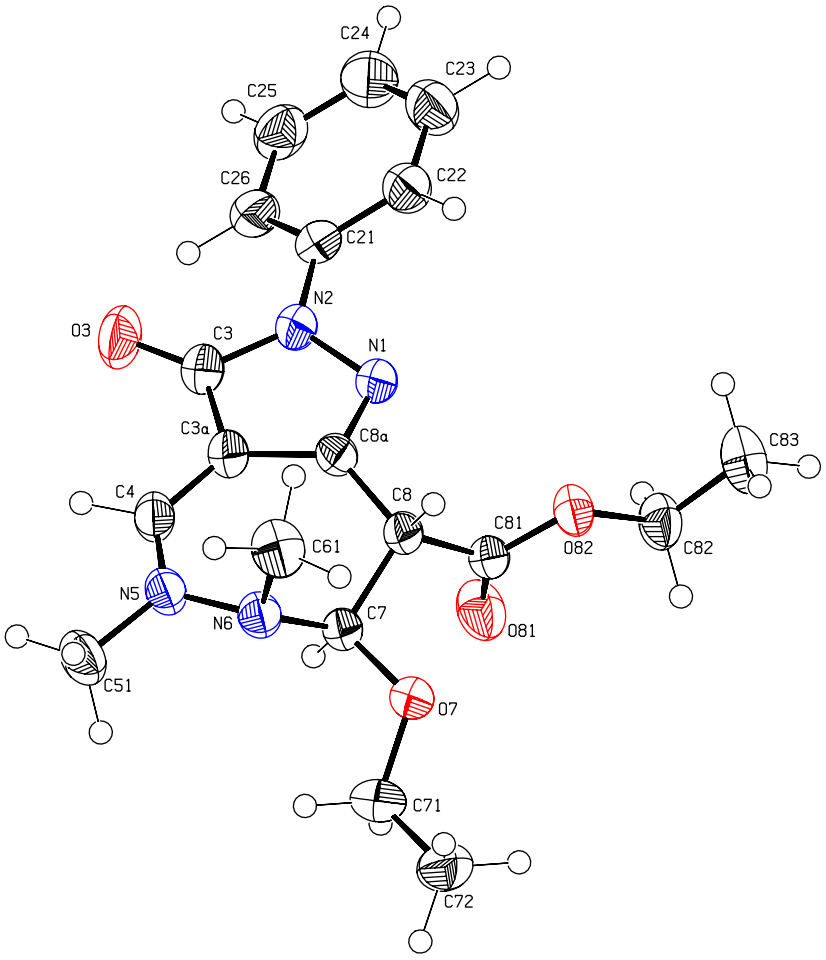



**Figure 1**.

diastereomers. The *anti*-orientation of the 7-alkoxy and 8-ester groups in compound **4** was established on the basis of the vicinal coupling constant, $J_{7\text{-H},8\text{-H}} \approx 10$ Hz. The position of the 7-alkoxy group was established from the HMBC spectrum for compound **4b**. The structure of compound **4b** was confirmed by X-ray diffraction analysis (Fig. 1).

## 4. Conclusion

Substituted 2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates **4** were obtained from ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**), via substitution of both dimethylamino groups with 1,2-dialkylhydrazines **2**, and subsequent addition of alcohol to $C_7{=}C_8$ double bond. Reaction of pyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates **4** with an amine resulted in conversion into pyrazolo[4,3-*c*]pyridine-7-carboxylate **9**.

## 5. Experimental

### 5.1. General

Melting points were determined on a Kofler micro hot stage. The $^1$H NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for $^1$H, and 75.5 MHz for $^{13}$C nucleus, using $CDCl_3$ as solvents and TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400 II. 1,2-Dimethylhydrazine hydrochloride (**2a**), 1,2-diethylhydrazine hydrochloride (**2b**), and 4-methylaniline hydrochloride are commercially available (Fluka AG). Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) was prepared according to the literature procedure.[23]

### 5.2. General procedure for the preparation of ethyl (7*R**,8*S**)-5,6-dimethyl-7-alkoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates 4a–g

Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in alcohol (2 mL) were heated at the reflux temperature for 7 h. After cooling to −30 °C, the product precipitates, or water (2 mL) is added and the product gradually precipitates. The crystals were filtered off and crystallised from alcohol/water mixture.

**5.2.1. Ethyl (7*R**,8*S**)-7-methoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4a).** Ethyl (2*E*)-3-(dimethylamino)-

2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in methanol (3 mL) were heated at the reflux temperature for 1.5 h. After cooling, the product precipitates, and the crystals were collected by filtration and crystallised from methanol. Yield: 88 mg (74%) of yellow crystals. Mp: 225–229 °C. IR (KBr) $\nu_{max}$: 2980, 1730, 1670, 1610, 1490, 1650, 1320, 1100, 830, 750, 650 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.33 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 2.65 (3H, s, NMe), 3.41 (3H, s, NMe), 3.44 (3H, s, OMe), 4.10 (1H, d, $J$=10.1 Hz, 7-H), 4.24 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 4.35 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 4.62 (1H, d, $J$=10.1 Hz, 8-H), 7.09–7.14 (1H, m, Ph), 7.32–7.38 (2H, m, Ph), 7.62 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{18}H_{22}N_4O_4$ (358.39): C 60.32; H 6.19; N 15.63. Found: C 60.12; H 6.37; N 15.58.

**5.2.2. Ethyl (7*R**,8*S**)-7-ethoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4b).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in ethanol (3 mL) were heated under reflux temperature for 1.5 h. After cooling, the product precipitates, and the crystals were collected by filtration and crystallised from methanol. Yield: 100 mg (81%) of yellow crystals. Mp: 196–199 °C. IR (KBr) $\nu_{max}$: 2980, 1730, 1680, 1610, 1350, 1190, 1100, 840, 760 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.19 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 1.33 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 2.65 (3H, s, NMe), 3.40 (3H, s, NMe), 3.48 (1H, dd, $J$=9.6, 7.1 Hz, $OCH_2CH_3$), 3.81 (1H, dd, $J$=9.5, 7.1 Hz, $OCH_2CH_3$), 4.10 (1H, d, $J$=10.1 Hz, 7-H), 4.25 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 4.32 (1H, dq, $J$=9.6, 7.1 Hz, $OCH_2CH_3$), 4.72 (1H, d, $J$=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.62 (1H, s, 4-H), 7.95–7.98 (2H, m, Ph). $^{13}C$ NMR ($CDCl_3$): 14.7, 15.0, 29.6, 44.7, 50.2, 61.7, 64.3, 90.7, 100.3, 119.2, 124.6, 128.9, 139.7, 143.0, 148.9, 165.4, 165.4, 169.5. Anal. Calcd for $C_{19}H_{24}N_4O_4$ (372.42): C 61.28; H 6.49; N 15.04. Found: C 61.30; H 6.58; N 15.06.

**5.2.3. Ethyl (7*R**,8*S**)-7-*n*-propoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4c).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in *n*-propanol (3 mL) were heated at the reflux temperature for 4 h. After cooling, the product precipitates, and the crystals were collected by filtration and crystallised from *n*-propanol/water mixture. Yield: 107 mg (83%) of yellow crystals. Mp: 155–157 °C. IR (KBr) $\nu_{max}$: 1720, 1660, 1610, 1360, 1330, 1190, 1100, 840, 760 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.92 (3H, t, $J$=7.3 Hz, $CH_2CH_2CH_3$), 1.32 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 1.58 (2H, deg tq, $J$=7.3 Hz, $CH_2CH_2CH_3$), 2.66 (3H, s, NMe), 3.36 (1H, dt, $J$=9.3, 6.5 Hz, $CH_2CH_2CH_3$), 3.44 (3H, s, NMe), 3.72 (1H, dt, $J$=9.3, 6.5 Hz, $CH_2CH_2CH_3$), 4.11 (1H, d, $J$=10.1 Hz, 7-H), 4.25 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 4.31 (1H, dq, $J$=10.7, 7.1 Hz, $OCH_2CH_3$), 4.70 (1H, d, $J$=10.1 Hz, 8-H), 7.09–7.14 (1H, m, Ph), 7.32–7.38 (2H, m, Ph), 7.66 (1H, s, 4-H), 7.94–7.97 (2H, m, Ph). Anal. Calcd for $C_{20}H_{26}N_4O_4$ (386.44): C 62.16; H 6.78; N 14.50. Found: C 62.42; H 7.01; N 14.56.

**5.2.4. Ethyl (7*R**,8*S**)-7-*i*-propoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4d).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in 2-propanol (3 mL) were heated at the reflux temperature for 4 h. After cooling, water (~2 mL) was added. The precipitate was filtered off and crystallised from 2-propanol/water mixture. Yield: 53 mg (41%) yellow crystals. Mp: 192–194 °C. IR (KBr) $\nu_{max}$: 1750, 1680, 1630, 1350, 1240, 1090, 1060, 760 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.12 (3H, d, $J$=6.1 Hz, $CH_3CHCH_3$), 1.19 (3H, d, $J$=6.3 Hz, $CH_3CHCH_3$), 1.32 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 2.66 (3H, s, NMe), 3.42 (3H, s, NMe), 3.92 (1H, septet, $J$=6.3 Hz, $CH_3CHCH_3$), 4.09 (1H, d, $J$=10.1 Hz, 7-H), 4.27 (2H, q, $J$=7.1 Hz, $OCH_2CH_3$), 4.80 (1H, d, $J$=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.62 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{20}H_{26}N_4O_4$ (386.44): C 62.16; H 6.78; N 14.50. Found: C 62.36; H 6.98; N 14.53.

**5.2.5. Ethyl (7*R**,8*S**)-7-*n*-butoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4e).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in 1-butanol (2 mL) were heated at the reflux temperature for 2 h. Solvent was removed in vacuo and the residue was crystallised from ethanol/water mixture. Yield: 90 mg (67%) of yellow crystals. Mp: 153–154 °C. IR (KBr) $\nu_{max}$: 1730, 1670, 1610, 1360, 1110, 750 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.92 (3H, t, $J$=7.3 Hz, $CH_2CH_2CH_2CH_3$), 1.32 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 1.32–1.42 (2H, m, $CH_2CH_2CH_2CH_3$), 1.54 (2H, quintet, $J$=7.3 Hz, $CH_2CH_2CH_2CH_3$), 2.65 (3H, s, NMe), 3.39 (1H, dt, $J$=9.4, 6.3 Hz, $CH_2CH_2CH_2CH_3$), 3.45 (3H, s, NMe), 3.76 (1H, dt, $J$=9.4, 6.4 Hz, $CH_2CH_2CH_2CH_3$), 4.11 (1H, d, $J$=10.1 Hz, 7-H), 4.24 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 4.30 (1H, dq, $J$=10.8, 7.2 Hz, $OCH_2CH_3$), 4.70 (1H, d, $J$=10.1 Hz, 8-H), 7.09–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.68 (1H, s, 4-H), 7.93–7.97 (2H, m, Ph). Anal. Calcd for $C_{21}H_{28}N_4O_4$ (400.47): C 62.98; H 7.05; N 13.99. Found: C 62.77; H 7.17; N 13.91.

**5.2.6. Ethyl (7*R**,8*S**)-7-*tert*-butoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4f).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in *tert*-butanol (3 mL) were heated at the reflux temperature for 3 h. Solvent was removed in vacuo and the residue was crystallised from ethanol/water mixture. Yield: 119 mg (89%) of yellow crystals. Mp: 166–168 °C. IR (KBr) $\nu_{max}$: 1740, 1680, 1620, 1500, 1350, 1240, 1070, 840, 760 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.27 (9H, s, *t*-Bu),

1.32 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 2.66 (3H, s, NMe), 3.42 (3H, s, NMe), 4.12 (1H, d, $J$=9.8 Hz, 7-H), 4.23 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 4.28 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 5.06 (1H, d, $J$=9.8 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.61 (1H, s, 4-H), 7.93–7.98 (2H, m, Ph). Anal. Calcd for $C_{21}H_{28}N_4O_4$ (400.47): C 62.98; H 7.05; N 13.99. Found: C 62.99; H 7.26; N 13.96.

**5.2.7. Ethyl (7*R**,8*S**)-7-allyloxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4g).** Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-dimethylhydrazine hydrochloride (**2a**) (44 mg, 0.5 mmol) in allyl alcohol (2 mL) were heated at the reflux temperature for 7.5 h. Water (2 mL) was added, the product gradually crystallises. Crystals were filtered off and crystallised from allyl alcohol/water mixture. Yield: 113 mg (59%). Mp: 175–178 °C. IR (KBr) $\nu_{max}$: 1730, 1680, 1610, 1590, 1490, 1350, 1330, 1180, 1100, 830, 760, 520 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.32 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 2.66 (3H, s, NMe), 3.41 (3H, s, NMe), 4.04 (1H, deg dddd, $J$=12.8, 6.6, 1.3 Hz, $CH_2CH{=}CH_2$), 4.14 (1H, d, $J$=10.1 Hz, 7-H), 4.19–4.37 (3H, m, $CH_2CH{=}CH_2$, $OCH_2CH_3$), 4.79 (1H, d, $J$=10.1 Hz, 8-H), 5.20–5.31 (2H, m, $CH_2CH{=}CH_2$), 5.86 (1H, dddd, $J$=17.0, 10.4, 6.5, 5.0 Hz, $CH_2CH{=}CH_2$), 7.09–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.61 (1H, s, 4-H), 7.94–7.97 (2H, m, Ph). Anal. Calcd for $C_{20}H_{24}N_4O_4$ (384.43): C 62.49; H 6.26; N 14.57. Found: C 62.75; H 6.41; N 14.74.

### 5.3. General procedure for the preparation of ethyl (7*R**,8*S**)-5,6-diethyl-7-alkoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylates 4h–k

Ethyl (2*E*)-3-(dimethylamino)-2-{(4*Z*)-4-[(dimethylamino)-methylidene]-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl}propenoate (**1**) (119 mg, 0.5 mmol) and 1,2-diethylhydrazine hydrochloride (**2b**) (44 mg, 0.5 mmol) in alcohol (2 mL) were heated at the reflux temperature for 7 h. After cooling to −30 °C, the product precipitates, or water (2 mL) is added and the product gradually precipitates. The crystals were filtered off and crystallised from alcohol/water mixture.

**5.3.1. Ethyl (7*R**,8*S**)-5,6-diethyl-7-methoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4h).** In methanol. Yield: 65 mg (51%) of yellow crystals. Mp: 144–147 °C (methanol/water); IR (KBr) $\nu_{max}$: 3440, 2980, 1730, 1680, 1600, 1480, 1350, 1320, 1120, 820, 760, 690 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.19 (3H, t, $J$=7.2 Hz, $NCH_2CH_3$), 1.34 (3H, t, $J$=7.1 Hz, $NCH_2CH_3$), 1.48 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 3.08 (2H, dq, $J$=2.4, 7.2 Hz, $OCH_2CH_3$), 3.50 (3H, s, OMe), 3.63–3.77 (2H, m, $NCH_2CH_3$), 4.12 (1H, d, $J$=10.2 Hz, 7-H), 4.24 (1H, qd, $J$=7.1, 10.8 Hz, $OCH_2CH_3$), 4.35 (1H, qd, $J$=7.1, 10.8 Hz, $OCH_2CH_3$), 4.63 (1H, d, $J$=10.2 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.32–7.38 (2H, m, Ph), 7.69 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{20}H_{26}N_4O_4$ (386.44): C 62.16; H 6.78; N 14.50. Found: C 62.07; H 6.73; N 14.56.

**5.3.2. Ethyl (7*R**,8*S**)-5,6-diethyl-7-ethoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4i).** In ethanol. Yield: 82 mg (61%) of yellow crystals. Mp: 144–146 °C (ethanol/water). IR (KBr) $\nu_{max}$: 3440, 2980, 1730, 1680, 1600, 1480, 1350, 1320, 1080, 820, 760, 690, 580 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.18 (3H, t, $J$=7.3 Hz, $NCH_2CH_3$), 1.21 (3H, t, $J$=7.2 Hz, $NCH_2CH_3$), 1.33 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 1.46 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 3.09 (2H, q, $J$=7.2 Hz, $NCH_2CH_3$), 3.54 (1H, dq, $J$=9.3, 7.0 Hz, $NCH_2CH_3$), 3.61–3.75 (2H, m, $NCH_2CH_3$), 3.96 (1H, dq, $J$=9.3, 7.1 Hz, $OCH_2CH_3$), 4.12 (1H, d, $J$=10.1 Hz, 7-H), 4.25 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 7.32 (1H, dq, $J$=10.8, 7.1 Hz, $OCH_2CH_3$), 4.72 (1H, d, $J$=10.2 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.68 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{21}H_{28}N_4O_4$ (400.47): C 62.98; H 7.05; N 13.99. Found: C 63.05; H 7.21; N 14.12.

**5.3.3. Ethyl (7*R**,8*S**)-5,6-diethyl-3-oxo-2-phenyl-7-propoxy-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4j).** In *n*-propanol. Yield: 55 mg (40%). Mp: 118–121 °C (*n*-propanol/water). IR (KBr) $\nu_{max}$: 3440, 3000, 1730, 1670, 1590, 1350, 1320, 1180, 1120, 1080, 1020, 820, 760 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 0.93 (3H, t, $J$=7.4 Hz, $OCH_2CH_2CH_3$), 1.18 (3H, t, $J$=7.2 Hz, $NCH_2CH_3$), 1.33 (3H, t, $J$=7.1 Hz, $OCH_2CH_3$), 1.46 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 1.60 (2H, deg tq, $J$=7.4 Hz, $OCH_2CH_2CH_3$), 3.09 (2H, q, $J$=7.2 Hz, $NCH_2CH_3$), 3.41 (1H, dt, $J$=9.0, 6.4 Hz, $OCH_2CH_2CH_3$), 3.64 (1H, dt, $J$=20.8, 7.1 Hz, $NCH_2CH_3$), 3.71 (1H, dt, $J$=20.8, 7.1 Hz, $NCH_2CH_3$), 3.87 (1H, dt, $J$=9.0, 6.4 Hz, $OCH_2CH_2CH_3$), 4.13 (1H, d, $J$=10.1 Hz, 7-H), 4.25 (1H, dq, $J$=11.1, 7.2 Hz, $OCH_2CH_3$), 4.31 (1H, dq, $J$=11.1, 7.2 Hz, $OCH_2CH_3$), 4.71 (1H, d, $J$=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.69 (1H, s, 4-H), 7.95–7.98 (2H, m, Ph). Anal. Calcd for $C_{22}H_{30}N_4O_4$ (414.50): C 63.75; H 7.30; N 13.52. Found: C 63.76; H 7.49; N 13.85.

**5.3.4. Ethyl (7*R**,8*S**)-5,6-diethyl-7-*i*-propoxy-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-carboxylate (4k).** In *i*-propanol. Yield: 65 mg (47%) of yellow crystals. Mp: 184–186 °C (*i*-propanol/water). IR (KBr) $\nu_{max}$: 3460, 2980, 1740, 1670, 1600, 1490, 1360, 1180, 1120, 1070, 1020, 830, 760 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.12 (3H, d, $J$=6.1 Hz, $OCH(CH_3)_2$), 1.18 (3H, t, $J$=7.2 Hz, $NCH_2CH_3$), 1.22 (3H, d, $J$=6.3 Hz, $CH(CH_3)_2$), 1.32 (3H, t, $J$=7.1 Hz, $NCH_2CH_3$), 1.46 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 3.10 (2H, q, $J$=7.2 Hz, $NCH_2CH_3$), 3.64 (1H, dq, $J$=20.9, 7.2 Hz, $OCH_2CH_3$), 3.72 (1H, dq, $J$=21.0, 7.2 Hz, $OCH_2CH_3$), 4.10 (1H, d, $J$=10.1 Hz, 7-H), 4.10 (1H, septet, $J$=6.1 Hz, $OCH(CH_3)_2$), 4.27 (2H, q, $J$=7.1 Hz, $NCH_2CH_3$), 4.80 (1H, d, $J$=10.1 Hz, 8-H), 7.08–7.14 (1H, m, Ph), 7.31–7.38 (2H, m, Ph), 7.69 (1H, s, 4-H), 7.94–7.98 (2H, m, Ph). Anal. Calcd for $C_{22}H_{30}N_4O_4$ (414.50): C 63.75; H 7.30; N 13.52. Found: C 63.66; H 7.47; N 13.56.

### 5.4. Ethyl 5-(4-methylphenyl)-3-oxo-2-phenyl-3,5-dihydro-2*H*-pyrazolo[4,3-*c*]pyridin-7-carboxylate (9)

Ethyl (7*R**,8*S**)-7-methoxy-5,6-dimethyl-3-oxo-2-phenyl-2,3,5,6,7,8-hexahydropyrazolo[4,3-*d*][1,2]diazepine-8-

carboxylate (**4a**) (31 mg, 0.09 mmol) in 4-methylaniline hydrochloride (12 mg, 0.09 mmol) in methanol (3 mL) was heated at the reflux temperature for 12 h. After cooling to −30 °C, precipitate was filtered off. Product is identical to the product prepared from **1** and 4-methylaniline hydrochloride.[22,23] Yield: 12 mg (36%) of red crystals. Mp 233–235 °C (lit.[22,23] 233–235 °C) IR (KBr) $\nu_{max}$: 1730, 1670, 1650, 1490, 1310, 1150, 790, 760 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 1.48 (3H, t, $J$=7.2 Hz, $OCH_2CH_3$), 2.46 (3H, s, Me), 4.49 (2H, q, $J$=7.2 Hz, $OCH_2CH_3$), 7.18–7.24 (1H, m, Ph), 7.32–7.47 (6H, m, 2Ph), 8.19 (1H, d, $J$=1.9 Hz, 4-H), 8.24–8.27 (2H, m, Ph), 8.35 (1H, d, $J$=1.5 Hz, 6-H).

### 5.5. X-ray structure determination

Single crystal X-ray diffraction data of compound **4b** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[32] DENZO and SCALEPACK[33] were used for indexing and scaling of the data. The structure was solved by means of SIR97.[34] Refinement was done using Xtal3.4[35] program package and the crystallographic plot was prepared by ORTEP III.[36] Crystal structure was refined on $F$ values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were geometrically calculated and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina[37] weighting scheme was used.

The crystallographic data for compound **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary material with the deposition number: CCDC 298823. These data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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# Synthesis and separation of the atropisomers of 2-(5-benzo[*b*]fluorenyl)-2′-hydroxy-1,1′-binaphthyl and related compounds

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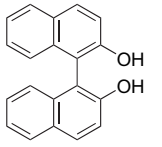
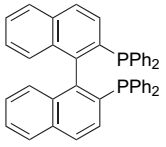
**Abstract**—Several *syn* and *anti* atropisomers of 2-(5-benzo[*b*]fluorenyl)-2′-hydroxy-1,1′-binaphthyl and related compounds were synthesized from 1,1′-binaphthyl-2,2′-diol (BINOL). It was possible to separate the *syn* and *anti* atropisomers by silica gel column chromatography. The *syn* atropisomers are potential hetero-bidentate ligands for complex formation with metals. By starting from enantiomerically pure (*R*)-(+)-BINOL and (*S*)-(−)-BINOL, four optically active *syn* atropisomers and two *anti* atropisomers with high enantiomeric purity were obtained. The structures of two *syn* atropisomers and one *anti* atropisomer were established by X-ray structure analyses.


## 1. Introduction

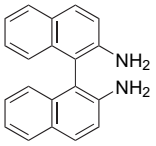
The use of 1,1′-binaphthyl-2,2′-diol (BINOL, **1**) as a chiral reagent for asymmetric synthesis has been extensively investigated.[1–5] The design and synthesis of modified BINOLs as ligands in asymmetric catalysis continue to be an area of intense current interest.[6,7] Conversion of both hydroxyl groups of BINOL to two other identical functional groups capable of coordinating with metals has led to the discovery of many useful $C_2$-symmetrical homo-bidentate ligands, including BINAP (**2**),[8–10] BINAM (**3**),[11] and 2,2′-bis(2-indenyl)-binaphthyl (**4**).[12]



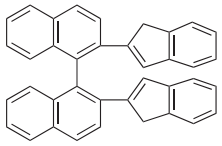
BINOL, **1**



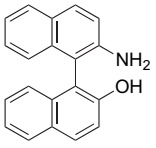
BINAP, **2**



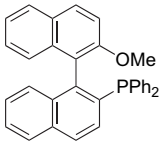
BINAM, **3**


**4**

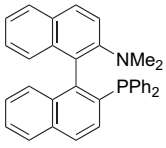
Conversion of only one of the two hydroxyl groups to a different functional group or conversion of both hydroxyl groups to two different functional groups to form hetero-bidentate binaphthyls, such as NOBIN (**5**),[13–17] MOP (**6**),[18–20] and MAP (**7**),[21] has also been investigated.[22] The barriers of rotation around the carbon–carbon single bond connecting the two C1 carbons of these 2,2′-di-substituted binaphthyls are high,[1–5,23,24] giving stability to the chiral configuration even at high temperature and allowing the molecules to be used in a variety of synthetic applications.



NOBIN, **5**



MOP, **6**



MAP, **7**

We recently reported an efficient synthetic pathway using ethynylarenes to produce the benzannulated enediynyl alcohols for subsequent cascade transformations to 5-aryl-11*H*-benzo[*b*]fluorenes.[25] This synthetic method was adopted for the preparation of structurally distorted 4,5-diarylphenanthrenes[26,27] and the atropisomers of 1,2-bis[5-(11*H*-benzo-[*b*]fluorenyl)]benzenes and related compounds.[28] We now report an additional application of this synthetic method using 2-ethynyl-2′-methoxy-1,1′-binaphthyl (**13**), prepared from BINOL (Scheme 1), as the starting ethynylarene for the synthesis of 2-(5-benzo[*b*]fluorenyl)-2′-hydroxy-1,1′-binaphthyl and related compounds.

*Keywords*: 2-(5-Benzo[*b*]fluorenyl)-2′-hydroxy-1,1′-binaphthyls; Atropisomers; Benzannulated enyne-allenes; Cascade biradical cyclization.
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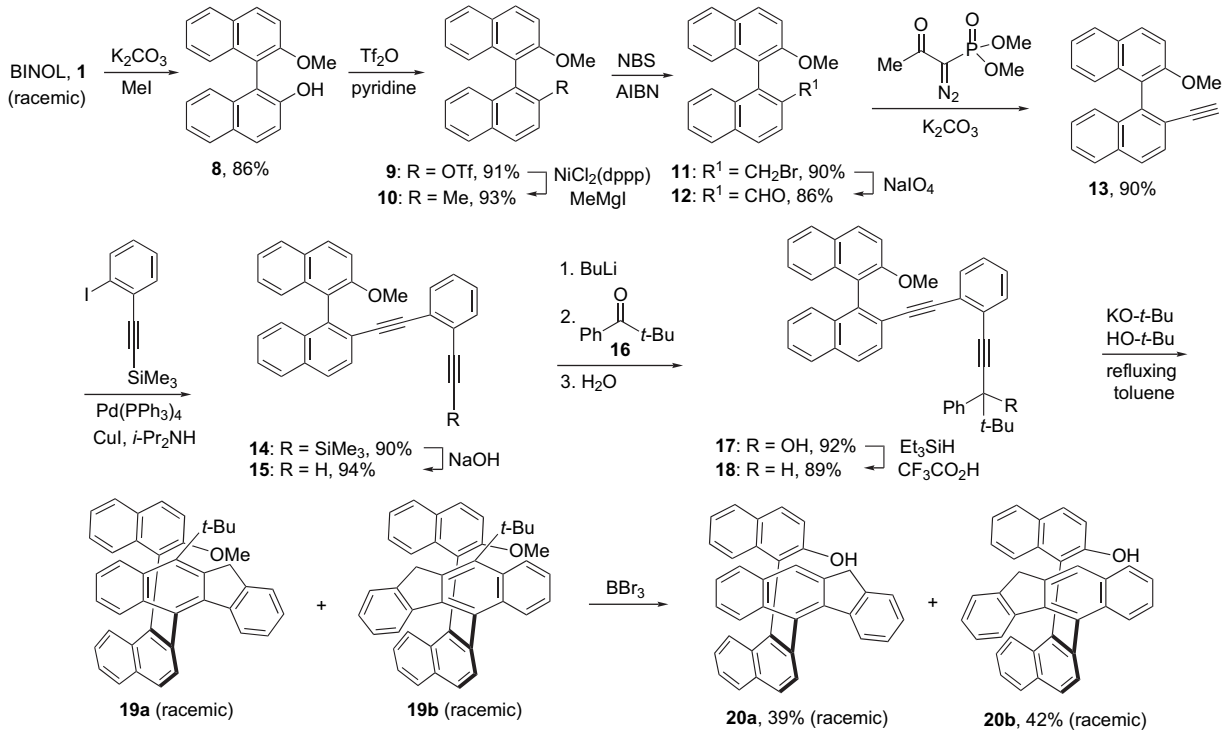


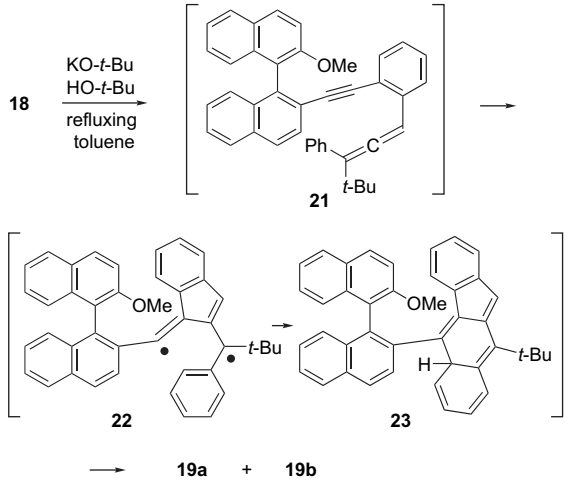

**Scheme 1**.

## 2. Results and discussion

Racemic BINOL was converted to 2-hydroxy-2′-methoxy-1,1′-binaphthyl (**8**)[29] for the subsequent transformation to the corresponding triflate **9**[30] as reported previously. The $NiCl_2$(dppp)-catalyzed (dppp=$Ph_2PCH_2CH_2CH_2PPh_2$) cross-coupling reaction[31,32] between **9** and methylmagnesium iodide led to 2-methoxy-2′-methyl-1,1′-binaphthyl (**10**),[33] which was brominated to give 2-(bromomethyl)-2′-methoxy-1,1′-binaphthyl (**11**).[34,35] Oxidation of **11** with $NaIO_4$[36] then produced 2-formyl-2′-methoxy-1,1′-binaphthyl (**12**).[37,38] Treatment of **12** with dimethyl (1-diazo-2-oxopropyl)phosphonate in the presence of potassium carbonate[39] then gave the requisite 2-ethynyl-2′-methoxy-1,1′-binaphthyl (**13**). Attempts to convert **9** to **13** directly by the Sonogashira reaction with (trimethylsilyl)ethyne followed by desilylation were unsuccessful. However, the Sonogashira reaction between **13** and 1-iodo-2-[(trimethylsilyl)ethynyl]benzene[40] furnished **14**, which was then desilylated to produce the benzannulated enediyne **15**.

Condensation between **15** and pivalophenone (**16**) gave the benzannulated enediynyl alcohol **17** as an essentially 1:1 mixture of two diastereomers. Reduction of **17** with triethylsilane in the presence of trifluoroacetic acid then led to the benzannulated enediyne **18**. Treatment of **18** with potassium *tert*-butoxide in refluxing toluene for 5 h then produced an essentially 1:1 mixture of the two atropisomers of 2-(5-benzo[*b*]fluorenyl)-2′-methoxy-1,1′-binaphthyl, the *syn* atropisomer **19a** (racemic) with the methoxyl group and the five-membered ring of the benzo[*b*]fluorenyl moiety *syn* to each other and the corresponding *anti* atropisomer **19b** (racemic). An AB quartet $^1$H NMR signals attributable to the methylene hydrogens of **19a** occurred at $\delta$ 4.44 ($J$=21.7 Hz) and 4.36 ($J$=21.8 Hz), whereas those attributable to **19b** occurred upfield at $\delta$ 4.00 ($J$=21.0 Hz) and 3.89 ($J$=21.0 Hz). On the other hand, the $^1$H NMR signal of the methoxyl group of **19b** at $\delta$ 3.20 is downfield from that of **19a** at $\delta$ 2.58.

Presumably, the transformation from **18** to **19a** and **19b** involved an initial 1,3-prototropic rearrangement to form the benzannulated enyne-allene **21** as proposed previously (Scheme 2).[25] A subsequent Schmittel cyclization reaction[41–44] then generated biradical **22** for an intramolecular radical–radical coupling to produce **23** and, after a second prototropic rearrangement, **19a** and **19b**.




**Scheme 2**.

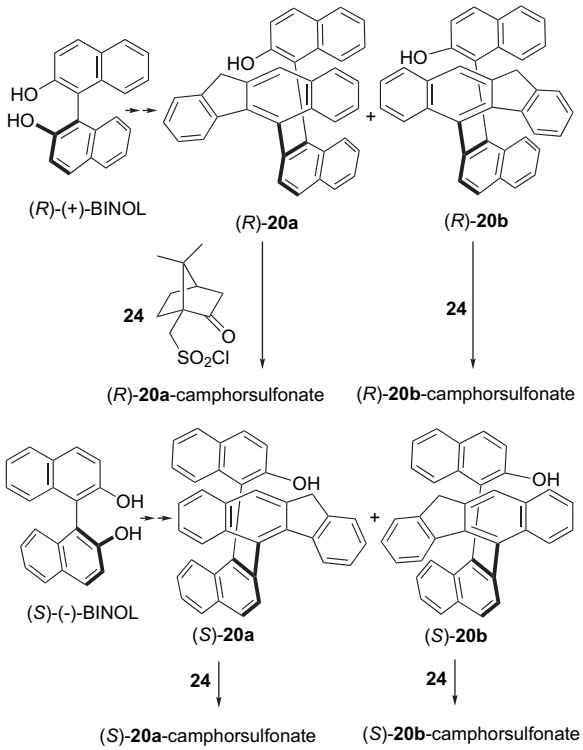
Compared to the dianion of **4** in which the indenyl anions possess a $C_2$ symmetry and the two faces are homotopic, the 5-benzo[*b*]fluorenyl substituent in **19a** and **19b** lacks

such a symmetry element and its two faces are heterotopic, making it possible to form the two atropisomers **19a** and **19b**. Treatment of the mixture of **19a** and **19b** with $BBr_3$ for demethylation then produced the corresponding *syn* atropisomer of 2-(5-benzo[*b*]fluorenyl)-2′-hydroxy-1,1′-binaphthyl (**20a**, racemic) and the corresponding *anti* atropisomer **20b** (racemic) also as a 1:1 mixture. The *tert*-butyl group was also removed under the reaction conditions. Presumably, the loss of the *tert*-butyl group occurred because of the presence of trace amount of acid in the reaction mixture, which protonated the C10 carbon of the benzofluorenyl substituent followed by the loss of a *tert*-butyl cation as observed in other aromatic systems.[45–48] It was possible to separate **20a** and **20b** by silica gel chromatography and to obtain single crystals of these two atropisomers for X-ray structure analyses.

The X-ray structures of **20a** and **20b** (Fig. 1) revealed that the benzofluorenyl substituent is essentially perpendicular to the central naphthyl ring onto which it is attached, and the other naphthyl ring bearing the hydroxyl group is also essentially perpendicular to the central naphthyl ring. The fact that **20a** and **20b** could be separated as atropisomers indicates that the rates of rotation around the carbon–carbon single bond connecting the C2 carbon of the binaphthyl system and the C5 carbon of the benzo[*b*]fluorenyl substituent and around the C1–C1′ single bond are slow at room temperature. Heating **20a** and **20b** in refluxing toluene (110 °C) for 5 h showed no interconversion between the two atropisomers. The AB quartet $^1$H NMR signals of the methylene hydrogens of **20a** occurred at $\delta$ 4.14 ($J$=22.2 Hz) and 4.08 ($J$=21.6 Hz), downfield from those of **20b** at $\delta$ 3.87 ($J$=21.6 Hz) and 3.68 ($J$=21.6 Hz).

By starting from enantiomerically pure (*R*)-(+)-BINOL with $[\alpha]_D^{25}$ +36.1 (*c* 1, THF) to prepare (*R*)-(+)-**15** with $[\alpha]_D^{25}$ +102 (*c* 0.90, THF) for condensation with **16**, the synthetic sequence led to (*R*)-**20a** and (*R*)-**20b**, which were separated by silica gel chromatography and were found to exhibit specific rotations of $[\alpha]_D^{25}$ +124 (*c* 0.53, THF) and $[\alpha]_D^{25}$ +44.4 (*c* 0.49, THF), respectively (Scheme 3). Similarly, by starting from (*S*)-(−)-BINOL with $[\alpha]_D^{25}$ −36.8 (*c* 1, THF) to prepare (*S*)-(−)-**15** with $[\alpha]_D^{25}$ −102 (*c* 1.1, THF), (*S*)-**20a** with $[\alpha]_D^{25}$ −126 (*c* 0.76, THF), and (*S*)-**20b** with $[\alpha]_D^{25}$ −44.9 (*c* 0.72, THF) were produced.

The four corresponding sulfonic esters, derived from the reactions of (*R*)-**20a**, (*R*)-**20b**, (*S*)-**20a**, and (*S*)-**20b** with




**Scheme 3**.

(1*S*)-(+)-10-camphorsulfonyl chloride (**24**), were found to be of high diastereomeric purity (>99% de) by $^1$H NMR analysis of the methyl signals recorded on a 600 MHz NMR spectrometer. The $^1$H NMR signals of the two methyl groups in (*R*)-**20a**-camphorsulfonate occurred at $\delta$ 0.82 and 0.51, clearly separated from those of (*S*)-**20a**-camphorsulfonate at $\delta$ 0.84 and 0.49, from those of (*R*)-**20b**-camphorsulfonate at $\delta$ 0.88 and 0.57, and from those of (*S*)-**20b**-camphorsulfonate at $\delta$ 0.85 and 0.66. The noise levels of the $^1$H NMR spectra of these four camphorsulfonates were low, allowing the $^{13}$C-satellites (0.55% each) of the methyl signals to be clearly discerned. As a result, it was possible to detect the presence of minute quantities (0.55%) of the three other isomers. For example, in the case of (*R*)-**20a**-camphorsulfonate, the $^{13}$C-satellites of the most upfield shift methyl signal occurred at $\delta$ 0.62 and 0.41 with peak heights significantly taller than any other signals that could be attributed to the methyl groups of the three other isomers at $\delta$ 0.49, 0.57, and 0.66. The ability to

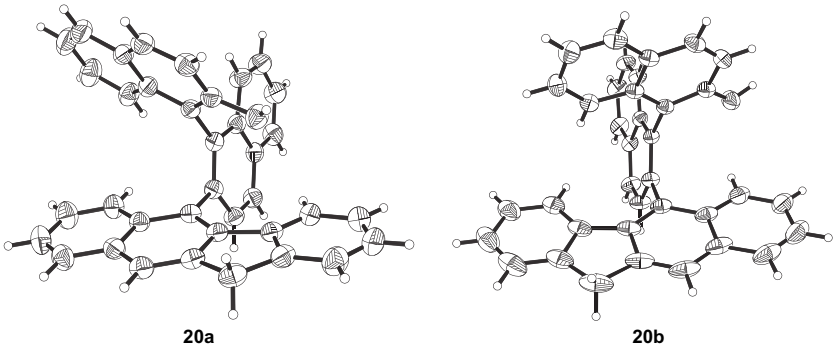
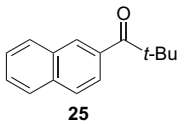
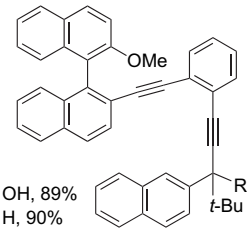
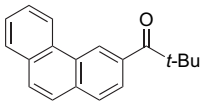
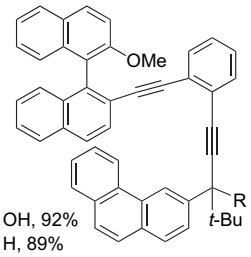



**Figure 1**. X-ray structures of the *syn* atropisomer **20a** and the *anti* atropisomer **20b**.

**Table 1**. Synthesis of benzannulated enediynyl alcohols and enediynes

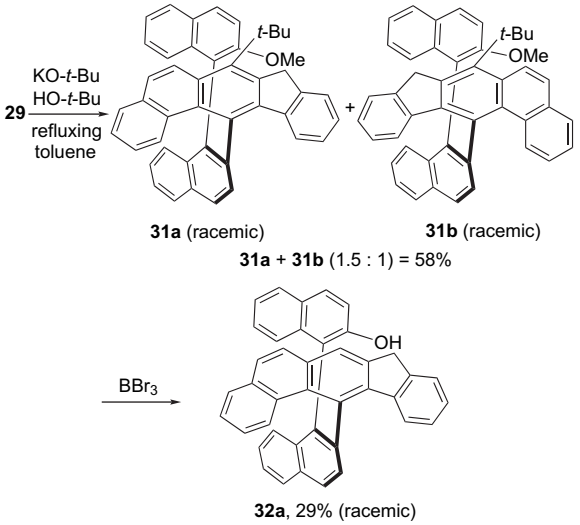
| Aryl ketones | Enediynyl alcohols and enediynes |
|---|---|
|  **25** |  **27**: R = OH, 89%<br>**29**: R = H, 90% |
|  **26** |  **28**: R = OH, 92%<br>**30**: R = H, 89% |

achieve high optical purity also suggests that no rotation occurred around the C1–C1′ single bond during the entire synthetic sequence.

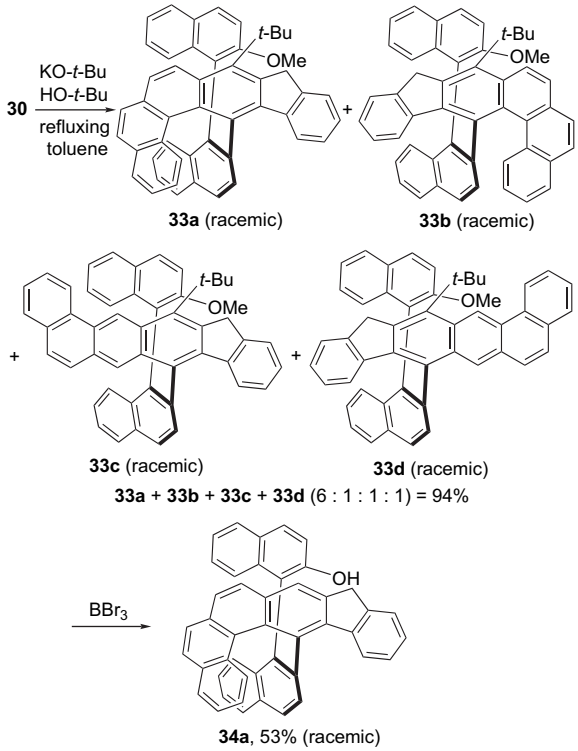
Similarly, the use of aryl ketone **25**, readily prepared from coupling between 2-naphthoyl chloride and *tert*-butylcopper in quantitative yield,[28,49] for condensation with **15** produced enediynyl alcohol **27** (Table 1). The use of aryl ketone **26**, likewise prepared by treatment of 3-phenanthrenecarboxylic acid[50] with thionyl chloride followed by *tert*-butylcopper (95% yield), for condensation with **15** produced **28**. Subsequent reduction of **27** and **28** with triethylsilane in the presence of trifluoroacetic acid then provided the benzannulated enediynes **29** and **30**, respectively. Treatment of **29** with potassium *tert*-butoxide in refluxing toluene for 5 h furnished the *syn* atropisomer **31a** and the *anti* atropisomer **31b** in a 1.5:1 ratio (Scheme 4). It is worth noting that the intramolecular radical–radical coupling reaction of the biradical derived from **29** involved only the α-position of the naphthyl ring originated from aryl ketone **25** to produce **31a** and **31b** as observed previously.[28] Attacking the β-position to form the corresponding indeno-fused anthracene derivatives did not appear to occur. The higher reactivity of the α-position than the β-position of naphthalene in the homolytic addition may be responsible for the regioselectivity.[51,52]

The $^1$H NMR signals of the methylene hydrogens of **31a** occurred as an overlapping singlet at $\delta$ 4.40, whereas those of **31b** occurred upfield as an AB quartet at $\delta$ 3.83 ($J$=20.5 Hz) and 3.54 ($J$=21.3 Hz), similar to those of **19b**. On the other hand, the $^1$H NMR signal of the methoxyl hydrogens of **31b** occurred at $\delta$ 2.44, downfield from that of **31a** at $\delta$ 2.29. A single crystal of **31a** suitable for X-ray structure analysis was obtained by recrystallization of the mixture from a mixture of methylene chloride/hexanes solution. Because of non-bonded steric interactions, the indeno-fused phenanthrene moiety in **31a** is non-planar with the phenanthrene unit showing a bend in the direction away from the 2-methoxynaphthyl ring system. Treatment of a mixture of **31a** and **31b** with $BBr_3$ for demethylation allowed the separation of **32a** from the resulting mixture by silica gel chromatography.

Treatment of **30** with potassium *tert*-butoxide in refluxing toluene for 5 h produced a more complex mixture of products with the $^1$H NMR spectrum showing four sets of methylene AB quartets in an approximately 6:1:1:1 ratio with the major AB quartet signals attributable to **33a** occurred at $\delta$ 4.51 ($J$=21.5 Hz) and 4.42 ($J$=21.0 Hz) (Scheme 5). The other three methylene AB quartets occurred between $\delta$ 4.60 and 3.91 could be tentatively attributed to **33b**, **33c**, and **33d**. As in the case of **31a** and **31b**, attacking the C4 carbon of the phenanthryl system originated from aryl ketone



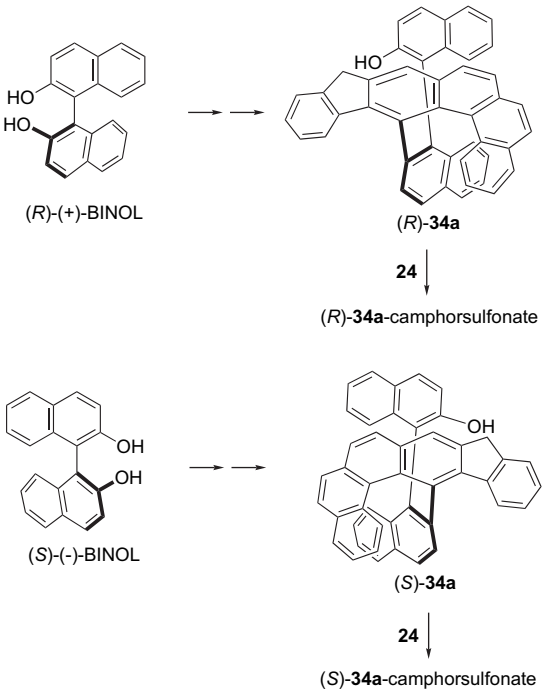

**Scheme 4**.




**Scheme 5**.

**26** during the intramolecular radical–radical coupling reaction could lead to **33a** and **33b**, whereas attacking the C2 carbon of the phenanthryl system could account for the formation of **33c** and **33d**. Treatment of the mixture with $BBr_3$ allowed the isolation of the *syn* atropisomer **34a** by silica gel chromatography.

Optically active (*R*)-**34a** with $[\alpha]_D^{20}$ −735 (*c* 1.2, THF) and (*S*)-**34a** with $[\alpha]_D^{20}$ +722 (*c* 0.92, THF) were also prepared from (*R*)-(+)-BINOL and (*S*)-(−)-BINOL, respectively (Scheme 6). The $^1H$ NMR spectra of the corresponding sulfonic esters, (*R*)-**34a**-camphorsulfonate and (*S*)-**34a**-camphorsulfonate, showed that these two binaphthyl derivatives were also of high diastereomeric purity (>97% de).




**Scheme 6**.

## 3. Conclusion

A synthetic pathway leading to the atropisomers of 2-(5-benzo[*b*]fluorenyl)-2′-hydroxy-1,1′-binaphthyl and related compounds was developed. The structures of *syn* atropisomers **20a** and **31a** and *anti* atropisomer **20b** were established by X-ray structure analyses. The presence of a hydroxyl group and a benzo[*b*]fluorenyl or a related group in these 2,2′-disubstituted 1,1′-binaphthyls could allow the formation of useful complexes with metals. The enantiomerically pure *syn* atropisomers, (*R*)-**20a**, (*S*)-**20a**, (*R*)-**34a**, and (*S*)-**34a**, hold potential as hetero-bidentate ligands for asymmetric catalysis.

## 4. Experimental

### 4.1. General

All reactions were conducted in oven-dried (120 °C) glassware under a nitrogen atmosphere. Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl prior to use. (*R*)-(+)-BINOL with $[\alpha]_D^{25}$ +36.1 (*c* 1, THF), (*S*)-(−)-BINOL with $[\alpha]_D^{25}$ −36.8 (*c* 1, THF), *n*-butyllithium (1.6 M) in hexanes, *tert*-butyllithium (1.7 M) in pentane, triethylsilane, trifluoroacetic acid, potassium *tert*-butoxide (1.0 M) in 2-methyl-2-propanol, 1-bromo-2-[(trimethylsilyl)ethynyl]benzene, $Pd(PPh_3)_4$, copper(I) iodide, $CuBr\cdot SMe_2$, diisopropylamine, pivalophenone (**16**), 2-naphthoyl chloride, boron tribromide, and (1*S*)-(+)-10-camphorsulfonyl chloride (**24**) with $[\alpha]_D^{22}$ +33 (*c* 1, $CHCl_3$) were purchased from chemical suppliers and were used as received. Compounds **8**[29] and **9**[30] were prepared according to the reported procedures. The $NiCl_2$(dppp)-catalyzed (dppp=$Ph_2PCH_2CH_2CH_2PPh_2$) cross-coupling reaction[31,32] between **9** and methylmagnesium iodide was employed for the synthesis of **10**[33] in 93% yield. Bromination of **10** with NBS produced **11**[34,35] in 90% yield. The subsequent oxidation of **11** with $NaIO_4$[36] then furnished **12**[37,38] in 86% yield. 1-Iodo-2-[(trimethylsilyl)ethynyl]benzene[40] was prepared by treatment of 1-bromo-2-[(trimethylsilyl)-ethynyl]benzene in THF with *n*-butyllithium at −78° C followed by iodine. Aryl ketone **25** was prepared in quantitative yield by coupling of 2-naphthoyl chloride with *tert*-butylcopper as described previously.[28,49] Aryl ketone **26** (95% yield) was likewise prepared by treatment of 3-phenanthrenecarboxylic acid with thionyl chloride followed by *tert*-butylcopper. 3-Phenanthrenecarboxylic acid was prepared from commercially available 3-acetylphenanthrene as reported previously.[50] $^1H$ (270 MHz) and $^{13}C$ (67.9 MHz) NMR spectra were recorded in $CDCl_3$ using $CHCl_3$ ($^1H$ $\delta$ 7.26) and $CDCl_3$ ($^{13}C$ $\delta$ 77.0) as internal standards unless otherwise indicated for those recorded on a 600 MHz NMR spectrometer.

**4.1.1. 2-Ethynyl-2′-methoxy-1,1′-binaphthyl (13).** To a solution of 0.420 g (1.35 mmol) of **12** and 0.373 g of potassium carbonate in 20 mL of anhydrous methanol was added 0.311 g (1.62 mmol) of dimethyl (1-diazo-2-oxopropyl)-phosphonate,[39] and the reaction mixture was stirred at room temperature for 24 h. The analysis of the reaction mixture by TLC indicated that **12** was completely consumed at this stage. The reaction mixture was then diluted with diethyl ether, washed with a 5% aqueous sodium bicarbonate solution, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/25% $CH_2Cl_2$ in hexanes) afforded 0.376 g of **13** (1.22 mmol, 90%) as a white solid: IR 3282, 1508, 1262, 1082 $cm^{-1}$; $^1H$ $\delta$ 8.01 (1H, d, *J*=8.9 Hz), 7.93–7.86 (3H, m), 7.72 (1H, d, *J*=8.4 Hz), 7.51–7.44 (2H, m), 7.37–7.19 (4H, m), 7.02 (1H, d, *J*=8.7 Hz), 3.80 (3H, s), 2.76 (1H, s); $^{13}C$ $\delta$ 154.8, 138.8, 133.6, 133.3, 132.7, 129.8, 129.0, 128.0, 127.9, 127.7, 126.59, 126.54, 126.48, 125.0, 123.6, 121.5, 120.6, 114.0, 83.3, 79.8, 57.0; MS *m*/*z* 331 ($MNa^+$), 239, 204; HRMS calcd for $C_{23}H_{16}ONa$ ($MNa^+$) 331.1099, found 331.1096.

Enantiomerically pure (*R*)-**13** with $[\alpha]_D^{25}$ +48.6 (*c* 1.2, THF) and (*S*)-**13** with $[\alpha]_D^{25}$ −49.5 (*c* 1.3, THF) were prepared from (*R*)-(+)-BINOL and (*S*)-(−)-BINOL, respectively.

**4.1.2. 2-Methoxy-2′-[2-[(trimethylsilyl)ethynyl]phenyl]-ethynyl-1,1′-binaphthyl (14).** To a mixture of 1-iodo-2-[(trimethylsilyl)ethynyl]benzene (0.126 g, 0.813 mmol),[40]

$Pd(PPh_3)_4$ (0.104 g, 0.090 mmol), and copper(I) iodide (0.052 g, 0.272 mmol) in 10 mL of toluene was added via cannula a solution of 0.209 g of **13** (0.679 mmol) in 3 mL of diisopropylamine. After 13 h of stirring at 70 °C, 20 mL of a saturated ammonium chloride solution and 20 mL of diethyl ether were added. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/25% methylene chloride in hexanes) afforded 0.292 g of **14** (0.608 mmol, 90%) as a white solid: IR 2157, 1249, 865 $cm^{-1}$; $^1H$ $\delta$ 8.04 (1H, d, $J$=9.1 Hz), 7.96–7.89 (3H, m), 7.80 (1H, d, $J$=8.4 Hz), 7.52–7.45 (2H, m), 7.37–7.27 (4H, m), 7.23 (1H, td, $J$=6.7, 1.2 Hz), 7.13 (1H, d, $J$=7.9 Hz), 7.07 (1H, td, $J$=7.3, 1.2 Hz), 6.98 (1H, td, $J$=7.7, 1.4 Hz), 6.24 (1H, dd, $J$=7.9, 1.4 Hz), 3.80 (3H, s), 0.32 (9H, s); $^{13}C$ $\delta$ 155.0, 138.3, 133.8, 133.1, 132.8, 131.92, 131.85, 129.7, 129.0, 128.5, 128.1, 127.84, 127.77, 127.63, 127.3, 126.5, 126.4, 126.1, 125.4, 124.6, 123.6, 121.92, 121.85, 103.5, 98.2, 93.8, 91.5, 57.0, 0.1.

**4.1.3. 2-(2-Ethynylphenyl)ethynyl-2′-methoxy-1,1′-binaphthyl (15).** To 0.292 g (0.608 mmol) of **14** in 10 mL of diethyl ether were added 4 mL of a 10% sodium hydroxide solution and 10 mL of methanol. After 30 min of stirring at room temperature, the organic solvent was removed in vacuo, and 20 mL of water and 20 mL of diethyl ether were added to the residue. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/25% methylene chloride in hexanes) afforded 0.232 g of **15** (0.569 mmol, 94%) as a white solid: IR 3282, 2205, 1507, 1267, 1082 $cm^{-1}$; $^1H$ $\delta$ 8.02 (1H, d, $J$=8.9 Hz), 7.95–7.88 (3H, m), 7.82 (1H, d, $J$=8.4 Hz), 7.50–7.43 (2H, m), 7.38–7.20 (5H, m), 7.15–7.08 (3H, m), 6.82–6.78 (1H, m), 3.77 (3H, s), 2.67 (1H, s); $^{13}C$ $\delta$ 155.0, 138.1, 134.1, 133.2, 132.9, 132.1, 131.9, 129.7, 129.06, 128.96, 128.1, 127.8, 127.7, 127.4, 126.5, 125.5, 123.9, 123.5, 121.9, 121.7, 114.2, 93.7, 90.9, 81.5, 80.8, 57.0; MS $m/z$ 431 ($MNa^+$), 381; HRMS calcd for $C_{31}H_{20}ONa$ ($MNa^+$) 431.1412, found 431.1409.

Enantiomerically pure (*R*)-**15** with $[\alpha]_D^{25}$ +102 (*c* 0.90, THF) and (*S*)-**15** with $[\alpha]_D^{25}$ −102 (*c* 1.1, THF) were prepared from (*R*)-(+)-BINOL and (*S*)-(−)-BINOL, respectively.

**4.1.4. Benzannulated enediynyl alcohol 17.** To 0.125 g (0.306 mmol) of **15** in 10 mL of anhydrous diethyl ether under a nitrogen atmosphere at 0 °C was added 0.20 mL of a 1.6 M solution of *n*-butyllithium (0.32 mmol) in hexanes. After 30 min of stirring, a solution of 0.055 g of **16** (0.340 mmol) in 4 mL of diethyl ether was introduced via cannula, and the reaction mixture was allowed to warm to room temperature. After an additional 2 h, 15 mL of water was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/5% diethyl ether in hexanes) provided 0.160 g (0.281 mmol, 92%) of **17** (essentially a 1:1 mixture of two diastereomers) as a yellow liquid: IR 3568, 1265 $cm^{-1}$; $^1H$ $\delta$ 8.03 (2H, dd, $J$=8.9, 1.5 Hz), 7.93–7.74 (8H, m), 7.59 (1H, d, $J$=7.2 Hz), 7.56 (1H, d, $J$=6.9 Hz), 7.51–7.44 (4H, m), 7.36–7.20 (16H, m), 7.17–7.06 (4H, m), 6.99 (2H, dt, $J$=7.6, 1.8 Hz), 6.26 (1H, dd, $J$=7.7, 0.7 Hz), 6.21 (1H, dd, $J$=7.7, 0.7 Hz), 3.78 and 3.76 (6H, two singlets), 2.46 and 2.43 (2H, two singlets), 1.13 (18H, s); $^{13}C$ $\delta$ 154.9, 142.1, 138.61, 138.57, 133.8, 133.1, 132.8, 132.2, 131.81, 131.77, 129.7, 129.1, 128.26, 128.20, 128.1, 127.84, 127.78, 127.68, 127.61, 127.4, 127.3, 127.1, 126.51, 125.9, 125.3, 124.2, 123.6, 122.1, 122.0, 121.6, 114.14, 114.07, 96.0, 93.6, 91.8, 91.7, 84.5, 79.5, 57.0, 56.9, 39.7, 25.6; MS $m/z$ 593 ($MNa^+$), 437, 381; HRMS calcd for $C_{42}H_{34}O_2Na$ ($MNa^+$) 593.2457, found 593.2454.

**4.1.5. Benzannulated enediyne 18.** To a mixture of **17** (0.162 g, 0.284 mmol) and triethylsilane (0.102 g, 0.875 mmol) in 15 mL of methylene chloride was added 0.20 mL of trifluoroacetic acid (0.309 g, 2.69 mmol). After 5 min of stirring at room temperature, 0.480 g of sodium carbonate (4.6 mmol) was added followed by 10 mL of water and 40 mL of diethyl ether. The organic layer was separated, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/10% $CH_2Cl_2$ in hexanes) provided 0.140 g (0.253 mmol, 89%) of **18** (essentially a 1:1 mixture of two diastereomers) as a yellow liquid: IR 2226, 1248, 726 $cm^{-1}$; $^1H$ $\delta$ 8.03 (2H, d, $J$=9.2 Hz), 7.92 (4H, d, $J$=7.9 Hz), 7.85 (2H, d, $J$=8.4 Hz), 7.55 (2H, d, $J$=8.4 Hz), 7.52–7.44 (9H, m), 7.37–7.20 (15H, m), 7.16–7.11 (2H, m), 7.07 (2H, td, $J$=7.7, 1.5 Hz), 6.95 (2H, t, $J$=7.7 Hz), 6.21 (2H, t, $J$=6.9 Hz), 3.79 (3H, s), 3.76 (3H, s), 3.70 (1H, s), 3.69 (1H, s), 1.09 (18H, s); $^{13}C$ $\delta$ 155.0, 139.2, 138.4, 133.8, 133.1, 132.8, 132.2, 131.8, 131.7, 129.8, 129.7, 129.1, 128.4, 128.0, 127.8, 127.6, 127.5, 127.3, 127.0, 126.7, 126.5, 126.4, 125.7, 125.4, 123.6, 122.1, 121.9, 114.1, 95.3, 93.2, 92.1, 82.4, 57.0, 50.6, 35.5, 27.8; MS $m/z$ 577 ($MNa^+$), 437, 381; HRMS calcd for $C_{42}H_{34}ONa$ ($MNa^+$) 577.2507, found 577.2506. The sample of **18** contains about 3% of residual hexanes as determined by the $^1H$ NMR spectrum.

**4.1.6. *syn* and *anti* Atropisomers of 2-(5-benzo[*b*]fluorenyl)-2′-hydroxy-1,1′-binaphthyl (20a and 20b).** To 0.089 g of **18** (0.161 mmol) in 5 mL of anhydrous toluene under a nitrogen atmosphere was added 0.2 mL of a 1.0 M solution of potassium *tert*-butoxide (0.2 mmol) in 2-methyl-2-propanol. The reaction mixture was then heated under reflux for 5 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of water and 30 mL of methylene chloride were introduced, and the organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/10% methylene chloride in hexanes) to provide 0.070 g of a 1:1 mixture of **19a** and **19b** (0.126 mmol, 78%) as a pale yellow solid. The AB quartet $^1H$ NMR signals of the methylene hydrogens of **19a** occurred at $\delta$ 4.44 ($J$=21.7 Hz) and 4.36 ($J$=21.8 Hz), whereas those of **19b** occurred at $\delta$ 4.00 ($J$=21.0 Hz) and 3.89 ($J$=21.0 Hz). The signal of the methoxyl hydrogens of **19a** occurred at $\delta$ 2.58 and that of **19b** occurred at $\delta$ 3.20.

To a mixture of **19a** and **19b** (0.073 g, 0.13 mmol) in 10 mL of methylene chloride was added dropwise 0.2 mL of boron

tribromide at 0 °C. The reaction mixture was stirred at 0 °C for 4 h before 10 mL of water and 20 mL of methylene chloride were introduced. The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/5% ethyl acetate in hexanes) to provide 0.024 g (0.050 mmol, 39%) of **20a** and 0.026 g (0.054 mmol, 42%) of **20b** as yellow solids. **20a**: $^1$H (600 MHz) $\delta$ 8.28 (1H, d, $J$=8.4 Hz), 8.16 (1H, d, $J$=7.8 Hz), 7.79 (1H, d, $J$=7.8 Hz), 7.77 (1H, s), 7.64 (1H, ddd, $J$=7.8, 6.6, 1.2 Hz), 7.57 (1H, d, $J$=7.2 Hz), 7.55 (1H, d, $J$=7.8 Hz), 7.52–7.50 (2H, m), 7.40–7.38 (2H, m), 7.35 (1H, d, $J$=7.8 Hz), 7.26 (1H, t, $J$=7.2 Hz), 7.20–7.14 (3H, m), 7.08 (1H, ddd, $J$=8.4, 6.6, 1.2 Hz), 7.03 (1H, t, $J$=7.8 Hz), 6.75 (1H, ddd, $J$=8.4, 6.6, 1.2 Hz), 6.69 (1H, d, $J$=9.0 Hz), 6.51 (1H, d, $J$=7.8 Hz), 4.82 (1H, s), 4.14 (1H, d, $J$=22.2 Hz), 4.08 (1H, d, $J$=21.6 Hz); $^{13}$C (150 MHz) $\delta$ 151.6, 144.5, 141.5, 140.5, 138.5, 137.3, 134.5, 133.54, 133.45, 132.3, 132.1, 131.6, 131.1, 130.0, 129.8, 129.5, 128.5, 128.4, 127.7, 127.4, 127.3, 127.2, 127.1, 126.9, 126.8, 126.7, 126.3, 125.9, 125.5, 125.1, 124.2, 123.0, 122.7, 121.5, 117.2, 116.6, 36.4; MS $m/z$ 484 ($M^+$), 313; HRMS calcd for $C_{37}H_{24}O$ 484.1827, found 484.1829. Recrystallization from a mixture of ethanol and methylene chloride produced a crystal suitable for X-ray structure analysis. **20b**: $^1$H (600 Hz) $\delta$ 8.29 (1H, d, $J$=8.4 Hz), 8.18 (1H, $J$=8.4 Hz), 7.92 (1H, dd, $J$=8.4, 0.6 Hz), 7.67 (1H, t, $J$=7.2 Hz), 7.59 (1H, d, $J$=7.8 Hz), 7.57 (1H, d, $J$=8.0 Hz), 7.56 (1H, s), 7.54 (1H, d, $J$=8.4 Hz), 7.47 (1H, t, $J$=7.2 Hz), 7.43 (1H, d, $J$=7.2 Hz), 7.36 (2H, t, $J$=7.8 Hz), 7.30 (1H, t, $J$=7.5 Hz), 7.25–7.23 (2H, m), 7.16 (1H, d, $J$=8.4 Hz), 7.10 (1H, t, $J$=7.8 Hz), 6.98 (1H, d, $J$=8.4 Hz), 6.84 (1H, t, $J$=7.5 Hz), 6.79 (1H, dd, $J$=9.0, 1.2 Hz), 6.22 (1H, t, $J$=7.5 Hz), 4.78 (1H, s), 3.87 (1H, d, $J$=21.6 Hz), 3.68 (1H, d, $J$=21.6 Hz); $^{13}$C (150 MHz) $\delta$ 150.6, 144.0, 141.6, 140.5, 138.7, 137.8, 133.6, 133.4, 133.1, 132.3, 132.2, 131.9, 131.6, 130.3, 129.3 (two carbons), 128.7, 128.1, 127.5, 127.3, 126.91, 126.86, 126.79, 126.5, 126.24, 126.21, 125.9, 125.0, 124.7, 124.5, 124.34, 124.32, 122.7, 122.5, 117.4, 117.1, 36.0; MS $m/z$ 484 ($M^+$), 215; HRMS calcd for $C_{37}H_{24}O$ 484.1827, found 484.1821. Recrystallization from a mixture of ethanol and methylene chloride produced a crystal suitable for X-ray structure analysis. The sample of **20b** contains about 5% of residual hexanes as determined by the $^1$H NMR spectrum.

Enantiomerically pure (*R*)-**20a** with $[\alpha]_D^{25}$ +124 (*c* 0.53, THF) and (*R*)-**20b** with $[\alpha]_D^{25}$ +44.4 (*c* 0.49, THF) were prepared from (*R*)-(+)-BINOL, whereas (*S*)-**20a** with $[\alpha]_D^{25}$ −126 (*c* 0.76, THF) and (*S*)-**20b** with $[\alpha]_D^{25}$ −44.9 (*c* 0.72, THF) were also prepared from (*S*)-(−)-BINOL.

**4.1.7. (*R*)-20a-Camphorsulfonate.** To 0.011 g of (*R*)-**20a** (0.023 mmol) and triethylamine (0.05 mL, 0.09 mmol) in 3 mL of anhydrous methylene chloride at 0 °C under a nitrogen atmosphere was added 0.031 g of (1*S*)-(+)-10-camphorsulfonyl chloride (**24**, 0.12 mmol). The reaction mixture was stirred at 0 °C for 3 h before 2 mL of a 10% aqueous sodium hydroxide solution was added. The reaction mixture was stirred for an additional 2 h. Water was added, and the reaction mixture was extracted with methylene chloride. The combined organic extracts were washed with brine and water, dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (silica gel/25% methylene chloride in hexanes) afforded 0.015 g of (*R*)-**20a**-camphorsulfonate (0.021 mmol, 91%) as a light yellow solid: IR 1739, 1366, 1218 cm$^{-1}$; $^1$H (600 Hz) $\delta$ 8.27 (1H, d, $J$=8.4 Hz), 8.15 (1H, d, $J$=8.4 Hz), 7.84 (1H, dd, $J$=8.4, 2.4 Hz), 7.71 (1H, s), 7.59 (1H, t, $J$=7.5 Hz), 7.55 (1H, d, $J$=8.4 Hz), 7.53–7.50 (2H, m), 7.48 (1H, d, $J$=8.4 Hz), 7.44 (1H, dd, $J$=9.0, 2.4 Hz), 7.39 (1H, t, $J$=7.5 Hz), 7.36 (1H, d, $J$=9.0 Hz), 7.29–7.26 (2H, m), 7.23 (1H, t, $J$=7.2 Hz), 7.20 (1H, t, $J$=8.4 Hz), 7.11 (1H, t, $J$=7.2 Hz), 7.02 (1H, td, $J$=8.4, 3.0 Hz), 6.99 (1H, d, $J$=8.4 Hz), 6.92 (1H, d, $J$=7.2 Hz), 6.58 (1H, t, $J$=7.8 Hz), 4.13 (1H, d, $J$=21.6 Hz), 4.03 (1H, d, $J$=21.0 Hz), 2.91 (1H, d, $J$=14.4 Hz), 2.22 (1H, d, $J$=18.0 Hz), 2.10 (1H, t, $J$=12.6 Hz), 1.97 (1H, d, $J$=14.4 Hz), 1.94 (1H, br t), 1.88–1.83 (1H, m), 1.79 (1H, d, $J$=18.6 Hz), 1.42–1.36 (1H, m), 0.82 (3H, s), 0.51 (3H, s); $^{13}$C (150 MHz) $\delta$ 213.5, 145.1, 144.0, 141.6, 140.9, 138.3, 137.8, 133.9, 133.11, 133.06, 132.7, 132.0, 131.9, 131.2, 130.9, 129.5, 129.2, 129.0, 128.4, 127.9, 127.7, 127.3, 127.1, 126.98, 126.96, 126.93, 126.73, 126.65, 126.3, 125.7, 125.3, 125.2, 124.7, 124.6, 123.7, 122.6, 121.1, 57.8, 48.7, 47.5, 42.7, 42.3, 36.4, 26.7, 24.9, 19.5, 19.4.

**4.1.8. (*S*)-20a-Camphorsulfonate.** The same procedure was repeated as described for (*R*)-**20a**-camphorsulfonate except that 0.014 g of (*S*)-**20a** (0.029 mmol) was used to afford 0.018 g of (*S*)-**20a**-camphorsulfonate (0.026 mmol, 90%) as a light yellow solid: IR 1739, 1366, 1217 cm$^{-1}$; $^1$H (600 MHz) $\delta$ 8.25 (1H, d, $J$=8.4 Hz), 8.14 (1H, d, $J$=8.4 Hz), 7.82 (1H, dd, $J$=7.8, 1.8 Hz), 7.72 (1H, s), 7.60–7.54 (3H, m), 7.52 (1H, d, $J$=7.2 Hz), 7.48 (1H, d, $J$=8.4 Hz), 7.44 (1H, d, $J$=8.4 Hz), 7.39 (1H, t, $J$=7.2 Hz), 7.36 (1H, d, $J$=8.4 Hz), 7.32 (1H, t, $J$=7.5 Hz), 7.26–7.19 (3H, m), 7.02 (1H, t, $J$=7.5 Hz), 7.00–6.95 (2H, m), 6.85 (1H, d, $J$=7.8 Hz), 6.49 (1H, t, $J$=7.5 Hz), 4.14 (1H, d, $J$=22.2 Hz), 4.05 (1H, d, $J$=21.6 Hz), 2.71 (1H, dd, $J$=15.0, 1.2 Hz), 2.31 (1H, dd, $J$=15.0, 1.2 Hz), 2.21 (1H, d, $J$=18.0 Hz), 1.97–1.92 (2H, m), 1.82 (1H, t, $J$=11 Hz), 1.76 (1H, d, $J$=18.6 Hz), 1.26–1.11 (2H, m), 0.84 (3H, s), 0.49 (3H, s); $^{13}$C (150 MHz) $\delta$ 213.3, 145.1, 144.1, 141.7, 140.9, 138.4, 137.8, 133.9, 133.2, 133.0, 132.6, 132.1, 131.8, 131.4, 130.7, 129.6, 129.2 (two carbons), 128.3, 127.9, 127.8, 127.6, 127.4, 127.0, 126.84, 126.81, 126.62, 126.60, 126.3, 125.8, 125.4, 125.0, 124.7, 124.6, 123.6, 122.6, 121.2, 57.8, 48.3, 47.3, 42.9, 42.2, 36.4, 26.7, 25.2, 19.7, 19.4.

**4.1.9. 1,1′-Binaphthyl 31a.** The same procedure was repeated as described for **19a** and **19b** except that 0.121 g (0.200 mmol) of **29** in 8 mL of anhydrous toluene was treated with 0.42 mL of a 1.0 M solution of potassium *tert*-butoxide (0.42 mmol) in 2-methyl-2-propanol, and the reaction mixture was heated under reflux for 5 h to afford 0.070 g of a mixture of **31a** and **31b** (**31a**:**31b**=1.5:1, 0.116 mmol, 58%) as a pale yellow solid. Recrystallization from a mixture of hexanes and methylene chloride produced a crystal of **31a** suitable for X-ray structure analysis. **31a**: $^1$H $\delta$ 8.41 (1H, d, $J$=8.7 Hz), 8.29 (1H, d, $J$=8.9 Hz), 8.13 (1H, d, $J$=8.2 Hz), 8.11 (1H, d, $J$=8.9 Hz), 7.70 (1H, d, $J$=9.7 Hz), 7.56–7.45 (2H, m), 7.34 (1H, d, $J$=8.6 Hz), 7.23–7.10 (5H, m), 6.95 (1H, t, $J$=8.4 Hz), 6.90–6.82 (2H, m), 6.75 (1H, d, $J$=9.4 Hz), 6.58 (1H, d, $J$=8.2 Hz), 6.48 (1H, d, $J$=9.2 Hz),

6.31 (1H, ddd, $J$=8.2, 6.7, 1.5 Hz), 5.94 (1H, d, $J$=8.7 Hz), 4.40 (2H, s), 2.29 (3H, s), 1.71 (9H, s); MS $m/z$ 604 ($M^+$), 547; HRMS calcd for $C_{46}H_{36}O$ 604.2766, found 604.2766.

The $^1$H NMR spectrum of the 1.5:1 mixture of **31a** and **31b** exhibited a set of AB quartet signals at $\delta$ 3.83 ($J$=20.5 Hz) and 3.54 ($J$=21.3 Hz) and a singlet at $\delta$ 2.44 attributable to the methylene hydrogens and methoxyl hydrogens of **31b**, respectively.

**4.1.10. 1,1′-Binaphthyl 32a.** To a mixture of **31a** and **31b** (0.058 g, 0.096 mmol) in 10 mL of methylene chloride was added dropwise 0.2 mL of boron tribromide at 0 °C. The reaction mixture was stirred at 0 °C for 6 h before 10 mL of water and 20 mL of methylene chloride were introduced. The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/5% ethyl acetate in hexanes) to provide 0.015 g (0.028 mmol, 29%) of **32a** as a yellow solid: $^1$H (600 MHz) $\delta$ 8.48 (2H, s), 8.25 (1H, d, $J$=8.4 Hz), 8.22 (1H, d, $J$=7.8 Hz), 7.74 (1H, s), 7.63 (1H, ddd, $J$=8.4, 7.2, 1.2 Hz), 7.60 (1H, d, $J$=7.2 Hz), 7.41 (1H, d, $J$=7.8 Hz), 7.31–7.24 (6H, m), 7.23 (1H, d, $J$=9.0 Hz), 7.173 (1H, d, $J$=8.4 Hz), 7.169 (1H, d, $J$=9.0 Hz), 7.06 (1H, ddd, $J$=8.4, 7.2, 1.2 Hz), 7.04 (1H, t, $J$=7.2 Hz), 6.78 (1H, ddd, $J$=7.8, 6.0, 1.8 Hz), 6.67 (1H, d, $J$=8.4 Hz), 6.52 (1H, d, $J$=9.0 Hz), 6.26–6.21 (2H, m), 4.32 (1H, s), 4.14 (1H, d, $J$=21.6 Hz), 4.06 (1H, d, $J$=21.0 Hz); MS $m/z$ 534 ($M^+$), 265; HRMS calcd for $C_{41}H_{26}O$ 534.1984, found 534.1970.

**4.1.11. 1,1′-Binaphthyl 34a.** The same procedure was repeated as described for **19a** and **19b** except that 0.087 g (0.133 mmol) of **30** in 5 mL of anhydrous toluene was treated with 0.30 mL of a 1.0 M solution of potassium *tert*-butoxide (0.30 mmol) in 2-methyl-2-propanol, and the reaction mixture was heated under reflux for 5 h to afford 0.082 g of a mixture of **33a**, **33b**, **33c**, and **33d** (**33a**:**33b**:**33c**:**33d**=6:1:1:1, 0.125 mmol, 94%) as a yellow solid. A dominant set of AB quartet $^1$H NMR signals at $\delta$ 4.51 ($J$=21.5 Hz) and 4.42 ($J$=21.0 Hz) attributable to **33a** along with three minor sets of AB quartet signals between $\delta$ 4.60 and 3.91 attributable to **33b–d** were also observed.

To a mixture of **33a**, **33b**, **33c**, and **33d** (0.039 g, 0.060 mmol) in 5 mL of methylene chloride was added dropwise 0.1 mL of boron tribromide at 0 °C. The reaction mixture was stirred at 0 °C for 2 h before 10 mL of water and 20 mL of methylene chloride were introduced. The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/5% ethyl acetate in hexanes) to provide 0.019 g (0.032 mmol, 53%) of **34a** as a yellow solid: IR 3541, 1517, 1141 cm$^{-1}$; $^1$H (600 MHz) $\delta$ 8.84 (1H, d, $J$=9.0 Hz), 8.60 (1H, d, $J$=8.4 Hz), 8.15 (1H, d, $J$=8.4 Hz), 7.93 (1H, d, $J$=8.4 Hz), 7.87 (1H, s), 7.61 (2H, t, $J$=6.9 Hz), 7.47 (1H, d, $J$=8.4 Hz), 7.43 (1H, d, $J$=7.8 Hz), 7.40 (1H, t, $J$=7.8 Hz), 7.39 (1H, d, $J$=7.8 Hz), 7.31 (1H, d, $J$=7.8 Hz), 7.29–7.27 (2H, m), 7.21 (1H, d, $J$=9.0 Hz), 7.04–6.99 (3H, m), 6.97 (1H, d, $J$=8.4 Hz), 6.96 (1H, d, $J$=8.4 Hz), 6.79 (1H, d, $J$=7.8 Hz), 6.73 (1H, d, $J$=8.4 Hz), 6.61 (1H, t, $J$=7.8 Hz), 6.37 (1H, d, $J$=8.4 Hz), 5.19 (1H, d, $J$=8.4 Hz), 4.24 (1H, d, $J$=21.6 Hz), 4.20 (1H, d, $J$=21.0 Hz), 3.98 (1H, s); $^{13}$C (150 MHz) $\delta$ 149.9, 145.0, 141.9, 141.4, 139.8, 139.5, 134.5, 134.0, 133.7, 133.1, 132.65, 132.63, 131.6, 131.5, 131.4, 130.9, 129.2, 128.6, 128.5, 128.0, 127.85, 127.80, 127.5, 127.30, 127.26, 127.22, 127.21, 127.0, 126.41, 126.38, 126.17, 126.10, 125.92, 125.84, 125.75, 125.4, 125.1, 124.5, 124.2, 123.3, 122.5, 121.7, 116.05, 116.01, 36.6; MS $m/z$ 584 ($M^+$), 315; HRMS calcd for $C_{45}H_{28}O$ 584.2140, found 584.2150. The sample of **34a** contains about 5–10% of residual hexanes as determined by the $^1$H NMR spectrum.

Enantiomerically pure (*R*)-**34a** with $[\alpha]_D^{20}$ −735 (*c* 1.2, THF) and (*S*)-**34a** with $[\alpha]_D^{20}$ +722 (*c* 0.92, THF) were prepared from (*R*)-(+)-BINOL and (*S*)-(−)-BINOL, respectively.

## 5. Supplementary information

Experimental procedures and spectroscopic data for (*R*)-**20b**-camphorsulfonate, (*S*)-**20b**-camphorsulfonate, **27–30**, (*R*)-**34a**-camphorsulfonate, and (*S*)-**34a**-camphorsulfonate; $^1$H and/or $^{13}$C NMR spectra of compounds **13–15**, **17**, **18**, **20a**, **20b**, (*R*)-**20a**-camphorsulfonate, (*R*)-**20b**-camphorsulfonate, (*S*)-**20a**-camphorsulfonate, (*S*)-**20b**-camphorsulfonate, **27–30**, **31a**, **32a**, **34a**, (*R*)-**34a**-camphorsulfonate, and (*S*)-**34a**-camphorsulfonate; the ORTEP drawings of the crystal structures of **20a**, **20b**, and **31a**; Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre. The CCDC nos. 292506, 292507, and 292508 have been assigned for the compounds **20a**, **20b**, and **31a**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.06.004.

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# First asymmetric synthesis of an acyclic β,β-dialkylated-γ-aminobutyric acid

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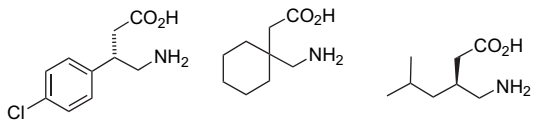
**Abstract**—Enantiomerically pure (*R*)-γ-amino-β-benzyl-β-methylbutyric acid, an acyclic β,β-dialkyl GABA derivative, is efficiently synthesised from (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate by a sequence based on benzylation, Arndt–Eistert homologation and nitrile reduction. Benzylation of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate using potassium carbonate under not strictly anhydrous conditions occurs diastereoselectively to afford (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*S*)-2-cyano-2-methyl-3-phenylpropanoate, the key chiral intermediate from which the desired γ-amino acid is obtained in five steps in 65% overall yield.


## 1. Introduction

In recent years the need for enantiomerically pure γ-amino acids has grown markedly, not only due to their biological activity[1] and presence in the structures of natural products with antitumoral activity,[2] but also because peptides consisting of optically active γ-amino acids can form stable helical structures in solution and in the solid state, even for peptides consisting of as few as four residues.[3]

γ-Aminobutyric acid (GABA), the simplest γ-amino acid, is the major inhibitory neurotransmitter in the central nervous system (CNS) of mammalians.[4] Its derivatives, in particular those analogues bearing substituents at the β-position, have been the subject of extensive investigations because of their potential biological activity.[1b] A number of these compounds are important therapeutic agents for a range of CNS disorders (Fig. 1).




(*R*)-Baclofen, **1** Gabapentin, **2** (*S*)-Pregabalin, **3**

**Figure 1**. Structures of (*R*)-Baclofen, Gabapentin and (*S*)-Pregabalin.

For instance, γ-amino-β-(4-chlorophenyl)butyric acid, or Baclofen (**1**), was introduced in 1973 for the therapy of muscle spasticity and is still the prototype of a selective $GABA_BR$ agonist.[5] Although the desired biological activity is known to reside in the (*R*)-enantiomer,[6] Baclofen is therapeutically commercialised (Lioresal® and Baclon®) as a racemate for the treatment of multiple sclerosis and cerebral palsy.

Gabapentin (**2**), a β,β-disubstituted GABA analogue, has been commercialised by Pfizer under the name Neurontin®. Gabapentin is used for the treatment of cerebral diseases such us epilepsy, faintness, hypokinesis and cranial traumas.[7] Furthermore, to date it is the only drug specifically licenced for the treatment of neuropathic pain. This compound shows few, if any, toxic side effects at clinically relevant doses. Moreover, a Gabapentin-lactam is neuroprotective in retinal ischaemia.[8]

(*S*)-γ-Amino-β-isobutylbutyric acid, or Pregabalin (**3**), is another β-substituted GABA analogue. Like Gabapentin this compound has anticonvulsant, anxiolytic-like and analgesic properties but it displays more potent and robust activity than Gabapentin in preclinical models for epilepsy, neuropathic pain and anxiety.[9]

A careful search in Scifinder® database showed that among the several hundred scientific studies on β-substituted GABA analogues that have been published in the last 10 years, not one deals with the stereoselective preparation of acyclic β,β-dialkylated γ-aminobutyric acids. Thus, we wish to report here the development of a new, efficient and concise methodology for the asymmetric synthesis of this

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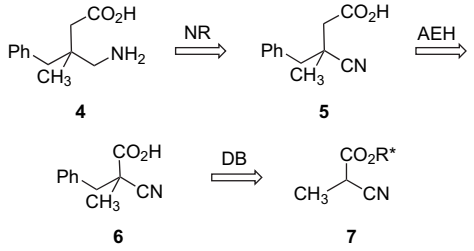
kind of γ-amino acid from chiral α-cyanoesters. As a model to establish the synthetic methodology, the preparation of enantiomerically pure (*R*)-γ-amino-β-benzyl-β-methylbutyric acid was selected. This route started from the 2-cyanopropanoate derived from the commercially available chiral alcohol (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol, known as (−)-Oppolzer's alcohol.[10]

## 2. Results and discussion

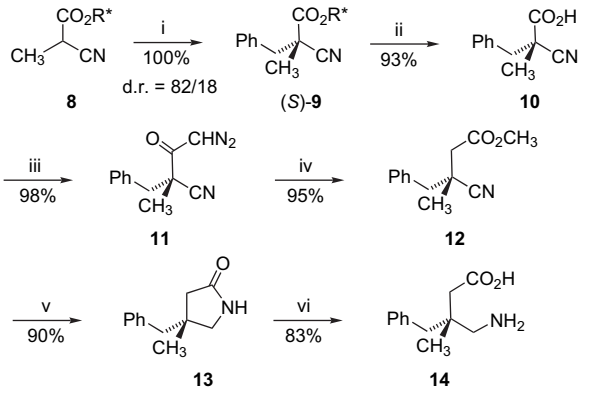
According to the retrosynthetic analysis shown in Scheme 1, we envisaged that the aminomethyl moiety in the target compound could be obtained by nitrile reduction (NR) of 3-cyano-3-methyl-4-phenylbutyrate and the carboxymethyl moiety could be obtained by Arndt–Eistert homologation[11] (AEH) of 2-cyano-2-methyl-3-phenylpropanoate. Enantiomerically pure 2-cyano-2-methyl-3-phenylpropanoate can be obtained by diastereoselective α-benzylation (DB) of a chiral 2-cyanopropanoate.




**Scheme 1**. Retrosynthetic steps to (*R*)-γ-amino-β-benzyl-β-methylbutyric acid from chiral cyanopropanoates.

In a previous paper,[12] we described how the diastereoselective α-benzylation of 2-cyanopropanoate **8**, yielded (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate **9** in 96% yield as a mixture of diastereoisomers (*S*/*R*=91/9). This reaction was performed using LDA as the base in an anhydrous medium and in the presence of HMPA.[13] As the reported p$K_a$ value of methyl α-cyanoacetate is about 13,[14] we reasoned that the α-benzylation reaction could be promoted by weaker bases than LDA. Such bases would not require the use of strictly anhydrous reaction conditions and harmful reagents. In this context the use of potassium carbonate as a base was tested. To our delight, treatment of a solution of 2-cyanopropanoate **8** and benzyl bromide in acetone with potassium carbonate at room temperature cleanly afforded compound **9** in quantitative yield as a mixture of diastereoisomers. A diastereomeric ratio of 82/18 was determined by $^1$H NMR spectroscopy of the crude reaction mixture. The major diastereoisomer (*S*)-**9** could be easily isolated in satisfactory yield by recrystallisation from methanol. Although the diastereoselectivity decreased slightly, these new reaction conditions are safer and more convenient for large-scale work.[15]

(*R*)-γ-Amino-β-benzyl-β-methylbutyric acid (**14**) was efficiently prepared from chiral 2-cyanopropanoate **8** by the six-step procedure outlined in Scheme 2. After benzylation the isolated cyanoacetate (*S*)-**9** was hydrolysed with 2 N potassium hydroxide in methanol to afford cyanoacid **10** in 93% yield. This compound was then subjected to the corresponding homologation process.




**Scheme 2**. Reagents and conditions: (i) $K_2CO_3$, BnBr, acetone; (ii) KOH, MeOH, Δ; (iii) $ClCO_2{}^tBu$, NMM, THF, −20 °C, then dry $CH_2N_2$ in ether; (iv) AgBzO, $Et_3N$, MeOH, THF; (v) $H_2$, Ni (Ra), $NH_3$/MeOH, 35 °C; (vi) HCl, Δ.

Arndt–Eistert reaction is the most important and most commonly used procedure for converting a carboxylic acid into its acid or ester homologue with one extra carbon in only two steps.[16] The synthesis of sterically hindered diazoketones is often inefficient or even impossible to achieve using standard procedures.[17] However, we tested the acylation of diazomethane using acyl chlorides or mixed anhydrides as activated carboxylic acid derivatives. Firstly, the α-cyanoacyl chloride obtained from **10** and thionyl chloride was treated with an excess of a dry ethereal solution of diazomethane.[18] This reaction yielded a mixture of the desired diazoketone **11**, with a quaternary α-carbon atom, and the methyl ester derived from **10** in a 3/1 ratio. Diazoketone **11** was a stable solid that could be isolated by column chromatography without noticeable degradation. The partial success of the aforementioned procedure is clearly due to the hydrolysis of the highly activated acid chloride under the reaction conditions and subsequent esterification with diazomethane. Alternatively, cyanoacid **10** was converted to a mixed anhydride using isobutyl chloroformate in the presence of *N*-methylmorpholine at low temperature. Subsequent addition of a dry ethereal solution of diazomethane gave rise to diazoketone **11** in 98% yield, which was sufficiently pure to be used in the next step without purification.

Wolff rearrangement[19] of diazoketone **11** to methyl ester **12** was achieved using the procedure described by Savithri et al.[20] This approach involved the addition of a catalytic amount of silver benzoate in triethylamine to a homogeneous solution of compound **11** and methanol in THF. Although it has recently been suggested[17] that the silver-catalysed Wolff rearrangement tends to fail with sterically hindered diazoketones, we cleanly obtained β-cyanoester **12** in 95% yield. Alternatively, we found that the triethylamine and silver benzoate-catalysed Wolff rearrangement of **11** also proceeded at 70 °C in a mixture of dioxane and water to give the corresponding β-cyanoacid in 90% yield. The configurational stability in the silver-catalysed Wolff rearrangement was assessed by $^1$H NMR using Eu(hfc)$_3$. The addition of 0.2 equiv of the lanthanide shift reagent, sufficient to cause splitting in a racemic mixture, to methyl ester **12** gave rise to only one set of signals. Accordingly, this compound was obtained with an enantiomeric excess greater than 96%.

Hydrogenation of the cyano group in compound **12** was cleanly achieved at atmospheric pressure and 35 °C using Raney nickel as catalyst and a solution of 0.5% ammonia in methanol as the solvent. This procedure afforded γ-lactam **13** in 90% yield. This compound was hydrolysed by heating under reflux with 5 N aqueous HCl. Elution of the γ-amino acid hydrochloride through an ion-exchange column yielded (*R*)-γ-amino-β-benzyl-β-methylbutyric acid (**14**) in 83% yield. It is worth mentioning that although compounds **12** and **13** were isolated for characterisation purposes by filtration through a short silica gel pad, the crude products were sufficiently pure to carry out the next step without any purification.

(*R*)-2-Cyano-2-methyl-3-phenylpropanoic acid *ent*-**9** can clearly be obtained by α-benzylation of the 2-cyanopropanoate derived from the commercially available (+)-Oppolzer's alcohol or, alternatively as described previously by us,[21] by diastereoselective α-methylation of the 3-phenyl-2-cyanopropanoate derived from (−)-Oppolzer's alcohol. Therefore, the methodology described here also constitutes a formal synthesis of (*S*)-γ-amino-β-benzyl-β-methylbutyric acid *ent*-**14**.

## 3. Conclusion

We have developed a concise, practical and efficient procedure for the asymmetric synthesis of (*R*)-γ-amino-β-benzyl-β-methylbutyric acid in overall high yield from a chiral ester derived from 2-cyanopropanoic acid and (1*S*,2*R*,4*R*)-(−)-10-dicyclohexylsulfamoylisoborneol as the chiral auxiliary. Highly diastereoselective α-alkylations of chiral 2-cyano esters derived from this alcohol have been achieved previously in our laboratory with good yields to afford a wide variety of enantiopure dialkylated cyanoacetates.[21] For this reason, we believe that the present synthetic methodology should find broad application in the stereoselective synthesis of other enantiopure β,β-dialkylated γ-amino acids of interest.

## 4. Experimental

### 4.1. General

All reagents for reactions were of analytical grade and were used as obtained from commercial sources. Compound **8** was obtained according to Ref. 12. Whenever possible the reactions were monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualised using UV light (254 nm) and phosphomolybdic acid. Column chromatography was performed using silica gel (Kieselgel 60, 230–400 mesh). Melting points were determined in open capillary tubes and are uncorrected. FTIR spectra of liquids were recorded as thin films on NaCl plates and FT-IR spectra of solids were recorded as Nujol dispersions on NaCl plates; $\nu_{max}$ values expressed in $cm^{-1}$ are given for the main absorption bands. Optical rotations were measured in a cell with a 10 cm path length and concentrations are given in g/100 mL. $^1H$ and $^{13}C$ NMR spectra were acquired at room temperature in the corresponding deuterated solvent at 300 and 75 MHz, respectively. The chemical shifts ($\delta$) are reported in parts per million and the coupling constants (*J*) in hertz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublets; m, multiplet; br s, broad singlet. Elemental analyses were performed using a C, H, N, S elemental analyser. High-resolution mass spectra were obtained using the $FAB^+$ ionisation mode with a 3-NBA matrix.

### 4.2. (1*S*,2*R*,4*R*)-10-Dicyclohexylsulfamoylisobornyl (*S*)-2-cyano-2-methyl-3-phenylpropanoate (*S*)-9

Potassium carbonate (3.45 g, 25 mmol) was added to a solution of (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl (*R*/*S*)-2-cyanopropanoate (**8**) (2.4 g, 5 mmol) and benzyl bromide (1.7 g, 10 mmol) in acetone (60 mL) and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the solid residue was washed with diethyl ether. The combined filtrates were concentrated in vacuo and the residue was dissolved in diethyl ether, washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 2.84 g (100% yield) of **9** as an 82/18 mixture of diastereoisomers. Silica gel column chromatography (first eluent: diethyl ether/hexanes 1/6, second eluent: diethyl ether/hexanes 1/2) and recrystallisation from methanol yielded 2.17 g (76% yield) of major diastereoisomer (*S*)-**9** as a white solid. The physical and spectroscopic data of the product are consistent with those reported previously.[12]

### 4.3. (*S*)-2-Cyano-2-methyl-3-phenylpropanoic acid 10

(*S*)-**9** (2.3 g, 4 mmol) was added to a solution of 2 N KOH in methanol (20 mL) and the reaction mixture was refluxed for 4 h. The resulting solution was cooled and the solvent was evaporated in vacuo. The residue was diluted in water (20 mL) and washed with diethyl ether (2×40 mL). The aqueous layer was then acidified and extracted with diethyl ether (2×40 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield 703 mg (93% yield) of **10** as a white solid. The physical and spectroscopic data of the product are consistent with those reported previously.[12]

### 4.4. (*S*)-2-Benzyl-4-diazo-2-methyl-3-oxobutyronitrile 11

*N*-Methylmorpholine (0.45 mL, 4.08 mmol) and isobutyl chloroformate (0.54 mL, 4.08 mmol) were consecutively added dropwise to a stirred solution of **10** (700 mg, 3.70 mmol) in dry THF (65 mL) at −20 °C under argon and stirred at this temperature for 30 min. An excess of dry ethereal solution of diazomethane in diethyl ether (ca. 10 mmol) was added and the solution was allowed to warm to room temperature. [*Caution*: diazomethane is a very harmful reagent and must be handled with extreme care in an efficient fume cupboard.][22] After 2 h, several drops of acetic acid were added to destroy the excess diazomethane and the solvent was removed by distillation in vacuo. The residue was dissolved in diethyl ether (40 mL) and the resulting organic solution was washed successively with 10% aqueous citric acid (20 mL), saturated aqueous sodium hydrogen carbonate (20 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield 772 mg (98% yield) of **11** as a white solid. Mp=72 °C; $[\alpha]_D^{26}$ 245.0 (*c* 2,

$CHCl_3$); IR (Nujol) 2236, 2118, 1639 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.54 (s, 3H), 2.91 (d, 1H, $J$= 13.5 Hz), 3.21 (d, 1H, $J$=13.5 Hz), 5.72 (s, 1H), 7.21–7.33 (m 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 23.3, 43.3, 48.1, 55.3, 121.3, 127.7, 128.5, 130.1, 134.4, 188.7. Elemental analysis calcd (%) for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.78; H, 5.11; N, 19.58.

### 4.5. (*R*)-Methyl 3-cyano-3-methyl-3-phenylbutyrate 12

A solution of silver benzoate (220 mg, 0.96 mmol) in triethylamine (3.09 mL, 22.1 mmol) was added dropwise to a stirred solution of **11** (717 mg, 3.36 mmol) and methanol (0.34 mL, 8.4 mmol) in dry THF (20 mL) at room temperature under argon. After 3 h, an additional solution of silver benzoate (110 mg, 0.48 mmol) in triethylamine (1.55 mL, 11.1 mmol) and methanol (0.17 mL, 4.2 mmol) was added. After 4 h, the solvent was evaporated under reduced pressure and the residue was dissolved in diethyl ether (40 mL). The organic layer was filtered, then washed successively with 1 N aqueous HCl, saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude methyl ester was purified by filtration through a short silica gel pad using a mixture of diethyl ether/hexane 1/1 as eluent to give 692 mg (95% yield) of **12** as an oil. $[\alpha]_D^{24}$ −5.2 (*c* 2, $CHCl_3$); IR (film) 2236, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.43 (s, 3H), 2.49 (d, 1H, $J$=15.8 Hz), 2.60 (d, 1H, $J$=15.8 Hz), 2.92 (d, 1H, $J$=13.6 Hz), 3.03 (d, 1H, $J$=13.6 Hz), 3.72 (s, 3H), 7.23–7.36 (m 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 24.0, 35.1, 41.7, 44.3, 51.8, 122.7, 127.4, 128.3, 130.2, 134.5, 169.4. HRMS ($FAB^+$) calcd for $C_{13}H_{16}NO_2$ ($MH^+$): 218.1181. Found: 218.1175.

### 4.6. (*R*)-4-Benzyl-4-methyl-2-pyrrolidinone 13

A solution of **12** (698 mg, 3.22 mmol) in 0.5% ammonia/methanol (40 mL) was hydrogenated at 35 °C and atmospheric pressure using 50% slurry of Raney® nickel 2800 in water (1.36 mL) as the catalyst. The reaction was monitored by TLC and, on completion (20 h), the catalyst was filtered off and washed with several portions of ethanol and dichloromethane. The filtrate was evaporated to dryness in vacuo and the residue was purified by filtration through a short silica gel pad using ethyl acetate as eluent to give 547 mg (90% yield) of **13** as a white solid. Mp=110 °C; $[\alpha]_D^{26}$ −12.7 (*c* 2, $CHCl_3$); IR (Nujol) 1681, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.12 (s, 3H), 2.01 (d, 1H, $J$=16.6 Hz), 2.36 (d, 1H, $J$=16.6 Hz), 2.73 (s, 2H), 2.98 (d, 1H, $J$=9.6 Hz), 3.32 (d, 1H, $J$=9.6 Hz), 6.31 (br s, 1H), 7.10–7.31 (m 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 25.4, 40.1, 43.5, 45.9, 53.3, 126.6, 128.2, 130.1, 137.6, 177.7. Elemental analysis calcd (%) for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.97; H, 8.15; N, 7.53.

### 4.7. (*R*)-γ-Amino-β-benzyl-β-methylbutyric acid 14

A mixture of compound **13** (473 mg, 2.5 mmol) and 5 N aqueous HCl (10 mL) was heated under reflux for 20 h. The solvent was removed under reduced pressure to give a residue, which was dissolved in water. The resulting aqueous solution was washed with dichloromethane and evaporated in vacuo to give the crude γ-amino acid hydrochloride. This material was submitted to ion-exchange column chromatography on Dowex 50Wx8 to afford 430 mg (83% yield) of **14** as a white solid. Mp=159 °C; $[\alpha]_D^{25}$ 13.6 (*c* 1, $H_2O$); IR (Nujol) 1624 $cm^{-1}$; $^1H$ NMR ($D_2O$, 300 MHz) $\delta$ 0.96 (s, 3H), 2.29 (s, 2H), 2.61 (d, 1H, $J$=13.3 Hz), 2.75 (d, 1H, $J$=13.3 Hz), 2.90 (d, 1H, $J$=13.1 Hz), 3.00 (d, 1H, $J$=13.1 Hz), 7.15–7.40 (m 5H); $^{13}C$ NMR ($D_2O$, 75 MHz) $\delta$ 22.0, 35.4, 44.8, 47.2, 48.4, 126.9, 128.4, 131.0, 136.9, 180.5. Elemental analysis calcd (%) for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.87; H, 8.33; N, 6.64.

## Acknowledgements

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# Spectroscopic characterization of the oxidation control of the *iso*-pentaphyrin/pentaphyrin system

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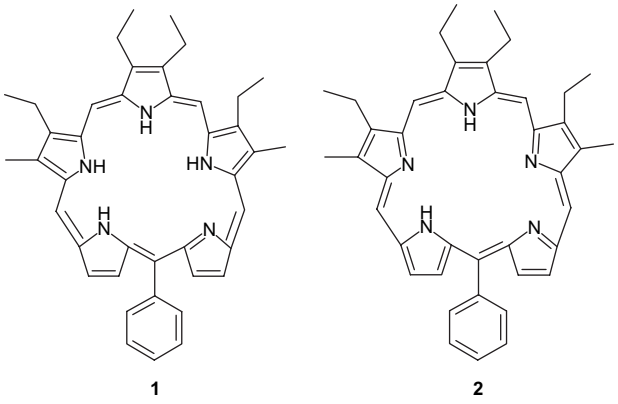
**Abstract**—We have recently described the synthesis of two porphyrogenic macrocycles: 20-phenyl-2,13-dimethyl-3,7,8,12-tetraethyl-[24]*iso*-pentaphyrin (**1**) and 20-phenyl-2,13-dimethyl-3,7,8,12-tetraethyl-[22]pentaphyrin (**2**) (*J. Med. Chem.* **2006**, *49*, 196–204). We found that the structure of *iso*-pentaphyrin is influenced by the acidity of the medium. By adjusting the TFA concentration, we solved two isomers of *iso*-pentaphyrin: **1** and **1A**. At high TFA concentration *iso*-pentaphyrin is present only as **1**, which is slowly oxidized into the aromatic macrocycle **2** upon exposure to air. The correlation between acidic conditions, isomer structures, and oxidation is discussed.


## 1. Introduction

The interest in expanded porphyrins has grown recently due to the enormous versatility of these particular molecules and their potential use in a variety of applications.[1–4] Besides the ability to coordinate with metal cations,[3,5–7]to act as receptor of anions ($F^-$, $Cl^-$, $N_3^-$)[8] and neutral molecules,[9] expanded porphyrins may be used as photosensitizers in photodynamic therapy.[10–14] Recently, it has been reported that some expanded porphyrins exist in different oxidation states.[4,15—18] This was observed also in our laboratory when we synthesized and isolated two new porphyrinoids belonging to the class of pentaphyrins[1.1.1.1.1]: *iso*-pentaphyrin nonaromatic 24 π-electrons (20-phenyl-2,13-dimethyl-3,7,8,12-tetraethyl-[24]*iso*-pentaphyrin) and the corresponding aromatic pentaphyrin 22 π-electrons (20-phenyl-2,13-dimethyl-3,7,8,12-tetraethyl-[22]pentaphyrin) (Fig. 1).[12] We found that the oxidation state of the newly synthesized pentaphyrins depended on the acidic conditions under which the molecules were equilibrated. Indeed, the isolated *iso*-pentaphyrin **1** could be oxidized in air to pentaphyrin **2** by treatment with a high concentration of trifluoroacetic acid. This behavior suggests that the protonation somehow favors the oxidation or different structures may be adopted by the *iso*-pentaphyrin under different acidic conditions. This last hypothesis is supported by the following observations:




1 2

**Figure 1**. Molecular structures of *iso*-pentaphyrin **1** (20-phenyl-2,13-dimethyl-3,7,8,12-tetraethyl-[24]*iso*-pentaphyrin) and pentaphyrin **2** (20-phenyl-2,13-dimethyl-3,7,8,12-tetraethyl-[22]pentaphyrin). *iso*-Pentaphyrin **1** is characterized by a 24 π-electron nonaromatic macrocycle, while pentaphyrin **2** is characterized by a 22 π-electron aromatic macrocycle.

1. Pentaphyrins[1.1.1.1.1] are a class of expanded porphyrins with five pyrrolic units connected to each other through five *meso* carbon atoms. The presence of five *meso* carbon bridges makes the molecule flexible; hence *iso*-pentaphyrin/pentaphyrin can adopt different conformations.
2. Nonplanarity and conformational structures of expanded porphyrins[19–22] are critically dependent on the nature of *meso* substituents and on the degree of protonation[23,24] and some of the expanded porphyrins display conformational changes in different acidic conditions.[24,25]
3. Conformational variations can affect the highest occupied (HOMO) and the lowest unoccupied (LUMO)

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molecular orbital levels of the macrocycle and thereby modulate their redox potentials (and light absorption properties).[26–32]

In order to investigate the relationship between acidic conditions and the structure adopted by **1**, we performed a series of NMR experiments at different TFA concentrations and the results obtained are reported in this paper.

## 2. Results and discussion

### 2.1. *iso*-Pentaphyrin in acidic media

As previously reported,[12] the synthesis of **1** was accomplished by a 3+2 approach, coupling tripyrrane diacid and dipyrromethane dialdehyde in degassed dichloromethane. The oxidation with DDQ yielding **1** was conducted under neutral conditions. This procedure allowed the isolation of **1** in 40% yield after HPLC. The $^1$H NMR spectrum of *iso*-pentaphyrin **1** as free base (spectra were recorded in $CDCl_3$ that had been stored over $NaHCO_3$) could not be resolved due to excessive line-broadening. As TFA was added to the sample solution, the $^1$H NMR spectrum of *iso*-pentaphyrin changed depending on the amount of acid added. When less than 2 equiv of TFA were added, the $^1$H NMR spectrum suggested the presence of *iso*-pentaphyrin at different degrees of protonation. In fact, NMR titration experiments showed that different protonated species are formed in solution as the acid concentration is increased. It was found that up to 2 equiv of added acid, there was no prevalence of a species in solution, as the different protonated forms co-existed in solution. When 2 equiv of TFA were added, the composition of this mixture changed in favor of a species, namely **1A** (Fig. 2), which became predominant, although it was not the only one, in solution. It is worth noting that similar behavior was also observed for other expanded porphyrins.[21,23] Compound **1A** remains the major species in solution until 40 equiv of TFA were added. By contrast, when an excess of TFA was added to the sample solution (50% TFA or pure $CF_3COOD$), a new spectrum was observed corresponding to only one species that formed slowly in solution (within 1 h). The LC–MS analysis showed that this species was *iso*-pentaphyrin and the NMR analysis demonstrated that its structure is attributed to **1** (Fig. 3). Interestingly, when the NMR solutions were first washed with 10% NaOH and water and then re-dissolved in $CDCl_3$+2 equiv of TFA, a spectrum that corresponded to **1A** was re-obtained. These findings suggest that **1A** and **1** are two different protonated states. When an excess of TFA is added to the solution, the data show that the transformation of *iso*-pentaphyrin **1A** into **1** is slow. This suggests that a structural rearrangement takes place rather than a protonation process. As described in the next sections, the NMR exchange peaks between **1A** and **1** were detectable and used for the final assignment of structure **1A**. Together, the data suggest that **1** and **1A** are different isomers of the same compound (*iso*-pentaphyrin) in equilibrium with each other.

### 2.2. *iso*-Pentaphyrin in 50% TFA/$CDCl_3$

As previously reported,[12] performing NMR experiments (Fig. 1S, Supplementary data) in $CDCl_3$+50% TFA, we assigned the $^1$H NMR peaks and resolved the structure of

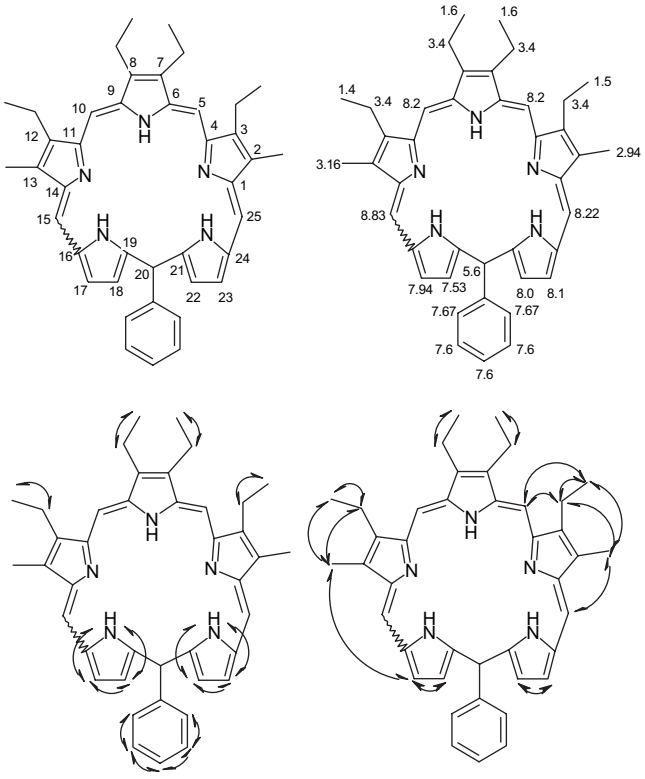


**Figure 2**. (top left) Structure of 20-Phenyl-2,13-dimethyl-3,7,8,12-tetraethyl-[24]*iso*-pentaphyrin as **1A** and with numbering; (top right) $^1$H NMR chemical shift values. The NH resonances in $CDCl_3$ containing 6% v/v TFA are detected at 2.1, 2.2, and 4.3 ppm; (bottom left) COSY correlations observed for **1A**; (bottom right) NOESY correlations observed for **1A**.

*iso*-pentaphyrin **1**. Its $^1$H NMR spectrum (Fig. 3) demonstrates the nonaromatic character of the compound, as there are no ring current effects on the chemical shift values. Moreover, chemically equivalent protons have the same chemical shift value indicating that the molecule adopts a symmetric structure under these conditions. When **1** is treated with a high quantity of acid, a slow reaction takes place in the NMR tube. After 20 h, a completely new $^1$H NMR spectrum was obtained, which clearly presented aromatic signature in the negative region (Fig. 4). The compound obtained was converted to its free base by treatment with 10% NaOH and washing with water. When analyzed by LC–MS and HRMS, it was found that *iso*-pentaphyrin **1** was subjected to oxidation (elimination of two protons). The HRMS, COSY, NOESY, and HSQC NMR experiments (Fig. 2S, Supplementary data) demonstrated that the new compound formed in this reaction was pentaphyrin **2**. It is worth noting that all the signals of the molecule undergo a shift due to the ring current effect. Comparing the $^1$H NMR spectrum of **1** (50% TFA in $CDCl_3$) with that of **2** (at 10% TFA in $CDCl_3$ because at 50% TFA one signal overlaps with that of TFA), the NHs experience a huge upfield shifting of the $\delta$ values from 12 and 11.6 ppm in **1** to −1.82, −3.3, and −3.4 ppm in **2**. The signals belonging to the alkylic chains in the periphery of the macrocycle are all shifted downfield as well as the β-pyrrolic protons and the *meso*-CH that are now detected at 9.8, 9.2 and 11.7, 11.5 ppm, respectively. It is important to emphasize that the $\delta$ values of the β-pyrrolic protons as well as the *meso*-

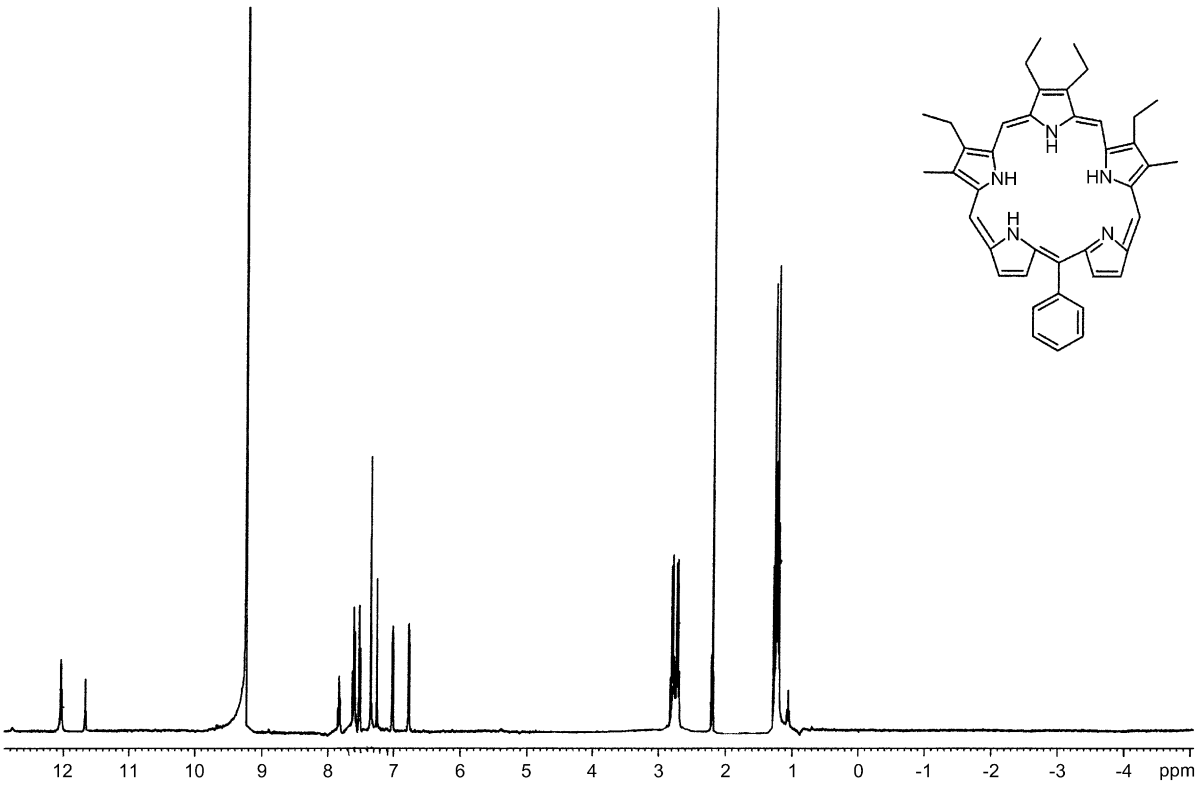


**Figure 3**. $^1$H NMR spectrum of *iso*-pentaphyrin **1** in 50% TFA in $CDCl_3$.

CH are shifted downfield. It demonstrates that in compound **2**, none of the β-unsubstituted pyrroles or the *meso*-CH is flipped inside the ring. The possibility of an inversion of the pyrrolic units by varying the acid concentration was investigated. In contrast with what has been observed for other expanded porphyrin[24] and in particular for

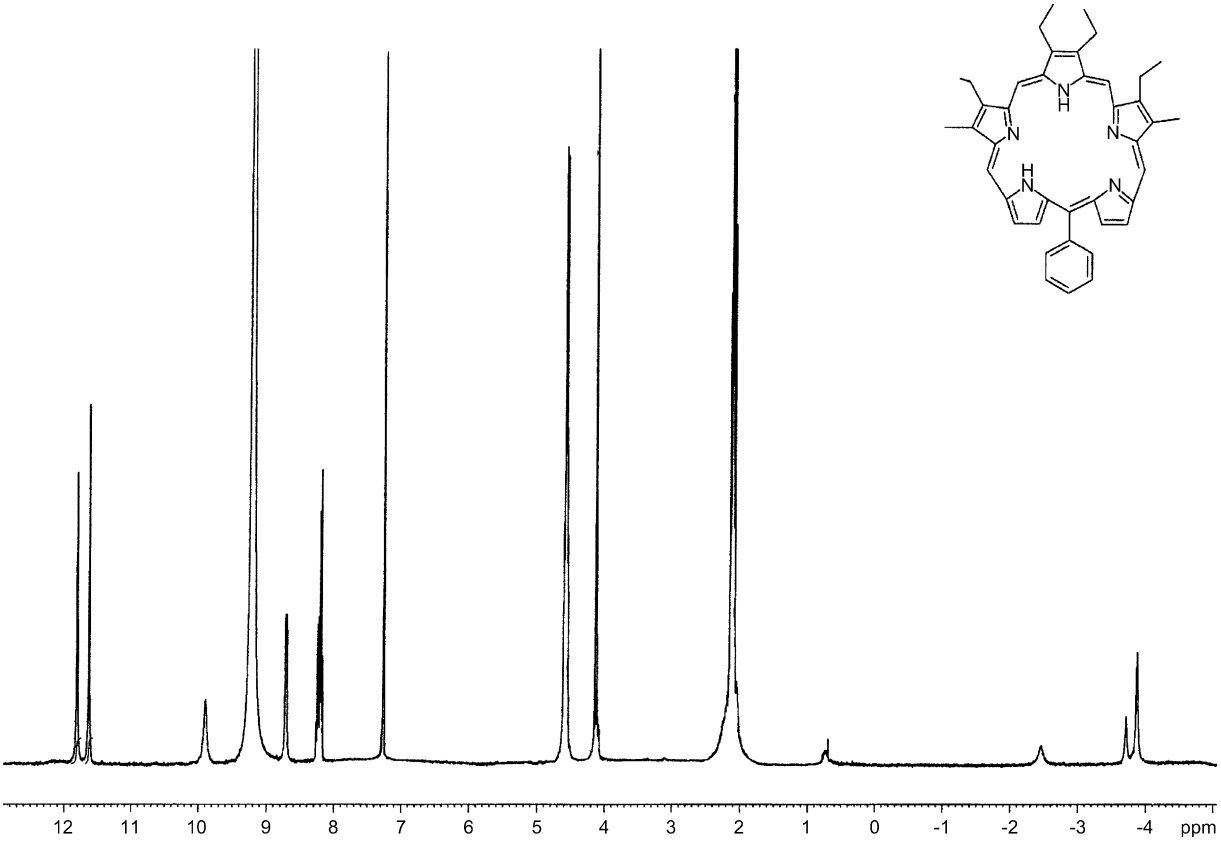


**Figure 4**. $^1$H NMR spectrum of pentaphyrin **2** in 50% TFA in $CDCl_3$.

[22]pentaphyrin[1.1.1.0.0],[23] the data show that [22]pentaphyrin[1.1.1.1.1] **2** does not invert the pyrrolic units at any of the concentrations of TFA studied.

### 2.3. *iso*-Pentaphyrin in $CDCl_3$ and 2 equiv of TFA

When *iso*-pentaphyrin is treated with 2 equiv of TFA, its $^1H$ NMR spectrum indicates the low degree of symmetry (large number of peaks) of the molecule and its nonaromatic character. The absence of a large ring current is indicated by the lack of characteristic upfield shifts of NH (no signals detected in the negative part of the spectrum), and downfield shifts of the *meso*-CH protons (no signals detected above 9 ppm). The structure of the prevalent species at 2 equiv TFA was determined by $^1H$, COSY, NOESY, and HSQC experiments that allowed the assignment of the peaks as depicted in Figure 2. The unexpected pattern of signal at 8.83 ppm (position 15), with no COSY or NOESY connectivity, and signal at 7.94 ppm (position 17), with a NOESY correlation with the methyl group at position 13, required more investigation. For this purpose, we performed an NMR experiment at 6% TFA. Under this condition *iso*-pentaphyrin is present as isomer **1A**. During the experimental time a fraction of **1A** was converted into **1**, although **1A** still remained as the predominant species. Because of this conversion chemical exchange (CE) cross-peaks were detected in the NOESY spectrum.[33] The signals at 8.1 and 7.94 ppm of **1A** exchanged with the signal at 7.00 ppm of **1**, which was unambiguously assigned to protons at positions 17 and 23. The position 17 in **1A** has been assigned to the proton at 7.94 ppm on the basis of its NOE pattern, and consequently the signal at 8.1 has been assigned to the β-pyrrolic proton at position 23. The signal at 6.74 ppm of **1** was unambiguously assigned to the protons at position 18 and 22. This signal is in chemical exchange with the signals at 8.00 and 7.53 ppm of **1A**. Therefore, these signals are the β-pyrrolic protons at position 18 and 22, respectively. Chemical exchange between **1A** and **1** could also be clearly observed for other signals. The NOE correlation between the proton at position 17 and the methyl group at position 13 as well as the absence of a spatial correlation between the protons at positions 15 and 17 might indicate that the *meso*-CH is pointing inside the ring of the macrocycle. This type of flipping, already invoked for a [22]pentaphyrin[1.1.1.0.0],[23] would introduce a severe deformation of the molecule that would account for the full lack of NMR signal equivalence recorded for this isomer. Moreover, the lack of NOE correlation between protons at position 18 and 20, 22 and 20 could indicate a rotation of this pyrrolic unit with the NH pointing toward proton at position 20. On going from isomer **1A** to isomer **1**, the signal at position 20 disappears and NMR signal equivalence is observed (Fig. 1S, supplementary data).

### 2.4. Oxidation behavior and acidic conditions

The acid concentration was found to be the key factor in tuning the oxidation state of the molecule. In fact, our experiments showed that when the concentration of acid is such that *iso*-pentaphyrin is present in solution as isomer **1A**, the oxidation reaction to **2** did not take place while it was quantitative in air when 50% of acid was used and *iso*-pentaphyrin was present as isomer **1**. This is a strong indication that also for this type of porphyrogenic macrocycles, the redox potential is highly influenced by the structure of the molecule and in this case the structure is controlled by the concentration of acid. It is reasonable to suppose that the highly distorted structure adopted by isomer **1A** requires a higher energetic jump to achieve the symmetric conformation required by **2**. The energetic expense becomes more accessible when the conformation of the *iso*-pentaphyrin is as close as possible to the conformation of the product **2**, i.e., when the *iso*-pentaphyrin is present as **1**.

## 3. Conclusion

*iso*-Pentaphyrin is a flexible molecule that exists in solution in different isomeric forms. The composition of the isomer solutions depends on the concentration of TFA. By carefully adjusting the TFA concentration, it was possible to obtain solve the structures of two isomers of *iso*-pentaphyrin: **1A** and **1**. The NMR patterns of both isomers are nonaromatic with no ring current effects on NH and *meso*-CH. The most relevant observation is that on going from isomer **1A** to isomer **1**, the molecule undergoes a spatial rearrangement corresponding to a change in symmetry. Isomer **1A** has low symmetry, which at high concentration of TFA flips to a molecule with higher symmetry **1**. This change in conformation, brought about by the concentration of acid in solution, has an important consequence on the chemical behavior of the *iso*-pentaphyrin. In fact, it has been observed that when the compound is present as **1A** its oxidation to **2** is not possible, while when it is present as **1** its further oxidation to **2** becomes quantitative in air.

## 4. Experimental

### 4.1. General

All compounds were used as received from the suppliers. Analytical LC–MS was conducted on a JASCO system using Alltima $C_{18}$ analytical column (5 μm particle size, flow: 1.0 ml/min). Absorbance was measured at 214 and 254 nm. Solvent system: A, 100% water; B, 100% acetonitrile; C, 0.5% TFA. Gradients of B were applied over 30 min unless otherwise stated. Mass spectra were recorded on a Perkin–Elmer Sciex API 165 equipped with a custom-made Electrospray Interface (ESI). Purifications were conducted on a BioCAD 'Vision' automated HPLC system (PerSeptive Biosystems, Inc.), supplied with a semi-preparative Alltima $C_{18}$ column (5 μm particle size, running at 4 ml/min). Solvent system: A, 100% water; B, 100% acetonitrile; C, 1% TFA. Gradients of acetonitrile (B) in (A) containing 10% of C were applied over 3 column volumes (CV). $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker 200 MHz, a Bruker AV-400 (400/100 MHz) or a Bruker DMX-600 (600/150 MHz) spectrometer. Chemical shifts are given in parts per million ($\delta$) relative to tetramethylsilane ($^1H$ NMR) as an internal standard or to the peak of the solvent used.

### 4.2. Synthesis

The [24]*iso*-pentaphyrin[1.1.1.1.1] **1** and the [22]pentaphyrin[1.1.1.1.1] **2** were synthesized and characterized as previously reported.[12]

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# Efficient synthesis of brominated tetrathiafulvalene (TTF) derivatives: solid-state structure and electrochemical behaviour

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**Abstract**—An efficient synthesis is reported for 4,5-dibromo-[1,3]dithiole-2-thione (**1**) and 4-bromo-1,3-dithiole-2-thione (**7**) by bromination of lithiated vinylene trithiocarbonate. Compound **1** acts as a convenient precursor to a number of asymmetric electron donors. This is exemplified by the formation of 4,5-dibromo-4′,5′-bis(2′-cyanoethylsulfanyl)TTF (**3**) by cross-coupling methodology and subsequent conversion into 4,5-dibromo-4′,5′-ethylenedithioTTF (**4**) by reaction with caesium hydroxide and 1,2-dibromoethane. The new donor 4,5-dibromo-4′,5′-ethylenedithiodiselenadithiafulvalene (**5**) was prepared by cross-coupling of **1** and 4,5-ethylenedithio-1,3-diselenol-2-one (**6**). The X-ray structures of **3** and **5** are reported.


## 1. Introduction

Within the field of molecular conductors, organosulfur and organoselenium donor molecules have been a major focus for research in the preparation of conductive molecular systems.[1] Tetrathiafulvalene (TTF) and its derivatives have played a leading role in the formation of charge-transfer complexes and radical ion salts since the planarity and high chemical stability of the radical cation favours the intermolecular delocalisation of charge carriers.[2] Studies have concentrated on the electrical and magnetic properties[3] but extend to include an examination of the role of intermolecular S···S attractions, polymorph formation and phase transitions. It is in this context that crystal engineering has emerged as a key topic.[4]

Close inter-stack S···S interactions increase the dimensionality in most TTF derivatives,[1] but the role played by intermolecular hydrogen bonding and interactions involving halogen atoms have gained increasing attention.[5] The addition of halogen substituents to TTF reduces the π-electron donating ability and this effect is additive with the increasing number of halogens on the TTF system.[5] The key motivation of this work was the study of new brominated derivatives and the role played by the halogen atoms in modifying the donating ability of the new donors.

## 2. Results and discussion

According to the literature,[6] reactions to obtain iodinated derivatives of TTF[7] have proven until recently difficult and even unreliable, but conversely the synthesis of brominated derivatives seemed to be more straightforward[8] although the proportion of monobrominated versus dibrominated derivatives seemed to be difficult to control. In the simplest reaction, direct bromination of the TTF leads to good yields of the monobrominated derivative, but treatment of the TTF core with more than 1 equiv of LDA produced a mixture of mono- and polybrominated derivatives, which proved difficult to separate and were recovered in very low yields.[9] In order to overcome this problem, the lithiation of vinylene trithiocarbonate followed by reaction with a series of brominating agents (e.g., *p*-toluenesulfonyl bromide[6] or 1,2-dibromotetrachloroethane[10]) has been attempted by various groups. However, these attempts[6] have been reported to yield a mixure of mono- and dibromo derivatives in comparatively low yields (25–30%). In our hand, the use of 1,2-dibromotetrachloroethane, which had been previously utilised to obtain **4** in good yields from direct lithiation and bromination of the parent ethylenedithioTTF,[8] produced a much more reliable reaction, allowing mono- or dibrominated derivatives to be selectively prepared in good yields (~80%). The extent of bromination could be controlled by adjusting the amount of lithiating agent in the mixture, i.e., reaction of vinylene trithiocarbonate with 1 equiv of LDA followed by treatment with 1,2-dibromotetrachloroethane produced exclusively the monobrominated derivative **7**, whereas reaction with 3 equiv of LDA led to the isolation of the dibrominated derivative **1** (Scheme 1).

There are numerous routes to functionalised TTFs,[11] although coupling (or cross-coupling) of two 1,3-2-thione (or dithiocarbonate) half-units, usually in the presence of a trialkyl phosphite is the most widespread. In order to ascertain the possibility of using **1** and **7** as building blocks in the

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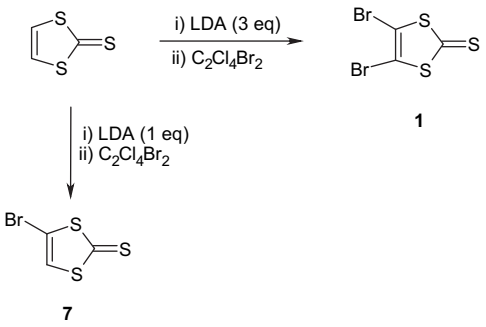


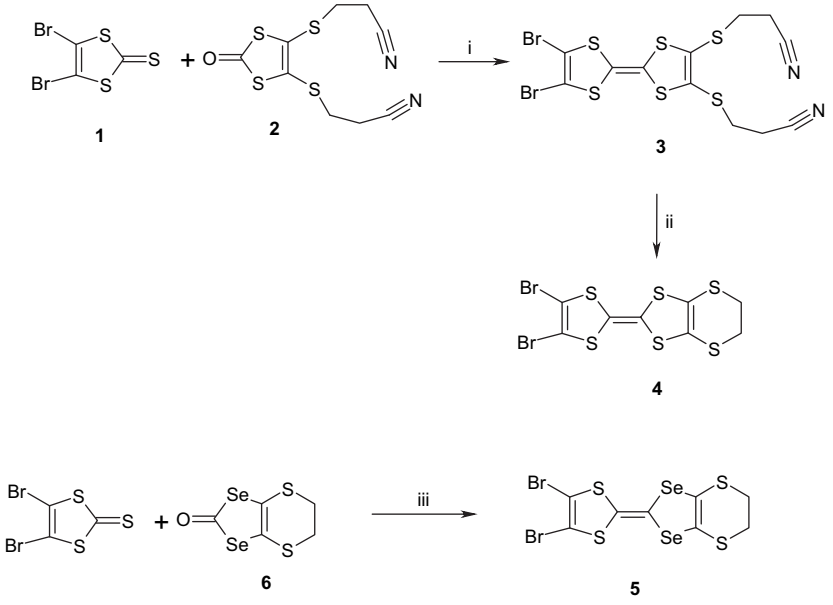

**Scheme 1**.

synthesis of brominated TTF derivatives, the synthesis of the known donor **4** and the new donor **5** was attempted.

Cross-coupling of **1** with **2** (Scheme 2) gave the TTF derivative **3** with no loss of bromine in good yields (60–70%). Removal of the cyanoethyl groups under Becher's conditions[12] generated the dithiolate species, which was trapped in situ with 1,2-dibromoethane to afford **4**.

In order to illustrate the application of this methodology to the synthesis of Se containing derivatives, **1** was cross-coupled with the selenium analogue **6** affording the new donor **5**, which was recovered in high yields by column chromatography.

In previous reports,[6] crystallisation of **3** from dichloromethane yielded a polymorph, which crystallised in the orthorhombic space group *Pbca*.† In our hands, a new polymorph, which crystallised in the orthorhombic space group $Pca2_1$ with one molecule in the asymmetric unit, was isolated




X-Ray crystal structures

| | 3 | 5 |
|---|---|---|
| **Empirical Formula** | $C_{12}H_8Br_2N_2S_6$ | $C_8H_4Br_2S_4Se_2$ |
| **T/K** | 180(2) | 293(2) |
| **λ/Å** | 0.71073 | 0.71073 |
| **Crystal system** | orthorhombic | monoclinic |
| **Space Group** | $Pca2_1$ | $P2_1/n$ |
| ***a*/Å** | 29.988(6) | 6.67520(10) |
| ***b*/Å** | 8.7474(17) | 8.1972(2) |
| ***c*/Å** | 6.9526(14) | 24.320(5) |
| α/° | 90 | 90 |
| β/° | 90 | 96.35(3) |
| γ/° | 90 | 90 |
| **V /Å$^3$** | 1823.8 (6) | 1322.5(3) |
| **μ /mm$^{-1}$** | 5.126 | 12.232 |
| **F(000)** | 1040 | 1016 |
| **θ range/°** | 3.80≤ θ ≤22.50 | 2.62≤θ ≤ 22.50 |
| **Reflections collected** | 8580 | 8910 |
| **Unique reflections** | 2084 | 1713 |
| **$R_1$ (I > 2σ(I))** | 0.0288 | 0.0635 |
| ***w*$R_2$ (all data)** | 0.0651 | 0.1266 |
| **Largest peak/hole eÅ$^{-3}$** | 0.71 and -0.34 | 0.95 and -0.85 |

**Scheme 2**. Reaction conditions: (i) $P(OEt)_3$, toluene, reflux; (ii) CsOH, THF–methanol, then dibromoethane; (iii) $P(OEt)_3$, toluene, reflux.

† Unit cell dimensions $a$=14.609(4) Å, $b$=11.607(4) Å, $c$=21.020(5) Å.

from acetonitrile. In this new polymorph, the planes of the rings form a pseudo-butterfly conformation along the long axis of the molecule (Figs. 1–3), with increased deviation from planarity ca. 35° compared to previously reported structures ca. 3°.[6]

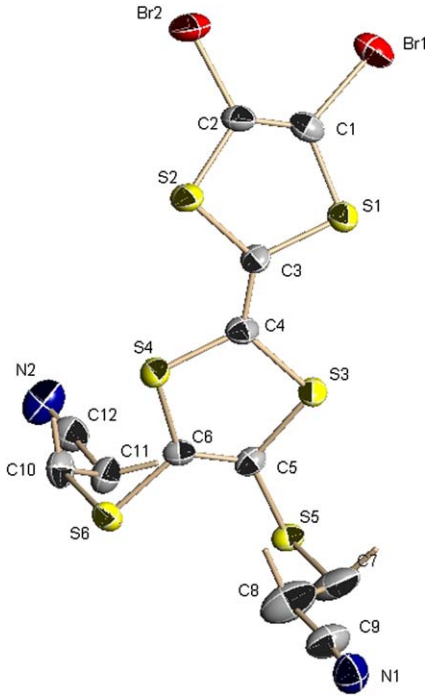



**Figure 1**. Asymmetric unit of **3** with numbering scheme.

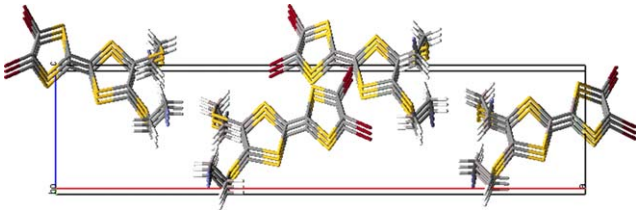


**Figure 2**. View of the stacks, approximately down the *b*-axis.

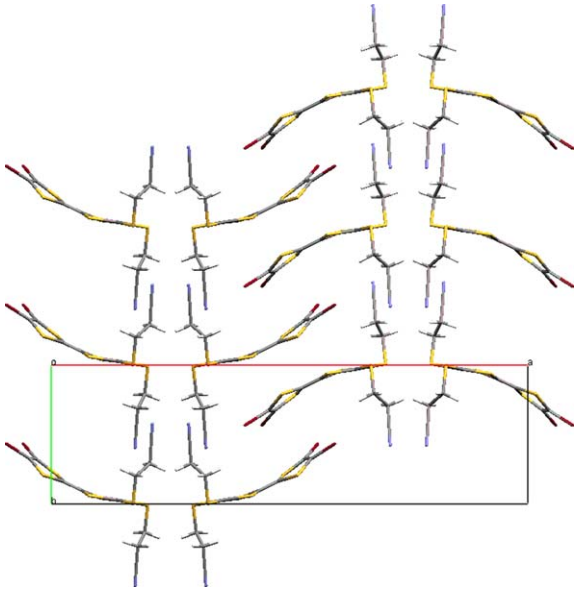


**Figure 3**. View perpendicular to the *ab* plane.

There are no contacts less than the sum of the van der Waals radii between the softer Br and S atoms, which are expected to contribute most significantly to dispersion forces. The shortest contact 3.873(3) Å is comparable with the sum of the van der Waals radii (~3.5 Å). In the current case the $CH_2CH_2CN$ groups adopt a trans conformation with respect to the dithiole rings, which facilitates CN···H interactions (2.612–2.658 Å) generating chains along the *b*-axis. The adoption of this alternative trans geometry may arise out of solvation effects in which the polar $HCH_2CN$ may provide competing sites as improved solvation of the $CH_2CH_2CN$ substituents in the trans orientation.

In order to illustrate the application of this methodology to the synthesis of brominated Se containing derivatives, **1** was cross-coupled with the selenium analogue **6** affording the new donor **5**, which was recovered in high yields by column chromatography.

The molecular structure and packing diagram of **5** are shown in Figure 4.

The introduction of two bromine atoms into the framework leads to a slight lengthening of the C=C bonds of the TTF core, as expected due to the stronger electron-withdrawing ability of Br compared with S. The bromine atoms and the TTF core are essentially co-planar, with the maximum deviation from the least-squares plane being 0.4321(2) Å. Compound **5** packs in the centrosymmetric group $P2_1/n$. There is only one S···Br contact, which is less than the sum of the van der Waals radii [Br(1)···S(3) 3.388(4) Å], whilst all the other intermolecular contacts fall beyond the van der Waals distances.

Figure 5 illustrates the traditional herring-bone motif associated with this space group.

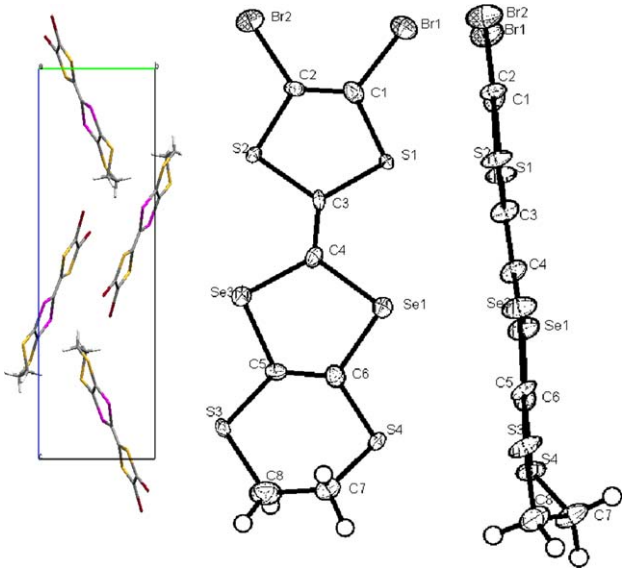



**Figure 4**. Packing diagram of **5** (left), and molecular structure and numbering scheme (centre and right).

**Figure 5**. View perpendicular to the *bc* plane.

## 3. Solution electrochemical data

The solution electrochemical data, obtained by cyclic voltammetry for the two halo-TTF derivatives reported herein, along with model compounds for comparison are collated in Table 1.

**Table 1**

| Compound | $E_1^{1/2}$/mV | $E_2^{1/2}$/mV | $\Delta E$ |
|---|---|---|---|
| EDT-TTF | 340 | 700 | 360 |
| **4** | 640 | 910 | 270 |
| **5** | 510 | 830 | 320 |
| BETS | 230 | 480 | 250 |

A comparison of **4** and **5** with their nonhalogenated derivatives reveals the expected trend resulting from halogen substitution, i.e., both the first and second oxidation potentials are raised significantly, in agreement with previous observations.[6]

Despite the poorer donor ability of **5** in relation to BETS, it was possible to isolate a charge transfer salt of **5** with tetracyano-*p*-quinodimethane (TCNQ) from slow evaporation of a dichloromethane solution, which yielded very small malformed dark needles (elemental analysis supports a 2:1 (**5**:TCNQ) complex) and showed conductivities (compressed pellet measurements) of $0.5\times10^{-1}$ S cm$^{-1}$. We have so far been unable to grow crystals of similar charge-transfer compounds with **4**. Experiments to obtain single crystals of the CT-complexes and radical-cation salts by electrocrystallisation are underway.

## 4. Conclusion

This study shows that although the halogenated derivatives (**4**, **5**) display lower donor abilities, their oxidation potentials are comparable to those of BEDTF-TTF, which is a well-known donor. Indeed it is possible to form charge-transfer complexes with them. The availability of the brominated derivatives in synthetically useful amounts will enable further charge-transfer complexes and ion radical salts to be obtained, enhancing the understanding of the role that halogen substituents play in this class of material.

## 5. Experimental

### 5.1. General

$^1$H and $^{13}$C NMR spectra were obtained on a Bruker AM-400 MHz spectrometer. Mass spectra were recorded on a Kratos MS890-EI mass spectrometer. Elemental analyses were recorded on an Exeter CE-440 Elemental Analyser. Cyclic voltammetric data were obtained on an Autolab Electrochemical Instrument with PGSTAT20 (0.001 M solution of donor in acetonitrile, 0.1 M tetrabutylammonium tetrafluoroborate supporting electrolyte, platinum working and counter electrodes, Ag/AgCl reference electrode, 20 °C). Conductivity data were obtained using routine four-probe methods.

Reactions were carried out under a nitrogen atmosphere; reagents were used as supplied; solvents were dried where necessary using standard procedures and distilled. Compounds **2**[13] and **6**[14] were synthesised as previously described.

**5.1.1. 4,5-Dibromo-[1,3]dithiole-2-thione 1.** To a stirred solution of diisopropylamine (0.3 g, 5 mmol) in THF (5 mL) at −78 °C was added *n*-butyl lithium (4 mL, 5.3 mmol of a 1.6 M solution in hexane) and the mixture stirred for 1 h. Vinylene trithiocarbonate (200 mg, 1.49 mmol) in diethyl ether (20 mL) was added dropwise, and the solution stirred at −78 °C for a further 3 h. A solution of 1,2-dibromotetrachloroethane (1.45 g, 4.4 mmol) in diethyl ether (10 mL) was added, the solution stirred at −78 °C for a further 3 h, and then the solution was allowed to reach room temperature overnight.

The solvent was removed in vacuo, and the residue extracted with dichloromethane. The organic extract was washed with water, separated, dried ($MgSO_4$) and evaporated to afford the crude product. Chromatography on a silica column (eluent hexane/toluene 4:1 v/v) afforded **1** as golden yellow crystals, mp 90–92 °C [lit. 90–92 °C[6]] (324 mg, 81%) (Analysis found: C, 12.41; $C_3Br_2S_3$ requires: C, 12.33%); *m*/*z* (EI) 292 ($M^+$, 100%); $\delta_C$ ($CDCl_3$) 106.7, 207.8. The NMR data were consistent with that described in the literature.[6]

**5.1.2. 4,5-Dibromo-4′,5′-bis(2′-cyanoethylsulfanyl)tetrathiafulvalene 3.** A solution of **1** (100 mg, 0.35 mmol) and **2** (400 mg, 1.4 mmol) in toluene (15 mL) was heated to reflux and then triethyl phosphite (0.35 mL, 2.0 mmol) was added dropwise, the mixture was refluxed for a further 2 h.

Removal of the solvent in vacuo gave a crude product, which was purified by chromatography on a silica column, with dichloromethane as eluent to afford **3** as yellow crystals, mp 132–134 °C [lit. 132–134 °C[6]] (138 mg, 76%) (Analysis found: C, 27.48; H, 1.49; N, 4.94; $C_{12}H_8Br_2N_2S_6$ requires: C, 27.07%; H, 1.51%; N, 5.26%); $\delta_H$ ($CDCl_3$) 3.09 (4H, t, $J$=7 Hz), 2.73 (4H, t, $J$=7 Hz). The NMR data were consistent with that described in the literature.[6]

**5.1.3. 4,5-Dibromo-4′,5′-ethylenedithiotetrathiafulvalene 4.** To a stirred solution of **3** (118 mg, 0.22 mmol) in tetrahydrofuran (20 mL) at 20 °C was added a solution of caesium hydroxide hydrate (35 mg, 0.21 mmol) in methanol (5 mL). Stirring was continued for 0.5 h whereupon 1,2-dibromoethane (260 mg, 0.22 mmol) was added. The mixture was stirred at room temperature overnight. Removal of the solvent in vacuo gave a crude product, which was purified on a silica column with $CS_2$ as eluent to yield **4** as red crystals, mp 169 °C [lit. 166–168 °C[8]] (60 mg, 61%) (Analysis found: C, 21.41; H, 1.11; $C_8H_4Br_2S_6$ requires: C, 21.24%; H, 0.89%); $\delta_H$ ($CDCl_3$–$CS_2$) 3.29 (s, 4H); $m/z$ (EI) 452 $M^+$; $\delta_C$ ($CDCl_3$–$CS_2$) 113.9, 112.1, 111.3, 101.6, 30.3. The NMR data were consistent with that described in the literature.[8]

**5.1.4. 4,5-Dibromo-4′,5′-ethylenedithiodiselenadithiafulvalene 5.** A solution of **1** (200 mg, 0.7 mmol) and **6** (180 mg, 0.7 mmol) in toluene (20 mL) was refluxed and then triethyl phosphite (10 mL, 60 mmol) added dropwise over 5 min. The reaction mixture was refluxed for a further 2 h. Removal of the solvent in vacuo gave a crude product, which was purified by chromatography on a silica column, with $CS_2$ as eluent to afford **5** as dark red crystals (305 mg, 80%) (Analysis found: C, 17.54; H, 0.63; $C_8H_4Br_2S_4Se_2$ requires: C, 17.60%; H, 0.73%), mp 271 °C; IR (KBr) 3075, 3021 $cm^{-1}$; $\delta_H$ ($CDCl_3$–$CS_2$) 3.33 (s, 4H); $\delta_C$ ($CDCl_3$–$CS_2$) 117.3, 114.8, 101.7, 100.6, 31.1.

**5.1.5. 4-Dibromo-[1,3]dithiole-2-thione 7.** To a stirred solution of diisopropylamine (0.09 g, 1.5 mmol) in THF (5 mL) at −78 °C was added *n*-butyl lithium (1.2 mL, 1.6 mmol of a 1.6 M solution in hexane) and the mixture stirred for 1 h. Vinylene trithiocarbamate (200 mg, 1.49 mmol) in diethyl ether (20 mL) was added dropwise, and the solution stirred at −78 °C for a further 3 h. A solution of 1,2-dibromotetrachloroethane (0.75 g, 2.2 mmol) in diethyl ether (10 mL) was added, the solution stirred at −78 °C for a further 3 h, and then the solution was allowed to reach room temperature overnight.

The solvent was removed in vacuo, and the residue extracted with dichloromethane. The organic extract was washed with water, separated, dried ($MgSO_4$) and evaporated to afford the crude product. Chromatography on a silica column (eluent hexane/toluene 4:1 v/v) afforded **7** as yellow crystals, mp 92–94 °C [lit. 92–95 °C[6]] (231 mg, 72%) (Analysis found: C, 17.40; H, 0.61; $C_3HBrS_3$ requires: C, 16.90%; H, 0.47%); $m/z$ (EI) 214 ($M^+$, 100%); $\delta_H$ (DMSO-$d_6$) 7.71(s). The NMR data were consistent with that described in the literature.[6]

**5.1.6. Complex $[5]_2$·TCNQ.** Solutions of compound **5** in dry dichloromethane and TCNQ in dry dichloromethane were mixed at 20 °C and allowed to slowly evaporate to afford tiny black crystals (Analysis found: C, 26.01; H, 1.12; N, 4.14; $C_{28}H_{12}Br_4N_4S_8Se_4$ requires: C, 25.94%; H 0.93%; N 4.32%).

## 6. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre CCDC No. 298122 and 298123. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033, e-mail: deposit@ccdc.cam.ac.uk).

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.06.006.

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# Substituent-induced regioselective synthesis of 1,2-teraryls and pyrano[3,4-*c*]pyran-4,5-diones from 2*H*-pyran-2-ones☆

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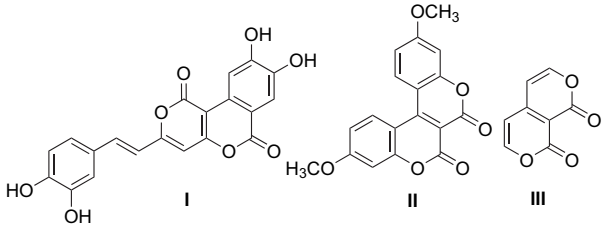
**Abstract**—Substituent-controlled regioselective synthesis of highly functionalized 1,2-teraryls **3a**–**k** has been achieved through ring transformation of 6-aryl-4-(pyrrolidin-1-yl/piperidin-1-yl)-2*H*-pyran-2-one-3-carbonitriles **1a**–**g** by aryl acetones **2a**–**c** in the presence of powdered KOH in DMF in very good yield. Under similar reaction conditions, 6-aryl-4-methylsulfanyl-2*H*-pyran-2-ones **5a**–**f** afforded 1,7-diaryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **6a**–**j** as major products and 3,4-diaryl-2-methyl-6-methylsulfanylbenzonitriles as minor constituents **7a**–**j**.


## 1. Introduction

1,2-Teraryls, an important class of polyaromatic compounds, derived through aryl–aryl coupling are often found in various natural products, pharmaceuticals, and agrochemicals.[1] Besides these, triaromatic rings are backbone of some of the most efficient and selective ligands for asymmetric catalysis.[1] These compounds have broad applications, such as liquid crystals,[2] laser dyes,[3] and conducting polymers.[4] The 1,2- and 1,4-teraryls have various industrial applications as heat storage, heat transfer agents, and textile dye carriers.[5] The presence of the 1,2-teraryl moiety as a subunit in various bioactive natural products and pharmacologically active compounds has increased its therapeutic interest.[6] Unsymmetrical 1,2-teraryls are also known to be potent selective dihydroorotate dehydrogenase (DHODH) inhibitors against parasitic or bacterial enzymes.[7] The wide range of applications of 1,2-teraryls prompted us to develop an economically viable route for the synthesis of these unsymmetrical polyaromatics in high yields.

Through an extensive computerized literature search on the chemistry of pyrano[3,4-*c*]pyran-4,5-diones and 1,2-teraryls, it was realized that the compounds of both these ring systems have been meagerly explored. Numerous compounds of pyrano[3,4-*c*]pyran-4,5-dione ring systems **I** and **II** are present as substructures in various natural and synthetic products and display anticancer[8,9] and antibacterial[10] activities. These compounds also exhibit photochemical[11] and luminescence properties.[12]

Except for MO calculations, correlation of delocalization energy, π-bond order, and π-charge density of 20 different hypothetical pyranopyrandiones including pyrano[3,4-*c*]-pyran-4,5-dione[13] **III**, no other additional information is available in the literature.




Meshimakobnol **I** is a natural product isolated from the fruit body of *Phellinus linteus* and possesses anticancer activity.[8] The synthetic pyranopyrandione **II** has been obtained[10] from the reaction of 3-methoxyphenol and diethyl ethoxymethylenemalonate in poor yield. Except structural commonality of the benzopyran moiety in **I** and **II** they differ in the site of fusion of pyranone rings.

The unexplored chemistry and therapeutic potential of pyrano[3,4-*c*]pyran-4,5-diones inspired us to develop an innovative route for their construction.

Most of the earlier procedures reported for the synthesis of 1,2-teraryls require harsh reaction conditions[14a–c] and suffer from a lack of selectivity and generality. This necessitated the development of an easy synthesis of this class of

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compound. The transition metal-catalyzed cross-coupling of Grignard reagents with dihalobenzenes[14d,e] was an earlier approach for the synthesis of this class of compound, but the methodology required the use of expensive reagents and gave poor yields of the product. These compounds have also been prepared by the photochemical reaction[14f] of 1,2-dihalobenzene with arenes. Recently, Pd-catalyzed Suzuki coupling reactions[14g–i] of 1,2-diaryl halides with aryl boronic acids has been conveniently used for the regioselective synthesis of 1,2-teraryls, but it also suffers from limitations,[15] including the coupling of aryl boronic acids with the phenyl group of triphenylphosphine, used as a ligand, as well as self-coupling.

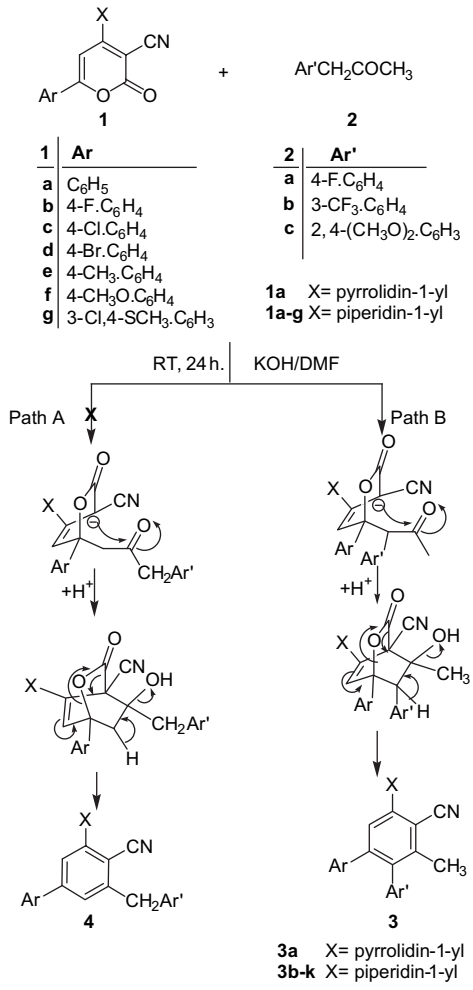
Recently, Takagi et al.[16] have developed new methodology for the construction of this class of compounds by consecutive cross-coupling of *o*-phenylenedizinc iodode with aryl halides in the presence of Pd(0)-tris(2,4,6-trimethoxyphenyl)phosphine in excellent yields. Nomura et al.[17] have also reported the Pd catalyzed regioselective diarylation, through reaction of aryl iodides with activated 2-phenylphenol. Recently, the microwave-assisted Suzuki coupling of 4,5-dicyanopyridazine with diphenylacetylene in xylene followed by ring transformation has been reported to obtain 1,2-teraryls.[5,18]

## 2. Results and discussion

Our approach to the regioselective synthesis of 1,2-teraryls is based on the ring transformation of 6-aryl-4-pyrrolidin-1-yl/piperidin-1-yl-2*H*-pyran-2-one-3-carbonitriles **1a**–**g** by aryl acetones **2a**–**c**. Thus, a reaction mixture of 2*H*-pyran-2-one **1**, aryl acetone **2**, and powdered KOH in DMF was stirred at ambient temperature for 24 h. After completion, the reaction mixture was poured into ice water with vigorous stirring. The aqueous solution was neutralized with 10% HCl and the crude product isolated was purified by silica-gel column chromatography.

There are three electrophilic centers, C-2, C-4, and C-6, in the molecular makeup of the pyran ring in which the latter is highly prone to nucleophilic attack due to extended conjugation and presence of electron-withdrawing substituent at position 3 of the pyran ring.[19] Aryl acetones **2** used as a source of the nucleophile for the ring transformation reaction has two possible sites, C-1 and C-3, for the enolate formation and accordingly two possible products **3** and **4** were expected. Isolation of only one product, **3**, from this reaction confirmed the formation of carbanion at C-1 due to the combined resonance and inductive effects of the aryl and CO groups, respectively. The enolate generated in situ from aryl acetones **2** attacks at position 6 of the pyran ring followed by ring closure, then elimination of carbon dioxide and water yields 1,2-teraryls regioselectively. One possible mechanism is shown in Scheme 1. The presence of methyl protons at $\delta$ 2.30 and the absence of methylene protons in the $^1$H NMR also confirmed the involvement of C-1 of aryl acetones **2** in the ring transformation reactions.

In order to assess the effect of the C-4 substituent of 2*H*-pyran-2-ones on regioselectivity and the course of the reaction, the ring transformation of 6-aryl-4-methylsulfanyl-



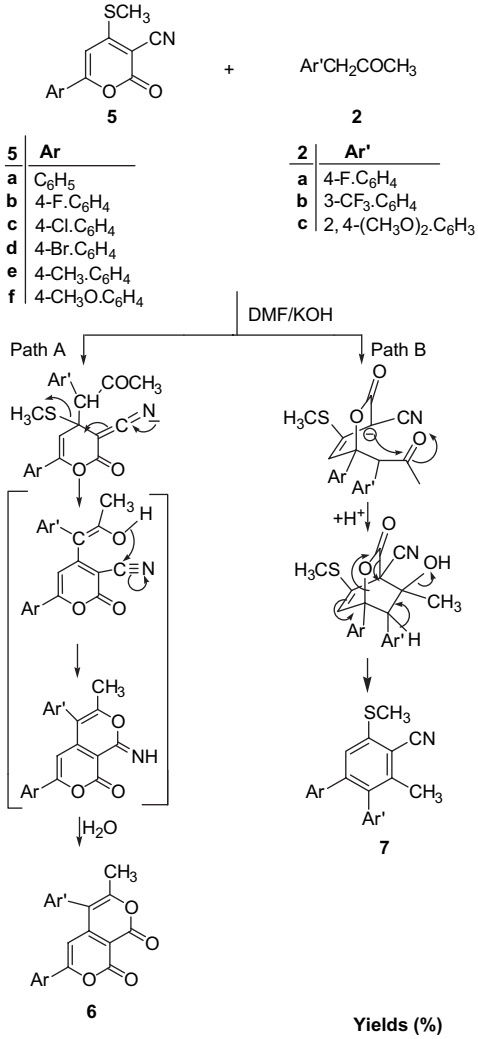

| 3 | Ar | Ar' | Yields (%) |
|---|---|---|---|
| a | $C_6H_5$ | 4-F.$C_6H_4$ | 76 |
| b | $C_6H_5$ | 3-$CF_3$.$C_6H_4$ | 81 |
| c | $C_6H_5$ | 4-F.$C_6H_4$ | 84 |
| d | 4-F.$C_6H_4$ | 4-F.$C_6H_4$ | 73 |
| e | 4-Cl.$C_6H_4$ | 4-F.$C_6H_4$ | 89 |
| f | 4-Cl.$C_6H_4$ | 2,4-$(CH_3O)_2$.$C_6H_3$ | 63 |
| g | 3-Cl,4-$SCH_3$.$C_6H_3$ | 3-$CF_3$.$C_6H_4$ | 71 |
| h | 4-Br.$C_6H_4$ | 4-F.$C_6H_4$ | 80 |
| i | 4-$CH_3$.$C_6H_4$ | 4-F.$C_6H_4$ | 69 |
| j | 4-$CH_3O$.$C_6H_4$ | 4-F.$C_6H_4$ | 73 |
| k | 4-$CH_3O$.$C_6H_4$ | 3-$CF_3$.$C_6H_4$ | 83 |

**Scheme 1**.

2*H*-pyron-2-one-3-carbonitriles **5** by aryl acetones **2** was studied under similar reaction conditions. It is evident from the topography of 2-*H*-pyran-2-ones **5** that the C-4 and C-6 positions are highly electropositive and susceptible to nucleophilic attack. In this reaction, the enolate generated from aryl acetones **2** attacks at both C-4 and C-6 positions and accordingly two products, 1,7-diaryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **6** and 3,4-diaryl-2-methyl-6-methylsulfanylbenzonitriles **7** as minor constituents, were isolated.

In the case of 6-aryl-4-pyrrolidin-1-yl/piperidin-1-yl-2*H*-pyran-2-ones **1**, the ring transformation by aryl acetone is initiated through the attack at C-6 of the pyran ring,

producing 1,2-teraryls **3a–k** regioselectively. The regioselectivity of the reaction is directed by the substituent linked to the C-4 position of the pyran ring. It is understood that the electrophilicity of C-4 position is reduced due to the nucleophilic nature of the attached *sec*-amino group and thus, the carbanion does not attack at this position. The presence of the methylsulfanyl group at C-4 being a good leaving group does not affect the electrophilicity of the C-4, and easily undergoes substitution followed by cyclization involving the cyano function at C-3 to produce 1,7-diaryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **6** in good yields. The other site prone to carbanion attack in **5** is C-6, which leads to the formation of 3,4-diaryl-2-methyl-6-methylsulfanylbenzonitriles **7** in low yields (Scheme 2). Thus, substituent at C-4 in 2*H*-pyran-2-ones plays a crucial role in the regioselectivity.




| 5 | Ar |
|---|---|
| a | $C_6H_5$ |
| b | 4-F.$C_6H_4$ |
| c | 4-Cl.$C_6H_4$ |
| d | 4-Br.$C_6H_4$ |
| e | 4-$CH_3$.$C_6H_4$ |
| f | 4-$CH_3O$.$C_6H_4$ |

| 2 | Ar' |
|---|---|
| a | 4-F.$C_6H_4$ |
| b | 3-$CF_3$.$C_6H_4$ |
| c | 2, 4-$(CH_3O)_2$.$C_6H_3$ |

| 6/7 | Ar | Ar' | Yields (%) 6 | 7 |
|---|---|---|---|---|
| a | $C_6H_5$ | 4-F.$C_6H_4$ | 60 | 19 |
| b | $C_6H_5$ | 3-$CF_3$.$C_6H_4$ | 73 | 9 |
| c | $C_6H_5$ | 2,4-$(CH_3O)_2$.$C_6H_3$ | 73 | 11 |
| d | 4-F.$C_6H_4$ | 4-F.$C_6H_4$ | 70 | 21 |
| e | 4-Cl.$C_6H_4$ | 4-F.$C_6H_4$ | 73 | 16 |
| f | 4-Br.$C_6H_4$ | 3-$CF_3$.$C_6H_4$ | 71 | 16 |
| g | 4-Br.$C_6H_4$ | 4-F.$C_6H_4$ | 68 | 18 |
| h | 4-$CH_3$.$C_6H_4$ | 4-F.$C_6H_4$ | 71 | 18 |
| i | 4-$CH_3O$.$C_6H_4$ | 4-F.$C_6H_4$ | 60 | 21 |
| j | 4-$CH_3O$.$C_6H_4$ | 3-$CF_3$.$C_6H_4$ | 69 | 13 |

**Scheme 2**.

## 3. Conclusion

Here, we report a one-pot regioselective synthesis of 1,7-diaryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **6** and 3,4-diaryl-2-methyl-6-*sec*-aminobenzonitriles **3** by base-catalyzed ring transformation of readily available 6-aryl-4-substituted-2*H*-pyran-2-one-3-carbonitriles (**1** and **5**) by aryl acetones **2**.[20,21]

Our methodologies provide an easy access to the synthesis of 1,2-teraryls **3** and 4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **6** in high yields in one step using economical reagents without catalyst. The workup of the reaction is also very simple.

## 4. Experimental

### 4.1. General

All reactions were conducted in flame-dried glassware. Precoated Merck TLC plates were used for monitoring the reactions. Column chromatographic separation was performed on silica gel (60–120 mesh). IR spectra were recorded on a Shimadzu 8201 PC FTIR Spectrophotometer. $^1$H NMR spectra were recorded on a Bruker DRX 200 spectrometer in deuterated solvents with TMS as an internal reference. HRMS were recorded on JEOL JMS-600H (HRMS) spectrometer. Melting points were determined on Büchi-530 capillary melting point apparatus and are uncorrected.

### 4.2. General procedure for the synthesis of 3′-methyl-5′-*sec*-amino-[1,1′,2′,1″]terphenyl-4′-carbonitriles (3a–k)

A mixture of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles, **1a–g** (1 mmol), aryl acetones **2a–c** (1 mmol), KOH (84 mg, 1.5 mmol) in dry DMF (10 mL) was stirred for 24 h at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% aqueous HCl. The precipitate obtained was filtered, washed with water, and finally purified on Si gel column using 0.5% ethyl acetate in hexane as an eluent.

**4.2.1. 4″-Fluoro-3′-methyl-5′-pyrrolidin-1-yl-[1,1′;2′,1″]-terphenyl-4′-carbonitrile (3a).** White powder; yield 76%; mp 154–156 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.97–2.04 (m, 4H, $2CH_2$), 2.30 (s, 3H, $CH_3$), 3.65 (t, $J$=6.5 Hz, 4H, $H_2CNCH_2$), 6.55 (s, 1H, ArH), 6.86–6.90 (m, 4H, ArH), 6.97–7.02 (m, 2H, ArH), 7.13–7.16 (m, 3H, ArH); IR (KBr) 2202 cm$^{-1}$ (CN); MS $m/z$ 357 ($M^+$+1); HRMS (EI): calcd for $C_{24}H_{21}FN_2$ 356.1689, found 356.1691.

**4.2.2. 3′-Methyl-5′-piperidin-1-yl-3″-trifluoromethyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3b).** White powder; yield 81%; mp 98–100 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.61–1.64 (m, 2H, $CH_2$), 1.76–1.86 (m, 4H, $2CH_2$), 2.33 (s, 3H, $CH_3$), 3.21 (t, $J$=5.2 Hz, 4H, $H_2CNCH_2$), 6.89 (s, 1H, ArH), 6.93–6.98 (m, 2H, ArH), 7.12–7.15 (m, 3H, ArH), 7.23–7.28 (m, 2H, ArH), 7.34 (d, $J$=7.8 Hz, 1H, ArH), 7.43 (d, $J$=7.8 Hz, 1H, ArH); IR (KBr) 2216 cm$^{-1}$ (CN); MS $m/z$ 421 ($M^+$+1); HRMS (EI): calcd for $C_{26}H_{23}F_3N_2$ 420.1813, found 420.1812.

**4.2.3. 4″-Fluoro-3′-methyl-5′-piperidin-1-yl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3c).** White powder; yield 84%; mp 158–160 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.60–1.66 (m, 2H, $CH_2$), 1.75–1.86 (m, 4H, $2CH_2$), 2.31 (s, 3H, $CH_3$), 3.18 (t, $J$=6.5 Hz, 4H, $H_2CNCH_2$), 6.86 (s, 1H, ArH), 6.89–7.01 (m, 6H, ArH), 7.14–7.17 (m, 3H, ArH); IR (KBr) 2214 cm$^{-1}$ (CN); MS $m/z$ 371 ($M^+$+1); HRMS (EI): calcd for $C_{25}H_{23}FN_2$ 370.1845, found 370.1846.

**4.2.4. 4,4″-Difluoro-3′-methyl-5′-piperidin-1-yl-[1,1′;2′,1″]-terphenyl-4′-carbonitrile (3d).** White powder; yield 73%; mp 170–172 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.61–1.66 (m, 2H, $CH_2$), 1.75–1.86 (m, 4H, $2CH_2$), 2.31 (s, 3H, $CH_3$), 3.19 (t, $J$=5.2 Hz, 4H, $H_2CNCH_2$), 6.80 (s, 1H, ArH), 6.82–6.99 (m, 8H, ArH); IR (KBr) 2211 cm$^{-1}$ (CN); MS $m/z$ 389 ($M^+$+1); HRMS (EI): calcd for $C_{25}H_{22}F_2N_2$ 388.1751, found 388.1752.

**4.2.5. 4-Chloro-4″-fluoro-3′-methyl-5′-piperidin-1-yl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3e).** White powder; yield 89%; mp 198–200 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.61–1.63 (m, 2H, $CH_2$), 1.79–1.81 (m, 4H, $2CH_2$), 2.31 (s, 3H, $CH_3$), 3.19 (t, $J$=5.0 Hz, 4H, $H_2CNCH_2$), 6.81 (s, 1H, ArH), 6.90–6.94 (m, 6H, ArH), 7.13 (d, $J$=8.5 Hz, 2H, ArH); IR (KBr) 2202 cm$^{-1}$ (CN); MS $m/z$ 405 ($M^+$+1); HRMS (EI): calcd for $C_{25}H_{22}ClFN_2$ 404.1456, found 404.1458.

**4.2.6. 4-Chloro-2″,4″-dimethoxy-3′-methyl-5′-piperidin-1-yl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3f).** White powder; yield 63%; mp 188–190 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.57–1.62 (m, 2H, $CH_2$), 1.78–1.80 (m, 4H, $2CH_2$), 2.26 (s, 3H, $CH_3$), 3.18 (t, $J$=5.0 Hz, 4H, $H_2CNCH_2$), 3.59 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 6.33–6.36 (m, 2H, ArH), 6.68 (d, $J$=8.9 Hz, 1H, ArH), 6.79 (s, 1H, ArH), 6.96 (d, $J$=8.4 Hz, 2H, ArH), 7.12 (d, $J$=8.4 Hz, 2H, ArH); IR (KBr) 2214 cm$^{-1}$ (CN); MS $m/z$ 447 ($M^+$+1); HRMS (EI): calcd for $C_{27}H_{27}ClN_2O_2$ 446.1761, found 446.1754.

**4.2.7. 3-Chloro-3′-methyl-4-methylsulfanyl-5′-piperidin-1-yl-3″-trifluoromethyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3g).** White powder; yield 71%; mp 153–155 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.62–1.67 (m, 2H, $2CH_2$), 1.76–1.81 (m, 4H, $CH_2$), 2.31 (s, 3H, $CH_3$), 2.40 (s, 3H, $SCH_3$), 3.20 (t, $J$=5.2 Hz, 4H, $H_2CNCH_2$), 6.76 (s, 1H, ArH), 6.80–6.83 (m, 1H, ArH), 6.88–6.92 (m, 1H, ArH), 7.02–7.03 (m, 1H, ArH), 7.13 (d, $J$=7.6 Hz, 1H, ArH), 7.26–7.29 (m, 1H, ArH), 7.39 (d, $J$=7.6 Hz, 1H, ArH), 7.44 (d, $J$=7.8 Hz, 1H, ArH); IR (KBr) 2218 cm$^{-1}$ (CN); MS $m/z$ 501 ($M^+$+1); HRMS (EI): calcd for $C_{27}H_{24}ClF_3N_2S$ 500.1301, found 500.1297.

**4.2.8. 4-Bromo-4″-fluoro-3′-methyl-5′-piperidin-1-yl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3h).** White powder; yield 80%; mp 185–187 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.60–1.66 (m, 2H, $CH_2$), 1.75–1.86 (m, 4H, $2CH_2$), 2.30 (s, 3H, $CH_3$), 3.19 (t, $J$=5.2 Hz, 4H, $H_2CNCH_2$), 6.80 (s, 1H, ArH), 6.82–6.93 (m, 6H, ArH), 7.27 (d, $J$=8.8 Hz, 2H, ArH); IR (KBr) 2215 cm$^{-1}$ (CN); MS $m/z$ 448 ($M^+$), 450 ($M^+$+2); HRMS (EI): calcd for $C_{25}H_{22}BrFN_2$ 448.0950, found 448.0951.

**4.2.9. 4″-Fluoro-4,3′-dimethyl-5′-piperidin-1-yl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3i).** White powder; yield 69%; mp 187–189 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.60–1.62 (m, 2H, $CH_2$), 1.78–1.86 (m, 4H, $2CH_2$), 2.26 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 3.18 (t, $J$=5.1 Hz, 4H, $H_2CNCH_2$), 6.85 (s, 1H, ArH), 6.90–6.98 (m, 8H, ArH); IR (KBr) 2214 cm$^{-1}$ (CN); MS $m/z$ 385 ($M^+$+1); HRMS (EI): calcd for $C_{26}H_{25}FN_2$ 384.2002, found 384.2015.

**4.2.10. 4″-Fluoro-4-methoxy-3′-methyl-5′-piperidin-1-yl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3j).** White powder; yield 73%; mp 175–177 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.60–1.66 (m, 2H, $CH_2$), 1.78–1.80 (m, 4H, $2CH_2$), 2.30 (s, 3H, $CH_3$), 3.19 (t, $J$=5.1 Hz, 4H, $H_2CNCH_2$), 3.74 (s, 3H, $OCH_3$), 6.66 (s, 1H, ArH), 6.71 (s, 1H, ArH), 6.84–6.94 (m, 6H, ArH), 7.23 (s, 1H, ArH); IR (KBr) 2212 cm$^{-1}$ (CN); MS $m/z$ 401 ($M^+$+1); HRMS (EI): calcd for $C_{26}H_{25}FN_2O$ 400.1951, found 400.1952.

**4.2.11. 4-Methoxy-3′-methyl-5′-piperidin-1-yl-3″-trifluoromethyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (3k).** White powder; yield 83%; mp 120–122 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.59–1.63 (m, 2H, $CH_2$), 1.80–1.83 (m, 4H, $2CH_2$), 2.31 (s, 3H, $CH_3$), 3.20 (t, $J$=5.1 Hz, 4H, $H_2CNCH_2$), 3.73 (s, 3H, $OCH_3$), 6.65 (s, 1H, ArH), 6.69 (s, 1H, ArH), 6.86–6.90 (m, 3H, ArH), 7.15 (d, $J$=7.5 Hz, 1H, ArH), 7.30–7.37 (m, 2H, ArH), 7.45 (d, $J$=7.7 Hz, 1H, ArH); IR (KBr) 2215 cm$^{-1}$ (CN); MS $m/z$ 451 ($M^+$+1); HRMS (EI): calcd for $C_{27}H_{25}F_3N_2O$ 450.1919, found 450.1919.

### 4.3. General procedure for the synthesis of 3′-methyl-5′-methylsulfanyl-[1,1′,2′,1″]terphenyl-4′-carbonitriles (7a–j) and 3-methyl-4,6-diarylpyrano[3,4-*c*]pyran-1,8-diones (6a–j)

A mixture of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles, **5a–f** (1 mmol), aryl acetones **2a–c** (1 mmol), and KOH (90 mg, 1.5 mmol) in dry DMF (10 mL) was stirred for 24 h at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl. The precipitate obtained was filtered, washed with water, and finally purified on Si gel column using 0.5% ethyl acetate in hexane as eluent for 1,2-teraryl and 5% ethyl acetate in hexane as eluent for pyrano[3,4-*c*]pyran-4,5-diones.

**4.3.1. 4″-Fluoro-3′-methyl-5′-methylsulfanyl-[1,1′;2′,1″]-terphenyl-4′-carbonitrile (7a).** White powder; yield 19%; mp 156–158 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.34 (s, 3H, $CH_3$), 2.56 (s, 3H, $SCH_3$), 6.91 (s, 1H, ArH), 6.94–7.02 (m, 5H, ArH), 7.14–7.20 (m, 4H, ArH); IR (KBr) 2217 cm$^{-1}$ (CN); MS $m/z$ 334 ($M^+$+1); HRMS (EI): calcd for $C_{21}H_{16}FNS$ 333.0987, found 333.0987.

**4.3.2. 3′-Methyl-5′methylsulfanyl-3″-trifluoromethyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7b).** White powder; yield 9%; mp 164–166 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.35 (s, 3H, $CH_3$), 2.58 (s, 3H, $SCH_3$), 6.96 (s, 1H, ArH), 6.97–6.99 (m, 1H, ArH), 7.16–7.18 (m, 4H, ArH), 7.23–7.26 (m, 2H, ArH), 7.33–7.35 (m, 1H, ArH), 7.43–7.45 (m, 1H, ArH); IR (KBr) 2217 cm$^{-1}$ (CN); MS $m/z$ 384 ($M^+$+1); HRMS (EI): calcd for $C_{22}H_{16}F_3NS$ 383.0956, found 383.0958.

**4.3.3. 2″,4″-Dimethoxy-3′-methyl-5′-methylsulfanyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7c).** White powder; yield 11%; mp 148–150 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.23 (s, 3H, $CH_3$), 2.50 (s, 3H, $SCH_3$), 3.52 (s, 3H, $OCH_3$), 3.69 (s, 3H, $OCH_3$), 6.23–6.25 (m, 1H, ArH), 6.28 (s, 1H, ArH), 6.59–6.63 (m, 1H, ArH), 6.94–6.99 (m, 2H, ArH), 7.06–7.11 (m, 4H, ArH); IR (KBr) 2217 cm$^{-1}$ (CN); MS *m/z* 376 ($M^+$+1); HRMS (EI): calcd for $C_{23}H_{21}NO_2S$ 375.1293, found 375.1293.

**4.3.4. 4,4″-Difluoro-3′-methyl-5′-methylsulfanyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7d).** White powder; yield 21%; mp 204–206 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.33 (s, 3H, $CH_3$), 2.58 (s, 3H, $SCH_3$), 6.83–7.11 (m, 8H, ArH), 7.57 (s, 1H, ArH); IR (KBr) 2216 cm$^{-1}$ (CN); MS *m/z* 352 ($M^+$+1); HRMS (EI): calcd for $C_{21}H_{15}F_2NS$ 351.0893, found 351.0898.

**4.3.5. 4-Chloro-4″-fluoro-3′-methyl-5′methylsulfanyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7e).** White powder; yield 16%; mp 186–188 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.33 (s, 3H, $CH_3$), 2.57 (s, 3H, $SCH_3$), 6.92 (s, 1H, ArH), 6.93–6.96 (m, 5H, ArH), 7.07–7.18 (m, 3H, ArH); IR (KBr) 2214 cm$^{-1}$ (CN); MS *m/z* 368 ($M^+$+1); HRMS (EI): calcd for $C_{21}H_{15}ClFNS$ 367.0598, found 367.0602.

**4.3.6. 4-Bromo-3′-methyl-5′methylsulfanyl-3″-trifluoromethyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7f).** White powder; yield 16%; mp 162–164 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.34 (s, 3H, $CH_3$), 2.58 (s, 3H, $SCH_3$), 6.84 (d, *J*=8.4 Hz, 2H, ArH), 7.11–7.15 (m, 2H, ArH), 7.27–7.29 (m, 2H, ArH), 7.32–7.43 (m, 2H, ArH), 7.48–7.53 (m, 1H, ArH); IR (KBr) 2219 cm$^{-1}$ (CN); MS *m/z* 461 ($M^+$), 463 ($M^+$+2); HRMS (EI): calcd for $C_{22}H_{15}BrF_3NS$ 461.0061, found 461.0062.

**4.3.7. 4-Bromo-4″-fluoro-3′-methyl-5′methylsulfanyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7g).** White powder; yield 18%; mp 166–168 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.33 (s, 3H, $CH_3$), 2.57 (s, 3H, $SCH_3$), 6.87 (d, *J*=8.42 Hz, 2H, ArH), 6.92–6.96 (m, 4H, ArH), 7.09 (s, 1H, ArH), 7.31 (d, *J*=8.4 Hz, 2H, ArH); IR (KBr) 2213 cm$^{-1}$ (CN); MS *m/z* 411 ($M^+$), 413 ($M^+$+2); HRMS (EI): calcd for $C_{21}H_{15}BrFNS$ 411.0093, found 411.0092.

**4.3.8. 4″-Fluoro-4,3′-dimethyl-5′-methylsulfanyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7h).** White powder; yield 18%; mp 158–160 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.28 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 2.57 (s, 3H, $SCH_3$), 6.88 (d, *J*=8.2 Hz, 2H, ArH), 6.91–6.96 (m, 4H, ArH), 6.99 (d, *J*=8.04 Hz, 2H, ArH), 7.13 (s, 1H, ArH); IR (KBr) 2215 cm$^{-1}$ (CN); MS *m/z* 348 ($M^+$+1); HRMS (EI): calcd for $C_{22}H_{18}FNS$ 347.1144, found 347.1144.

**4.3.9. 4″-Fluoro-4-methoxy-3′-methyl-5′-methylsulfanyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7i).** White powder; yield 21%; mp 176–178 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.33 (s, 3H, $CH_3$), 2.57 (s, 3H, $SCH_3$), 3.75 (s, 3H, $OCH_3$), 6.71 (d, *J*=8.7 Hz, 2H, ArH), 6.90–6.96 (m, 6H, ArH), 7.12 (s, 1H, ArH); IR (KBr) 2215 cm$^{-1}$ (CN); MS *m/z* 364 ($M^+$+1); HRMS (EI): calcd for $C_{22}H_{18}FNOS$ 363.1093, found 363.1093.

**4.3.10. 4-Methoxy-3′-methyl-5′-methylsulfanyl-3″-trifluoromethyl-[1,1′;2′,1″]terphenyl-4′-carbonitrile (7j).** White powder; yield 13%; mp 144–146 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.28 (s, 3H, $CH_3$), 2.52 (s, 3H, $SCH_3$), 3.67 (s, 3H, $OCH_3$), 6.59 (d, *J*=8.7 Hz, 2H, ArH), 6.79 (d, *J*=8.7 Hz, 2H, ArH), 7.04 (s, 1H, ArH), 7.30–7.44 (m, 4H, ArH); IR (KBr) 2219 cm$^{-1}$ (CN); MS *m/z* 414 ($M^+$+1); HRMS (EI): calcd for $C_{23}H_{18}F_3NOS$ 413.1061, found 413.1064.

**4.3.11. 4-(4-Fluorophenyl)-3-methyl-6-phenylpyrano-[3,4-*c*]pyran-1,8-dione (6a).** Deep yellow powder; yield 60%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.14 (s, 3H, $CH_3$), 6.28 (s, 1H, ArH), 7.37–7.66 (m, 7H, ArH), 7.72–7.75 (m, 2H, ArH); IR (KBr) 1704 cm$^{-1}$ (CO), 1784 cm$^{-1}$ (CO); MS *m/z* 349 ($M^+$+1); HRMS (EI): calcd for $C_{21}H_{13}FO_4$ 348.0798, found 348.0799.

**4.3.12. 3-Methyl-6-phenyl-4-(3-trifluoromethylphenyl)-pyrano[3,4-*c*]pyran-1,8-dione (6b).** Deep yellow powder; yield 73%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.14 (s, 3H, $CH_3$), 6.24 (s, 1H, ArH), 7.52–7.60 (m, 3H, ArH), 7.71–7.76 (m, 3H, ArH), 7.82–7.96 (m, 3H, ArH); IR (KBr) 1710 cm$^{-1}$ (CO), 1784 cm$^{-1}$ (CO); MS *m/z* 399 ($M^+$+1); HRMS (EI): calcd for $C_{22}H_{13}F_3O_4$ 398.0766, found 398.0777.

**4.3.13. 4-(2,4-Dimethoxyphenyl)-3-methyl-6-phenyl-pyrano[3,4-*c*]pyran-1,8-dione (6c).** Deep yellow powder; yield 73%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.28 (s, 3H, $CH_3$), 3.75 (s, 3H, $OCH_3$), 3.91 (s, 3H, $OCH_3$), 6.31 (s, 1H, ArH), 6.61–6.65 (m, 2H, ArH), 7.02–7.07 (m, 1H, ArH), 7.38–7.41 (m, 3H, ArH), 7.68–7.72 (m, 2H, ArH); IR (KBr) 1706 cm$^{-1}$ (CO), 1759 cm$^{-1}$ (CO); MS *m/z* 391 ($M^+$+1); HRMS (EI): calcd for $C_{23}H_{18}O_6$ 390.1103, found 390.1114.

**4.3.14. 4,6-Bis-(4-fluorophenyl)-3-methylpyrano[3,4-*c*]-pyran-1,8-dione (6d).** Yellow powder; yield 70%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.10 (s, 3H, $CH_3$), 6.20 (s, 1H, ArH), 7.28–7.43 (m, 6H, ArH), 7.59–7.62 (m, 1H, ArH), 7.74–7.79 (m, 1H, ArH); IR (KBr) 1715 cm$^{-1}$ (CO), 1770 cm$^{-1}$ (CO); MS *m/z* 367 ($M^+$+1); HRMS (EI): calcd for $C_{21}H_{12}F_2O_4$ 366.0704, found 366.0710.

**4.3.15. 6-(4-Chlorophenyl)-4-(4-fluorophenyl)-3-methyl-pyrano[3,4-*c*]pyran-1,8-dione (6e).** Yellow powder; yield 73%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.13 (s, 3H, $CH_3$), 6.25 (s, 1H, ArH), 7.01–7.05 (m, 2H, ArH), 7.33–7.47 (m, 4H, ArH), 7.62–7.71 (m, 2H, ArH); IR (KBr) 1705 cm$^{-1}$ (CO), 1783 cm$^{-1}$ (CO); MS *m/z* 383 ($M^+$+1); HRMS (EI): calcd for $C_{21}H_{12}ClFO_4$ 382.0408, found 382.0411.

**4.3.16. 6-(4-Bromophenyl)-3-methyl-4-(3-trifluoromethylphenyl)-pyrano[3,4-*c*]pyran-1,8-dione (6f).** Dark yellow powder; yield 71%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.18 (s, 3H, $CH_3$), 6.11 (s, 1H, ArH), 7.48–7.61 (m, 5H, ArH), 7.68–7.84 (m, 3H, ArH); IR (KBr) 1705 cm$^{-1}$ (CO), 1798 cm$^{-1}$ (CO); MS *m/z* 475 ($M^+$), 479 ($M^+$+2); HRMS (EI): calcd for $C_{22}H_{12}BrF_3O_4$ 475.9871, found 475.9870.

**4.3.17. 6-(4-Bromophenyl)-4-(4-fluorophenyl)-3-methylpyrano[3,4-*c*]pyran-1,8-dione (6g).** Yellow powder; yield 68%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.14 (s, 3H, $CH_3$), 6.31 (s, 1H, ArH), 7.42–7.46 (m, 4H, ArH), 7.66–7.76 (m, 4H, ArH); IR (KBr) 1704 cm$^{-1}$ (CO), 1797 cm$^{-1}$ (CO); MS *m*/*z* 425 ($M^+$), 427 ($M^+$+2); HRMS (EI): calcd for $C_{21}H_{12}BrFO_4$ 425.9903, found 425.9908.

**4.3.18. 4-(4-Fluorophenyl)-3-methyl-6-*p*-tolylpyrano-[3,4-*c*]pyran-1,8-dione (6h).** Yellow powder; yield 71%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.06 (s, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$), 6.18 (s, 1H, ArH), 7.28–7.40 (m, 5H, ArH), 7.46–7.64 (m, 3H, ArH); IR (KBr) 1706 cm$^{-1}$ (CO), 1779 cm$^{-1}$ (CO); MS *m*/*z* 363 ($M^+$+1); HRMS (EI): calcd for $C_{22}H_{15}FO_4$ 362.0954, found 362.0958.

**4.3.19. 4-(4-Fluorophenyl)-6-(4-methoxyphenyl)-3-methylpyrano[3,4-*c*]pyran-1,8-dione (6i).** Deep yellow powder; yield 60%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.12 (s, 3H, $CH_3$), 3.84 (s, 3H, $OCH_3$), 6.16 (s, 1H, ArH), 7.02–7.06 (m, 2H, ArH), 7.37–7.46 (m, 4H, ArH), 7.67–7.72 (m, 2H, ArH); IR (KBr) 1706 cm$^{-1}$ (CO), 1773 cm$^{-1}$ (CO); MS *m*/*z* 379 ($M^+$+1); HRMS (EI): calcd for $C_{22}H_{15}FO_5$ 378.0904, found 378.0906.

**4.3.20. 6-(4-Methoxyphenyl)-3-methyl-4-(3-trifluoromethylphenyl)-pyrano[3,4-*c*]pyran-1,8-dione (6j).** Deep yellow powder; yield 69%; mp >250 °C; $^1$H NMR (DMSO-$d_6$, 200 MHz) $\delta$ 2.08 (s, 3H, $CH_3$), 3.79 (s, 3H, $OCH_3$), 6.08 (s, 1H, ArH), 7.02–7.06 (m, 2H, ArH), 7.63–7.71 (m, 3H, ArH), 7.77–7.88 (m, 3H, ArH); IR (KBr) 1703 cm$^{-1}$ (CO), 1788 cm$^{-1}$ (CO); MS *m*/*z* 429 ($M^+$+1); HRMS (EI): calcd for $C_{23}H_{15}F_3O_5$ 428.0872, found 428.0870.

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# Solvent-free reduction of aldehydes and ketones using solid acid-activated sodium borohydride

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This paper is dedicated to the late Professor Herbert C. Brown and his pioneer works on the hydride reductions

**Abstract**—A simple and convenient procedure for the reduction of aldehydes and ketones with sodium borohydride activated by solid acids such as boric acid, benzoic acid, and *p*-toluenesulfonic acid monohydrate under solvent-free conditions is described.


## 1. Introduction

Solvent-free reactions are not only of interest from ecological point of view, but in many cases, also offer considerable synthetic advantages in terms of yield, selectivity, and simplicity of the reaction procedure.[1] Sodium borohydride is an inexpensive, safe to handle, and environmental friendly reducing agent, which rapidly reduce aldehydes, ketones, and acid chlorides.[2] This reagent is commonly employed in hydroxylic solvents, such as methanol, ethanol, and 2-propanol, although it is unstable in both methanol and ethanol due to solvolysis.[2] There are few reports for the reduction of aldehydes and ketones with sodium borohydride under solvent-free conditions.[3] However, the reductions have disadvantage for practical utility, requiring long reaction times. For example, the reduction was complete when a mixture of benzophenone and a 10-fold molar amount of sodium borohydride was kept in a dry box at room temperature with occasional mixing and grinding using an agate mortar and pestle for 5 days.[3a] Very recently, we reported the first solvent-free reduction of imines using solid acid-activated sodium borohydride to give the corresponding amines in near quantitative yields.[4] The results prompted us to study the solvent-free reduction of aldehydes and ketones using the same methodology. This paper includes chemoselective reduction of functionalized aldehydes and ketones bearing other reducible functional groups, regioselective reduction of α,β-unsaturated aldehydes and ketones, and stereoselective reduction of cyclic ketones.

*Keywords*: Solvent-free reaction; Aldehyde and ketone reduction; Sodium borohydride.
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## 2. Results and discussion

### 2.1. Reduction of unfunctionalized aldehydes and ketones

We initially examined solvent-free reductions of benzaldehyde and acetophenone using solid acid-activated sodium borohydride. Boric acid, benzoic acid, and *p*-toluenesulfonic acid were chosen as representative solid acids. We also compared the same reductions using sodium borohydride itself. The reductions were carried out by grinding a 1:1 mixture of the aldehyde (or ketone) and sodium borohydride in the absence and presence of 1 equiv of each solid acid in an agate mortar and pestle at room temperature in air until TLC showed complete disappearance of the starting materials. Product alcohols were isolated by quenching the resulting mixture with saturated aqueous solution of $NaHCO_3$ or 1 N HCl solution to remove solid acid and unreacted sodium borohydride used, followed by extraction with $Et_2O$ or $CH_2Cl_2$ and yields were determined by capillary GC analysis or column chromatography. As shown in Table 1, benzaldehyde was rapidly reduced to benzyl alcohol even by sodium borohydride alone in the absence of solid acids. In this reduction, effectiveness of activators examined appeared to be not significant, although it was found that they enhanced the reduction. Also, meaningful differences of effects among them were not observed (entries 1–4). Using the same methodology, we examined the reductions of other aromatic, aliphatic, and heterocyclic aldehydes. In all cases, the reductions afforded the corresponding alcohols in high yields (entries 5–14). Unlike those of aldehydes, the reductions of ketones using sodium borohydride itself in the absence of activators proceeded very slowly. For example, the reduction of acetophenone without activators provided 1-phenylethanol in only

**Table 1**. Solvent-free reduction of simple aldehydes and ketones with sodium borohydride in the presence of activators[a]

| Run | Aldehydes and ketones | Activator | Time (min) | Product | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $C_6H_5CHO$ | None | 10 | $C_6H_5CH_2OH$ | >99 |
| 2 | | $H_3BO_3$ | 5 | | >99 |
| 3 | | $PhCO_2H$ | 5 | | >99 |
| 4 | | PTSA[c] | 5 | | >99 |
| 5 | 2-Naphthaldehyde | None | 60 | 2-Naphthylmethanol | 95 (5)[d] |
| 6 | | $PhCO_2H$ | 40 | | >99 |
| 7 | *n*-$C_6H_{13}CHO$ | None | 10 | *n*-$C_6H_{13}CH_2OH$ | 98 (2)[d] |
| 8 | | $PhCO_2H$ | 5 | | >99 |
| 9 | *c*-$C_6H_{11}CHO$ | None | 20 | *c*-$C_6H_{11}CH_2OH$ | 96 (4)[d] |
| 10 | | $PhCO_2H$ | 10 | | >99 |
| 11 | Furfural | None | 5 | Furfuryl alcohol | >99 |
| 12 | | $H_3BO_3$ | 5 | | >99 |
| 13 | 4-Pyridinecarboxaldehyde | None | 5 | 4-Pyridinemethanol | >99 |
| 14 | | $H_3BO_3$ | 5 | | >99 |
| 15 | $C_6H_5COCH_3$ | None | 120 | $C_6H_5CHOHCH_3$ | 18 (82)[d] |
| 16 | | $H_3BO_3$ | 10 | | >99 |
| 17 | | $PhCO_2H$ | 50 | | >99 |
| 18 | | PTSA[c] | 50 | | 70 (30)[d] |
| 19 | 2-Acetylnaphthalene[e] | None | 100 | α-Methyl-2-naphthalenemethanol | 17 (83)[d] |
| 20 | | $H_3BO_3$ | 100 | | 97[f] |
| 21 | 4′-Acetylbiphenyl[e] | None | 130 | 1-(4-Biphenyl)-1-ethanol | 16 (84)[d] |
| 22 | | $H_3BO_3$ | 130 | | 80 (20)[d] |
| 23 | Benzophenone[e] | None | 120 | Benzhydrol | 1 (99)[d] |
| 24 | | $H_3BO_3$ | 120 | | 98[f] |
| 25 | α-Tetralone | None | 50 | 1,2,3,4-Tetrahydro-1-naphthol | 5 (95)[d] |
| 26 | | $H_3BO_3$ | 50 | | >99 |
| 27 | 1-Indanone | None | 20 | 1-Indanol | 2 (98)[d] |
| 28 | | $H_3BO_3$ | 20 | | >99 |
| 29 | 2-Nonanone | None | 30 | 2-Nonanol | 2 (98)[d] |
| 30 | | $H_3BO_3$ | 20 | | >99 |
| 31 | Cyclohexanone | None | 10 | Cyclohexanol | >99 |
| 32 | | $H_3BO_3$ | 10 | | >99 |
| 33 | 2-Acetylfuran | None | 30 | 1-(2-Furyl)ethanol | 60 (40)[d] |
| 34 | | $H_3BO_3$ | 20 | | >99 |
| 35 | 5-Methyl-3-acetylfuran[g] | None | 40 | 1-(5-Methyl-2-furyl)ethanol | 27 (73)[d] |
| 36 | | $H_3BO_3$ | 20 | | >99 |
| 37 | 4-Acetylpyridine[g] | None | 30 | 1-(4-Pyridyl)ethanol | 78 (22)[d] |
| 38 | | $H_3BO_3$ | 15 | | >99 |

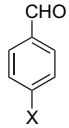
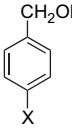
[a] A 1:1 mixture of substrate and $NaBH_4$ or 1:1:1 mixture of substrate, $NaBH_4$, and activator was ground in an agate mortar and pestle at room temperature (ca. 25 °C), unless otherwise indicated.
[b] Determined by capillary GC analysis after quenching the reaction with a saturated aqueous of $NaHCO_3$ or 1 N HCl solution.
[c] PTSA=*p*-toluenesulfonic acid monohydrate.
[d] Figures in parentheses indicate % yield of unreacted starting material.
[e] $NaBH_4$ (5 equiv) or a mixture of $NaBH_4$ (5 equiv) and $H_3BO_3$ (5 equiv) was used.
[f] Isolated yield.
[g] $NaBH_4$ (3 equiv) or a mixture of $NaBH_4$ (3 equiv) and $H_3BO_3$ (3 equiv) was used.

18% yield in 120 min with recovery of the unreacted starting ketone in 82% yield. However, the presence of 1 equiv of boric acid accelerated remarkably the reduction to give the product alcohol in a quantitative yield in 10 min (entry 15 vs 16). Of the activators examined, boric acid provided the best results (entries 15–18). This methodology was successfully applied to the reduction of other aromatic ketones such as 2-acetylnaphthalene, 4′-acetylbiphenyl, benzophenone, α-tetralone, and 1-indanone. Of these, 2-acetylnaphthalene, 4′-acetylbiphenyl, and benzophenone required 5 equiv of the reducing agent for their complete reductions. Again, these reductions with sodium borohydride itself were very sluggish (entries 19–28). In the cases of aliphatic ketones, the reduction of 2-nonanone was remarkably accelerated by the presence of 1 equiv of boric acid, although cyclohexanone was smoothly reduced by sodium borohydride alone (entries 29–32). Similarly, using boric acid-activated sodium borohydride, the reductions of heterocyclic ketones such as 2-acetylfuran, 5-methyl-2-acetylfuran, and 4-acetylpyridin to the corresponding alcohols were successfully achieved (entries 33–38).

## 2.2. Chemoselective reduction of functionalized aldehydes and ketones bearing other reducible functional groups

We next examined solvent-free chemoselective reduction of functionalized aldehydes and ketones including other reducible functional groups, such as ester, amide, cyano, bromo, and nitro groups, using boric acid-activated sodium borohydride. As shown in Table 2, benzaldehyde derivatives bearing various functional groups were chemoselectively reduced to the corresponding alcohols without reduction of any other functional groups in quantitative yields (entries 1–5). To explore the generality of this methodology, we examined the chemoselective reductions of other functionalized ketone analogues, such as benzoyl cyanide, methyl benzoylformate, benzoylacetonitrile, ethyl benzoylacetate, ethyl

**Table 2**. Solvent-free chemoselective reduction of aldehydes and ketones containing various functional groups with $H_3BO_3$-activated sodium borohydride[a]

| Run | Aldehydes and ketones | | Time (min) | Product | | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 |  | X=$CO_2Me$ | 5 (15)[c] |  | X=$CO_2Me$ | >99 (>99)[d] |
| 2 | | X=NHCOMe[e] | 20 (40)[c] | | X=NHCOMe | >99 (>99)[d] |
| 3 | | X=CN | 5 (15)[c] | | X=CN | >99 (>99)[d] |
| 4 | | X=Br | 5 (15)[c] | | X=Br | >99 (>99)[d] |
| 5 | | X=$NO_2$ | 5 (15)[c] | | X=$NO_2$ | >99 (>99)[d] |
| 6 | 4-$NO_2C_6H_4COCH_3$[e] | | 10 (30)[c] | 4-$NO_2C_6H_4CH(OH)CH_3$ | | >99 (>99)[d] |
| 7 | 4-$NCC_6H_4COCH_3$[e] | | 5 (30)[c] | 4-$NCC_6H_4CH(OH)CH_3$ | | >99 (>99)[d] |
| 8 | Benzoyl cyanide | | 30 (60)[c] | Mandelonitrile | | >99 (>99)[d] |
| 9 | Methyl benzoylformate | | 5 (15)[c] | Methyl mandelate | | >99 (>99)[d] |
| 10 | Benzoylacetonitrile | | 10 (30)[c] | $PhCH(OH)CH_2CN$ | | >99 (>99)[d] |
| 11 | Ethyl benzoylacetate | | 40 (60)[c] | $PhCH(OH)CH_2CO_2Et$ | | >99 (64)[d,f] |
| 12 | Ethyl acetoacetate | | 20 (40)[c] | $MeCH(OH)CH_2CO_2Et$ | | >99 (>99)[d] |
| 13 | 2-Methoxycarbonylcycloheptanone | | 15 (40)[c] | 2-Methoxycarbonylcycloheptanol | | >99 (>99)[d] |
| 14 | Benzoin[e] | | 40 (120)[c] | Hydrobenzoin | | >99 (>99)[d] |
| 15 | Methyl 5-acetylsalicylate[e] | | 90 (90)[c] | 5-$MeCH(OH)C_6H_3$-2-$(OH)CO_2Me$ | | 60 (40)[d,f] |
| 16 | 4-$BrC_6H_4COCH_2Br$[e] | | 60 (60)[c] | 4-$BrC_6H_4CH(OH)CH_2Br$ | | 50 (20)[d,f] |

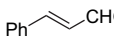
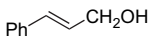
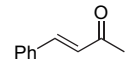
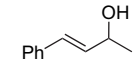
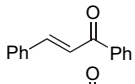
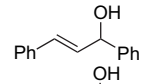
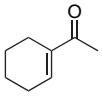
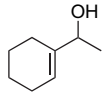
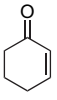
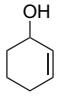
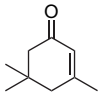
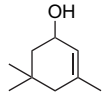
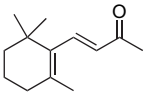
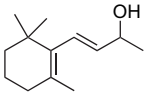
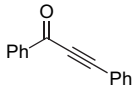
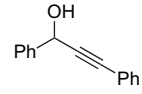
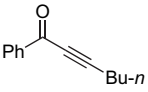
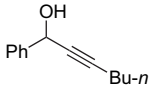
[a,b] See the corresponding footnotes in Table 1.
[c,d] The figures in parentheses indicated reaction time and yield obtained, respectively, when the reaction was carried out with $NaBH_4$ alone.
[e] $NaBH_4$ (3 equiv) or a 1:1 mixture of $NaBH_4$ (3 equiv) and $H_3BO_3$ (3 equiv) was used.
[f] Unreacted ketones were recovered.

acetoacetate, and 2-ethoxycarbonylcycloheptanone, using the same methodology. In all cases, the reductions provided the corresponding alcohols in high yields and chemoselectivities. The same reductions using sodium borohydride itself with no aid of boric acid underwent more slowly (entries 8–13). For the complete reduction of 4-acetamidobenzaldehyde, 4-nitroacetophenone, 4-cyanoacetophenone, and benzoin, 3 equiv of the activated borohydride was required (entries 2, 6, 7, and 14). However, the reductions of methyl 5-acetylsalicylate and 4′-bromophenacyl bromide under the same conditions were very sluggish (entries 15 and 16).

## 2.3. Regioselective reduction of α,β-unsaturated aldehydes and ketones

As shown in Table 3, the solvent-free reduction of an α,β-unsaturated aldehyde, (*E*)-cinnamaldehyde using sodium borohydride in the absence and presence of boric acid provided (*E*)-cinnamyl alcohol (1,2-addition product) without the formation of saturated alcohols (1,4-addition product) in quantitative yield.[5a] In this reaction, boric acid did not seem to play a significant role as activator for the reduction (entries 1 and 2). However, this activator was highly effective for accelerating dramatically the reduction of α,β-unsaturated ketones such as (*E*)-4-phenyl-3-butene-2-one,[5b] 1-acetyl-1-cyclohexene, and 2-cyclohexenone,[5c] comparing the same reductions without the activator. The reductions were complete within 10 min to give only 1,2-addition products in quantitative yields (entries 3, 4, and 8–11). For the complete reductions of (*E*)-chalcone and β-ionone to give the corresponding allylic alcohols was required 2 equiv of boric acid-activated borohydride. However, the reduction of isophorone under the identical conditions was more sluggish. Despite use of a large excess of sodium borohydride (5 equiv), these reductions in the absence of activator proceeded very slowly with recovery of unreacted starting ketones (entries 6, 7, and 12–15). In the cases of 2-cyclohexenone and isophorone, the reductions with sodium borohydride alone provided a mixture of 1,2- and 1,4-addition products (entries 10 and 12). On the other hand, the activated borohydride also reduced α,β-ynones such as diphenylpropynone and 1-phenyl-2-heptyn-1-one to the corresponding propargylic alcohols in high yields and regioselectivities (entries 16 and 19).

**Table 3**. Solvent-free regioselective reduction of α,β-unsaturated aldehydes and ketones using solid acid-activated sodium borohydride[a]

| Run | Aldehydes and ketones | Activator | Time (min) | Product | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 |  | None | 10 |  | 98 |
| 2 | | $H_3BO_3$ | 10 | | 98 |
| 3 |  | None | 60 |  | 96[c] |
| 4 | | $H_3BO_3$ | 10 | | 98[c] |
| 5 | | $PhCO_2H$ | 30 | | 96[c] |
| 6 |  | None | 120 |  | 8[d] |
| 7 | | $H_3BO_3$ | 60 | | 98[e] |
| 8 |  | None | 60 |  | 27 |
| 9 | | $H_3BO_3$ | 10 | | 98 |
| 10 |  | None | 30 |  | [f] |
| 11 | | $H_3BO_3$ | 10 | | 98 |
| 12 |  | None | 60 |  | [f] |
| 13 | | $H_3BO_3$ | 60 | | 48[e] |
| 14 |  | None | 120 |  | 8[d] |
| 15 | | $H_3BO_3$ | 90 | | 98[e] |
| 16 |  | None | 90 |  | 15[d] |
| 17 | | $H_3BO_3$ | 40 | | 98[e] |
| 18 |  | None | 90 |  | 21[d] |
| 19 | | $H_3BO_3$ | 40 | | 99[e] |

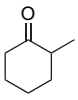
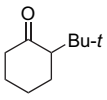
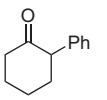
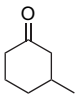
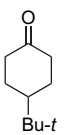
[a,b] See the corresponding footnotes in Table 1.
[c] Isolated yield.
[d] $NaBH_4$ (5 equiv) was used.
[e] A mixture of $NaBH_4$ (2 equiv) and boric acid (2 equiv) was used.
[f] A mixture of 1,2- and 1,4-reduction products was produced.

### 2.4. Stereoselective reduction of cyclic ketones

Using the same methodology, solvent-free stereoselective reductions of cyclic ketones, namely 2-methylcyclohexanone, 2-*tert*-butylcyclohexanone, 2-phenylcyclohexanone, 3-methylcyclohexanone, and 4-*tert*-butylcyclohexanone, were studied. As shown in Table 4, all the ketones examined were smoothly reduced to the corresponding alcohols in quantitative yields. All the reductions with one exception were satisfactorily accomplished even by sodium borohydride alone in the absence of activators. The reduction of 2-*tert*-butylcyclohexanone with sodium borohydride alone was very sluggish, giving the product alcohol in only 5% yield in 210 min. However, the same reduction with boric acid-activated sodium borohydride was completed in 120 min (entries 3 and 4). Comparing effectiveness of activators for the reduction of 2-phenylcyclohexanone and 4-*tert*-butylcyclohexanone, boric acid among solid acids selected provided the best results (entries 6–8 and 12–14). With respect to the stereoselection of product alcohols, all the reduction of cyclic ketones examined predominantly produced thermodynamically more stable alcohols, such as the ratio of 65% for *trans*-2-methylcyclohexanol, 40% for *trans*-2-*tert*-butylcyclohexanol, 65% for *trans*-2-phenylcyclohexanol, 86% for *cis*-3-methylcyclohexanol, and 92% for *trans*-4-*tert*-butylcyclohexanol. The results indicate that the reducing agents used preferentially attacks unhindered site of the carbonyl group of cyclic ketones examined.[6] Comparing the stereoselective ratios of product alcohols obtained, the effect of activators on the stereoselective reduction of the ketones examined was not significant.

On the other hand, in all the solvent-free reductions examined above, it was found that the order of mixing of the reactants had no discernible effects on the rate of reduction, yields, and the chemoselectivity, regioselectivity, and stereoselectivity of products. Also, the presence of moisture in air is not critical for the reduction. This hydride species of the mixture were stable in air at least for few hours with no loss of hydride activity. Although the structure of this reducing species of solid acid-activated sodium borohydride[7] and the mechanism of this reduction are unclear so far, it appears that a eutectic temperature with melting point lower than the ambient temperature exists in each case. In fact, the reaction mixture became oily or sticky during grinding the mixtures even though they are in powder states before grinding.

**Table 4**. Solvent-free stereoselective reduction of cyclic ketones using solid acid-activated sodium borohydride[a]

| Run | Ketone | Activator | Time (min) | Product alcohol | | Yield (%)[b] |
|---|---|---|---|---|---|---|
| | | | | *cis* | *trans* | |
| 1 |  | None | 45 | 38 | 62 | >99 |
| 2 | | $H_3BO_3$ | 15 | 35 | 65 | >99 |
| 3 |  | None | 210 | 53 | 47 | 5 |
| 4 | | $H_3BO_3$ | 120 | 56 | 43 | >99 |
| 5 |  | None | 30 | 31 | 69 | >99 |
| 6 | | $H_3BO_3$ | 20 | 35 | 65 | >99 |
| 7 | | $PhCO_2H$ | 20 | 38 | 62 | >99 |
| 8 | | PTSA[c] | 30 | 36 | 64 | >99 |
| 9 |  | None | 20 | 83 | 16 | >99 |
| 10 | | $H_3BO_3$ | 10 | 86 | 14 | >99 |
| 11 |  | None | 20 | 8 | 92 | >99 |
| 12 | | $H_3BO_3$ | 10 | 8 | 92 | >99 |
| 13 | | $PhCO_2H$ | 10 | 7 | 93 | >99 |
| 14 | | PTSA[c] | 10 | 8 | 92 | 80 (20)[d] |

[a–d] See the corresponding footnotes in Table 1.

## 3. Conclusion

We have established a convenient solvent-free reduction of aldehydes and ketones using solid acid-activated sodium borohydride. The reductions provided not only high chemoselectivity for functionalized aldehydes and ketones including other reducible functional groups, but also high regioselectivity for α,β-unsaturated aldehydes and ketones to give only the corresponding allylic alcohols. This is the first example for highly effective reduction of aldehydes and ketones under solvent-free conditions.

## 4. Experimental

### 4.1. General

The reactions were monitored by TLC using silica gel plates. GC analyses were performed on a Donam DS 6200 FID chromatograph, using a HP-1 (crosslinked methyl siloxane) capillary column (30 m). All GC yields were determined with use of a suitable internal standard and authentic mixture. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DPX FT (400 MHz) or Bruker Avance (300 MHz) spectrometer. The chemical shifts are expressed as units with $Me_4Si$ as the internal standard in $CDCl_3$. IR-spectra were recorded on a JASCO FTIR-460 and absorptions are reported in wave numbers ($cm^{-1}$).

### 4.2. Materials

Most of the organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation when necessary. Sodium borohydride, *p*-toluenesulfonic acid monohydrate, and benzoic acid were purchased from Aldrich or Lancaster and used without further purification.

#### 4.2.1. Solvent-free reduction of aldehydes and ketones using solid acid-activated sodium borohydride.

**4.2.1.1. General procedure.** A mixture of aldehyde or ketone (10 mmol), $NaBH_4$ (10 mmol), and boric acid, benzoic acid, or *p*-toluenesulfonic acid monohydrate (10 mmol) was ground with an agate mortar and pestle until TLC showed complete disappearance of the starting material. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ or 1 N HCl solution, followed by filtration of the resultant suspension to give product alcohol. When the product was liquid, it was isolated from extraction with $CH_2Cl_2$ or $Et_2O$ instead of filtration. All products were characterized by IR, $^1$H, and $^{13}$C NMR spectra. In the case of known compounds, their spectra were compared with those of authentic samples.

**4.2.1.2. 1-(5-Methyl-2-furyl)ethanol (Table 1, entry 36).** IR (neat, $cm^{-1}$): 3349, 2979, 2924, 2884, 1564, 1517, 1450, 1370, 1319, 1289, 1221, 1078, 1017; $^1H$ NMR ($CDCl_3$): $\delta$ 6.10 (d, $J$=3.1 Hz, 1H), 5.91–5.89 (m, 1H), 4.82 (q, $J$=6.6 Hz, 1H), 2.28 (s, 3H), 1.98 (br s, 1H), 1.52 (d, $J$=6.6 Hz, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.53, 21.17, 63.62, 105.81, 105.96, 151.67, 155.81.

**4.2.1.3. 4-Methoxycarbonylbenzyl alcohol (Table 2, entry 1).** IR (KBr, $cm^{-1}$): 3308, 3210, 3015, 2914, 2861, 1721, 1448, 1433, 1415, 1312, 1284, 1193, 1111, 1049; $^1H$ NMR ($CDCl_3$): $\delta$ 8.03 (d, $J$=8.3 Hz, 2H), 7.43 (d, $J$=8.6 Hz, 2H), 4.77 (s, 2H), 3.92 (s, 3H), 1.99 (br s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 52.13, 64.70, 126.47, 129.32, 129.86, 145.98, 166.98.

**4.2.1.4. 4-Acetamidobenzyl alcohol (Table 2, entry 2).** IR (KBr, $cm^{-1}$): 3421, 3246, 3188, 3126, 3074, 2924, 2882, 1670, 1608, 1549, 1517, 1411, 1371, 1323, 1273, 1211, 1002; $^1H$ NMR (DMSO): $\delta$ 9.88 (s, 1H), 7.50 (d, $J$=8.5 Hz, 2H), 7.21 (d, $J$=8.5 Hz, 2H), 5.08 (s, 1H), 4.41 (s, 2H), 2.01 (s, 3H); $^{13}C$ NMR (DMSO): $\delta$ 23.92, 62.60, 118.67, 126.86, 137.03, 137.91, 168.08.

**4.2.1.5. 4-Cyanobenzyl alcohol (Table 2, entry 3).** IR (neat, $cm^{-1}$): 3838, 3419, 2975, 2929, 2881, 2229, 1610, 1503, 1451, 1407, 1370, 1287, 1206, 1119, 1090, 1013; $^1H$ NMR ($CDCl_3$): $\delta$ 7.64 (d, $J$=8.4 Hz, 2H), 7.49 (d, $J$=8.1 Hz, 2H), 4.97 (q, $J$=6.5 Hz, 1H), 2.13 (s, 1H), 1.50 (d, $J$=6.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 25.42, 69.66, 111.07, 118.87, 126.07, 136.36, 151.12.

**4.2.1.6. 2-Methoxycarbonylcycloheptanol (Table 2, entry 13).** IR (neat, $cm^{-1}$): 3481, 2928, 2859, 1723, 1436, 1263, 1198, 1127, 1034; $^1H$ NMR ($CDCl_3$): $\delta$ 4.24–4.19 (m, 1H), 3.71 (s, 3H), 2.84 (s, 1H), 2.62 (dt, $J$=2.6, 10.0 Hz, 1H), 1.37–2.05 (m, 10H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 21.94, 24.18, 26.62, 27.82, 34.94, 49.76, 51.79, 70.27, 176.79.

**4.2.1.7. 1-(4′-Hydroxy-3′-methoxycarbonylphenyl)-ethanol (Table 2, entry 15).** IR (neat, $cm^{-1}$): 3341, 2972, 1684, 1617, 1595, 1490, 1442, 1318, 1214, 1086; $^1H$ NMR ($CDCl_3$): $\delta$ 10.71 (s, 1H), 7.84 (d, $J$=2.1 Hz, 1H), 7.48 (dd, $J$=2.2, 8.6 Hz, 1H), 6.97 (d, $J$=8.6 Hz, 1H), 4.86 (q, $J$=6.4 Hz, 1H), 3.96 (s, 3H), 1.79 (br s, 1H), 1.48 (d, $J$=6.39 Hz, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 25.12, 52.32, 69.64, 112.02, 117.76, 126.71, 133.16, 136.62, 160.96, 170.48.

**4.2.1.8. 2-Bromo-1-(4′-bromophenyl)ethanol (Table 2, entry 16).** IR (KBr, $cm^{-1}$): 3390, 2959, 2917, 1593, 1488, 1420, 1403, 1218, 1195, 1071, 1011; $^1H$ NMR ($CDCl_3$): $\delta$ 7.51 (d, $J$=8.4 Hz, 2H), 7.27 (d, $J$=8.1 Hz, 2H), 4.90 (dd, $J$=3.4, 8.8 Hz, 1H), 3.61 (dd, $J$=3.4, 10.5 Hz, 1H), 3.50 (dd, $J$=8.7, 10.1 Hz, 1H), 2.59 (br s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 39.89, 73.10, 122.37, 127.68, 131.82, 139.21.

**4.2.1.9. 1-(Cyclohexen-1-yl)ethanol (Table 3, entry 9).** IR (neat, $cm^{-1}$): 3349, 2972, 2929, 2858, 2837, 2661, 1668, 1437, 1366, 1293, 1166, 1137, 1096, 1060, 1007; $^1H$ NMR ($CDCl_3$): $\delta$ 5.67 (s, 1H), 4.17 (q, $J$=6.4 Hz, 1H), 1.97–2.05 (m, 4H), 1.53–1.67 (m, 4H), 1.26 (d, $J$=6.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 21.52, 22.61, 22.67, 23.67, 24.90, 72.18, 121.54, 141.27.

**4.2.1.10. 3,5,5-Trimethyl-2-cyclohexen-1-ol (Table 3, entry 13).** IR (neat, $cm^{-1}$): 3324, 3035, 2952, 2825, 2724, 1673, 1455, 1437, 1364, 1284, 1200, 1170, 1129, 1100, 1043, 1020; $^1H$ NMR ($CDCl_3$): $\delta$ 5.43 (s, 1H), 4.20–4.27 (m, 1H), 1.64–1.88 (m, 4H), 1.68 (s, 3H), 1.23 (dd, $J$=9.1, 12.4 Hz, 1H), 0.99 (s, 3H), 0.88 (s, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 23.54, 26.20, 31.07, 31.24, 44.12, 45.24, 66.84, 123.65, 136.02.

**4.2.1.11. 1,3-Diphenylpropyn-1-ol (Table 3, entry 17).** IR (neat, $cm^{-1}$): 3549, 3365, 3062, 3031, 2871, 2228, 1598, 1490, 1455, 1443, 1305, 1190, 1070, 1030; $^1H$ NMR ($CDCl_3$): $\delta$ 7.62–7.49 (m, 10H), 5.68 (s, 1H), 2.43 (br s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 65.10, 86.66, 88.70, 122.40, 126.74, 128.31, 128.44, 128.61, 128.67, 131.75, 140.62.

**4.2.1.12. 1-Phenyl-2-heptynol (Table 3, entry 19).** IR (neat, $cm^{-1}$): 3365, 3063, 3031, 2957, 2933, 2872, 2227, 1603, 1493, 1455, 1135, 1003; $^1H$ NMR ($CDCl_3$): $\delta$ 7.55–7.41 (m, 5H), 5.46 (s, 1H), 2.28 (dt, $J$=2.0, 6.9 Hz, 2H), 1.93 (br s, 1H), 1.89–1.56 (m, 4H), 0.92 (t, $J$=7.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.59, 18.51, 21.99, 30.66, 64.81, 79.95, 87.65, 125.92, 126.64, 128.18, 128.42, 128.52, 141.31.

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# (4+2) Cycloaddition to tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron for the rapid construction of a spiro[5.5]undecane system

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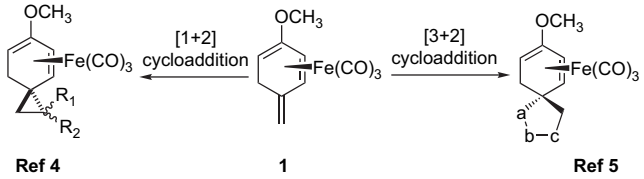
**Abstract**—Diels–Alder reactions of tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1** with 1,2,4,5-tetrazine-3,6-disubstituted derivatives **2a**,**b**,**d** and 2,3,4,5-tetrabromothiophene-1,1-dioxide **5** are reported. The (4+2) cycloaddition reactions took place exclusively with highly electron deficient dienes to form spiro[5.5]undecane system in good yield. The more electron rich nature of the 1,2,4,5-tetrazine-3,6-disubstituted derivatives **2b** did not react. The reaction also took place stereospecifically *exo* to the $Fe(CO)_3$ moiety.


## 1. Introduction

Development of effective methodology for the synthesis of spirocycles has been extensively reported because of their wide occurrence in a large number of natural products.[1] Among the numerous approaches for synthesizing spirocycles, the cycloaddition to an exocyclic double bond is one of the most rapid methods. Whereas the use of (3+2) cycloaddition to exocyclic double bond for the synthesis of spiro[4.*n*]alkanes has been widely reported,[2] and the use of (4+2) cycloaddition to exocyclic double bond is more restricted.[3] In our previous work, we investigated the (2+1) and (3+2) cycloaddition reactions to the exocyclic double bond of tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1** for the synthesis of spiro[5.2]octane and spiro[5.4]decane skeletons[4,5] (Scheme 1).




**Scheme 1**.

We envisioned that an efficient entry to the spiro[5.5]undecane skeleton can be similarly achieved by the use of (4+2) cycloaddition reactions to tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1**. More importantly, the lateral coordination of the bulky $Fe(CO)_3$ group should provide a high degree of regio-, stereo- and chemo-control during the (4+2) cycloaddition reaction with the 4π components. Herein we wish to report an efficient and practical method of constructing spiro[5.5]undecane skeletons with high regiospecific and stereospecific *exo*-selective Diels–Alder reactions.

## 2. Results and discussion

Initially, the exocyclic double bond of complex **1** was screened for its ability to react with electron rich dienes. The reaction of complex **1** with cyclopentadiene and 2,3-dimethylbutadiene did not afford any (4+2) cycloaddition products. This is consistent with our earlier findings that the exocyclic double bond in complex **1** behaves more like an electron rich double bond and undergoes electrophilic addition readily.[6] We next envisioned that the exocyclic double bond of complex **1** behaved as an electron rich dienophile and this required the use of electron deficient dienes for an inverse-electron demand (4+2) cycloaddition reaction. Surprisingly, complex **1** did not undergo (4+2) cycloaddition with hexa-2,4-dienedioic acid dimethyl ester.

Cycloheptatriene–tricarbonyliron complexes have been reported to undergo an inverse-electron demand (4+2) cycloaddition[7] with methyl 1,2,4,5-tetrazine-3,6-dicarboxylate. We first synthesized methyl 1,2,4,5-tetrazine-3,6-dicarboxylate **2a** according to the literature method.[8] The reaction of complex **1** with tetrazine **2a** afforded the (4+2) cycloaddition product **3a** that rapidly isomerizes into **4a** as the sole isolated product in 65% yield. The formation of **4a** can be attributed

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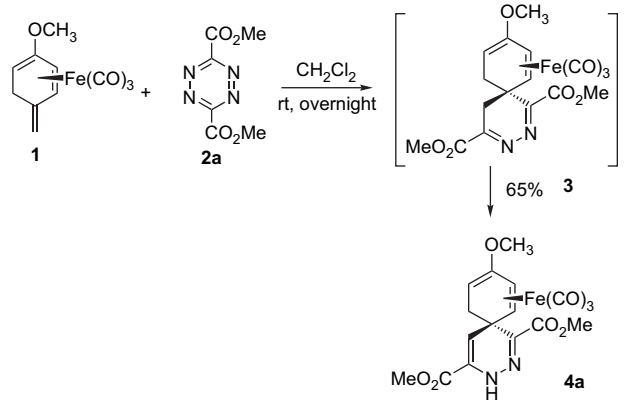
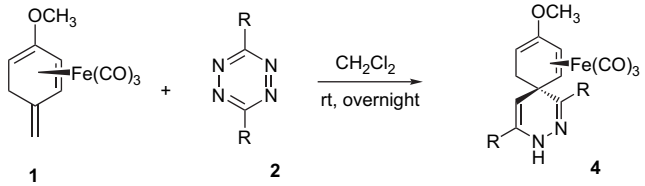
to the release of steric strain or perhaps the formation of a homoaromatic ring through intermediate **3** (Scheme 2). The structure of **4a** was assigned on the basis of IR and $^1$H NMR spectroscopic data. The IR spectrum of **4a** exhibited an NH band at 3415 cm$^{-1}$. Particular diagnostic signals present in the $^1$H NMR spectrum of **4a** include the presence of a C-5 methine proton at $\delta$ 5.61 and an NH peak at $\delta$ 8.33; whereas the C-5 methylene protons signal for **3a** was not observed. According to our previous study, cycloaddition reaction to the exocyclic double bond of complex **1** generally take place stereospecifically *exo* to the $Fe(CO)_3$ moiety and this was tentatively assigned.




**Scheme 2**. Inverse-electron demand (4+2) cycloaddition reaction.

We also synthesized other tetrazine derivatives **2b–d**[9,10] as the diene to react with complex **1**. Complex **1** was found to undergo cycloaddition reaction with tetrazine **2b** and **2d** to afford product **4b** and **4d** in 55% and 45%, respectively. Interestingly, **2c** did not undergo cycloaddition reaction with complex **1**. This can be attributed to the more electron rich nature of **2c** that possesses a methoxyphenyl substituent (Scheme 3).




| R= | Yield |
|---|---|
| b. -Phenyl | 45% |
| c. -4-Methoxyphenyl | no reaction |
| d. -Pyridiyl | 55% |

**Scheme 3**. Influence of substituent at the 1,2,4,5-tetrazine-3,6-derivatives **2** on the (4+2) cycloaddition reaction with complex **1**.

Another highly electron deficient diene that showed good reactivity with many electron rich dienophiles is 2,3,4,5-tetrabromothiophene-1,1-dioxide **5**.[11] 2,3,4,5-Tetrabromothiophene-1,1-dioxide **5** was prepared from thiophene via bromination followed by oxidation with *m*-chloroperoxybenzoic acid. When complex **1** was reacted with 2,3,4,5-tetrabromothiophene-1,1-dioxide **5**, at room temperature overnight, crystalline cycloaddition product **6** was obtained

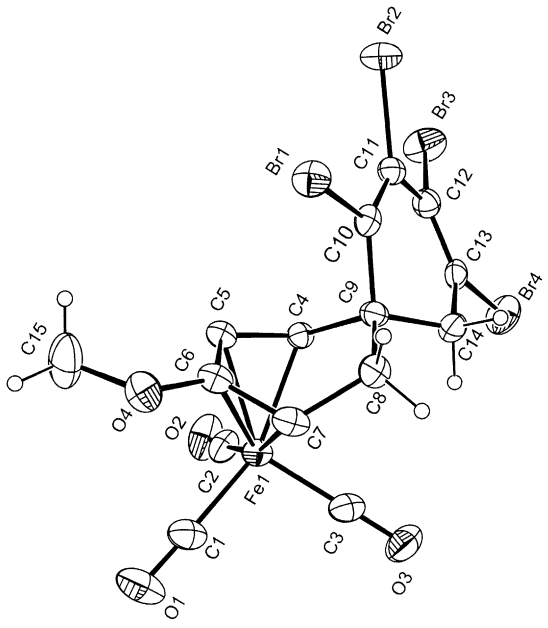
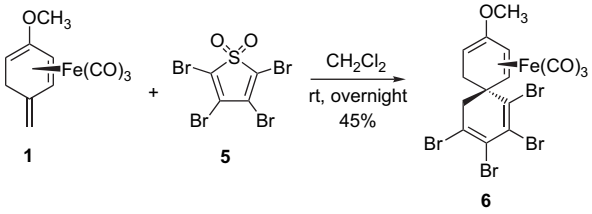



**Figure 1**. Single-crystal X-ray analysis and the ORTEP plot.

in 45% yield (Scheme 4). The structure of complex **6** was assigned on the basis of $^1$H NMR spectrum and further confirmed through single-crystal X-ray diffractometry, and the ORTEP plot[12] (Fig. 1) shows that the diene has approached the exocyclic double bond in complex **1** stereospecifically from less hindered *exo*-face.




**Scheme 4**. (4+2) Cycloaddition reaction of complex **1** with **5**.

In summary, the rapid methodology for the construction of spiro[5.5]undecane system from tricarbonyl[(1-4-η)-2-methoxy-5-methylene-cyclohexa-1,3-diene]iron **1** has been successfully developed. The reaction of complex **1** requires the use of highly electron deficient diene and take place stereospecifically *exo* to the $Fe(CO)_3$ moiety.

## 3. Experimental section

All reactions were performed under an atmosphere of dry nitrogen. IR spectra were measured with a Hitachi I-2001 spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on Varian Gemini-200 MHz or Varian UNITY INOVA 500 MHz using $CDCl_3$ as solvent and internal standard. Low- and high-resolution mass spectra were measured with a Hitachi M-52-Instrument or Bruker APEX II mass spectrometer. Melting points are uncorrected. Compounds **1**,[4,5] **2a–d**[7,8,9] and **5**[10] were prepared according to literature method.

### 3.1. General procedure for the (4+2) cycloaddition of triene complex 1 with diene

To a solution of triene complex **1** (1 mmol) in $CH_2Cl_2$ (10 mL) was added compound **3** or **4** (3 mmol). After stirring at room temperature overnight, the mixture was concentrated in vacuo and purified by preparative TLC to give the desired compound.

**3.1.1. Tricarbonyl{(7-9-η)-9-methoxy-2,3-diaza-spiro-[5.5]undeca-1,4,7,9-tetraene-1,4-dicarboxylic acid dimethyl ester}iron 4a.** Eluent: $CH_2Cl_2$. Yield: 65% as yellow solid. Mp: 142–143 °C. $R_f$: 0.22 ($CH_2Cl_2$). IR $\nu_{max}$ ($CH_2Cl_2$): 3415, 2047, 1972, 1719 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 8.33 (br s, N-H, 1H), 5.61 (d, $J$=2.5 Hz, 5-H, 1H), 4.95 (dd, $J$=6, 2.5 Hz, 8-H, 1H), 3.88 (s, –$CO_2$Me, 3H), 3.80 (s, –$CO_2$Me, 3H), 3.70 (s, –$OCH_3$, 3H), 3.39 (m, 10-H, 1H), 2.55 (dd, $J$=15, 2.5 Hz, *endo*-11-H, 1H), 2.33 (d, $J$=6 Hz, 7-H, 1H), 1.58 (dd, $J$=15, 2.5 Hz, *exo*-11-H, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 210.3 (CO), 163.8 ($CO_2$Me), 161.8 ($CO_2$Me), 141.9 (9-C), 135.3 (1-C), 126.9 (4-C), 115.7 (5-C), 62.7 (8-C), 56.7 (10-C), 54.7 (–$OCH_3$), 52.7 (7-C), 52.6 ($CO_2CH_3$), 52.3 ($CO_2CH_3$), 43.1 (11-C), 37.6 (6-C). Mass (FAB): *m/z* 433 ($M^+$+1), 432 ($M^+$), 404 ($M^+$−CO), 376 ($M^+$−2CO), 348 ($M^+$−3CO). HRMS (ESI) Calcd for $C_{17}H_{17}N_2O_8Fe$ ($M^+$+1): 433.0334; found: 433.0338. Anal. Calcd for $C_{17}H_{16}N_2O_8Fe$: C, 47.26; H, 3.73; N, 6.48. Found: C, 47.09; H, 3.83; N, 6.47.

**3.1.2. Tricarbonyl{(7-9-η)-9-methoxy-1,4-diphenyl-2,3-diaza-spiro[5.5]undeca-1,4,7,9-tetraene}iron 4b.** Eluent: $CH_2Cl_2$. Yield: 45% as yellow solid. Mp: 147–148 °C. $R_f$: 0.31 ($CH_2Cl_2$). IR $\nu_{max}$ ($CH_2Cl_2$): 3440, 2041, 1971 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 7.67 (br s, N-H, 1H), 7.33–7.51 (m, Ph, 10H), 4.84 (d, $J$=2 Hz, 5-H, 1H), 4.77 (dd, $J$=6.5, 2.5 Hz, 8-H, 1H), 3.45 (s, –$OCH_3$, 3H), 3.24 (m, 10-H, 1H), 2.63 (d, $J$=6.5 Hz, 7-H, 1H), 2.30 (dd, $J$=15, 2.5 Hz, *endo*-11-H, 1H), 1.77 (dd, $J$=15, 2.5 Hz, *exo*-11-H, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 211.2 (CO), 149.0 (1-C), 140.0 (9-C), 137.9 (4-C), 137.8 (Ph 1′-C), 134.5 (Ph 1-C), 129.7 (Ph 4-C), 128.9 (Ph 2-C), 128.8 (Ph 3′-C), 127.9 (Ph 3-C), 127.8 (Ph 2′-C), 125.5 (Ph 4′-C), 102.9 (4-C), 65.2 (8-C), 57.5 (10-C), 54.3 (–$OCH_3$), 52.9 (7-C), 43.4 (11-C), 40.8 (6-C). Mass (FAB): *m/z* 469 ($M^+$+1), 441 ($M^+$+1-CO), 412 ($M^+$−2CO), 384 ($M^+$−3CO). HRMS (FAB) Calcd for $C_{25}H_{21}N_2O_4Fe$ ($M^+$+1): 469.0852; found: 469.0840. Anal. Calcd for $C_{25}H_{20}N_2O_4Fe$: C, 64.15; H, 4.31; N, 5.98. Found: C, 64.13; H, 4.45; N, 6.04.

**3.1.3. Tricarbonyl{(7-9-η)-9-methoxy-1,4-dipyridyl-2,3-diaza-spiro[5.5]undeca-1,4,7,9-tetraene}iron 4d.** Eluent: $CH_2Cl_2$. Yield: 55% as yellow solid. $R_f$: 0.40 ($CH_2Cl_2$: EA = 10:1). IR $\nu_{max}$ ($CH_2Cl_2$): 3392, 2047, 1972 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 9.30 (br s, N-H, 1H), 8.56 (d, $J$=5 Hz, Py 2-H, 1H), 8.54 (d, $J$=5 Hz, Py 2′-H, 1H), 7.65–7.75 (m, Py-H, 4H), 7.20–7.25 (m, Py-H, 2H), 5.27 (d, $J$=1.5 Hz, 5-H, 1H), 4.84 (dd, $J$=6.5, 2.5 Hz, 8-H, 1H), 3.61 (s, –$OCH_3$, 3H), 3.36 (m, 10-H, 1H), 2.85 (dd, $J$=15, 2.5 Hz, *endo*-11-H, 1H), 2.68 (d, $J$=6.5 Hz, 7-H, 1H), 1.71 (dd, $J$=15, 2.5 Hz, *exo*-11-H, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 211.9 (CO), 156.5 (1-C), 150.3 (Py 2′-C), 148.3 (Py 6-C), 147.6 (Py 6′-C), 144.4 (Py 2-C), 141.9 (9-C), 136.7 (Py 4′-C), 136.0 (Py 4-C), 134.9 (4-C), 124.0 (Py 3-C), 123.0 (Py 5-C), 122.3 (Py 5′-C), 119.1 (Py 3′-C), 105.3 (5-C), 64.3 (8-C), 58.0 (10-C), 54.4 (–$OCH_3$), 53.2 (7-C), 42.9 (11-C), 39.6 (6-C). Mass (FAB): *m/z* 471 ($M^+$+1), 442 ($M^+$+1−CO), 414 ($M^+$−2CO), 386 ($M^+$−3CO). HRMS (FAB) Calcd for $C_{23}H_{19}N_4O_4Fe$ ($M^+$+1): 471.0757; found: 471.0762.

**3.1.4. Tricarbonyl{(7-9-η)-9-methoxy-1,2,3,4-tetra-bromo-spiro[5.5]undeca-1,3,7,9-tetraene}iron 6.** Eluent: hexane. Yield: 45% as yellowish crystals. Mp: 158–159 °C. $R_f$: 0.32 (hexane). IR $\nu_{max}$ ($CH_2Cl_2$): 2053, 1978 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.03 (dd, $J$=6.5, 2.5 Hz, 8-H, 1H), 3.70 (s, –$OCH_3$, 3H), 3.31 (m, 10-H, 1H), 2.82 (s, 5-H, 2H), 2.81 (d, $J$=6.5 Hz, 7-H, 1H), 2.33 (dd, $J$=15.5, 2.5 Hz, *endo*-11-H, 1H), 1.51 (dd, $J$=15.5, 2.5 Hz, *exo*-11-H, 1H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 210.4 (CO), 142.0 (9-C), 137.7 (4-C), 122.3 (1-C), 120.7 (2-C), 119.3 (3-C), 62.8 (8-C), 54.8 (–$OCH_3$), 52.6 (10-C), 52.4 (7-C), 49.0 (5-C), 46.8 (6-C), 43.3 (11-C). Mass (FAB): *m/z* 630 ($M^+$: $C_{15}H_{10}{}^{79}Br_2{}^{81}Br_2O_4Fe$), 602 ($M^+$−CO), 574 ($M^+$−2CO), 546 ($M^+$−3CO). HRMS (FAB) Calcd for $C_{15}H_{10}{}^{79}Br_2{}^{81}Br_2O_4Fe$ ($M^+$): 629.6619; found: 629.6635. Anal. Calcd for $C_{15}H_{10}Br_4O_4Fe$: C, 28.79; H, 1.61. Found: C, 28.75; H, 1.35.

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12. Crystal data for **6**: yellow crystal of $C_{15}H_7Br_4FeO_4$, MW=626.70, monoclinic, space group *P*-1 (no. 2), $a$=9.64(19) Å, $b$=13.82(3) Å, $c$=14.22(3) Å, $\alpha$=90.0°, $\beta$=99.8(3)°, $\gamma$=90.00°, $V$=1867(6) Å$^3$, $Z$=4, Dc=2.230 g cm$^{-3}$, $R$=0.052, Rw=0.134, GOF=1.03 for 3657 reflections with $I>2.00\sigma$. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Center under the following numbers: CCDC-605320.

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# Highly efficient microwave assisted α-trichlorination reaction of α-methylated nitrogen containing heterocycles

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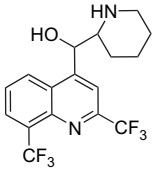
**Abstract**—A new methodology permitting the chlorination of different α-methylated nitrogen containing heterocycles into *N*-α-trichloromethylated derivatives is described here. The combination of microwave technology with a $PCl_5/POCl_3$ protocol has allowed to reach trichloromethyl derivatives with high yields in a few minutes.


## 1. Introduction

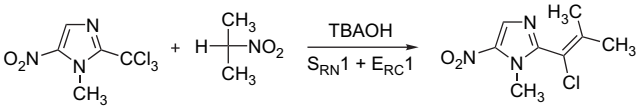
Trichloromethyl compounds are well-known precursors in the one-step synthesis of the corresponding trifluoromethyl structures, using fluorinating agents like $SbF_5$ or $SbF_3$.[1,2] Among trifluorinated structures, mefloquine can be mentioned as a major molecule of pharmaceutical interest (Scheme 1).




**Scheme 1**.

In order to optimize the global production of trifluoromethyl drug analogs, the efficient synthesis of the corresponding trichloromethyl substrates remains a preoccupation.

Aromatic α-trichloromethylated nitrogen containing heterocycles present another synthetic interest in the field of radical reactions, which are developed in our research team.[3] As shown in Scheme 2, trichloromethyl compounds, after being nitrated, are excellent substrates for consecutive $S_{RN}1$ and $E_{RC}1$ reactions with nitroalkane salts, leading to original vinyl chloride products.[4]




**Scheme 2**.

The methyl group trichlorination can be performed through radical mechanisms using *N*-chlorosuccinimide[5] or chlorine[6] with, respectively, purification and technical complications. Chupp's method[7] is also an original possibility for realizing this reaction in the case of methyl groups with acid protons, but has a more complicated protocol. Moreover, it presents real high yields when chloromethyl groups are transformed into trichloromethyl ones.

Kato[8–10] described another method concerning the specific trichlorination of a few α-methylated nitrogen containing heterocycles, using both phosphorus pentachloride and phosphorus oxychloride, providing medium yields, and requiring long reaction times.

Our laboratory being involved in the study of the microwave irradiation influence in organic chemistry,[3,11] we investigated the possibility of realizing such chlorination reactions through a microwave synthesis in order to optimize them and obtain the trichloromethyl derivatives in higher yields and much shorter reaction times. Applying this simple method, we studied the synthesis of various trichloromethyl compounds in quinoline, quinoxaline, quinazoline, benzoxazole, benzothiazole, and imidazo[2,1-*b*]thiazole series.

*Keywords*: Ionic polychlorination; Microwave assisted reactions; Nitrogen containing heterocycles.
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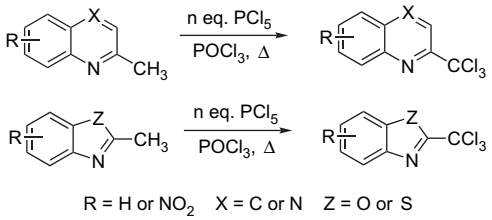
## 2. Results and discussion

From 1967 to 1981, Kato presented, in several publications,[8–10] a protocol permitting the trichlorination of the 'activated' methyl group in α-position of the $sp^2$ nitrogen atom in pyridine and quinoline series. This method uses phosphorus pentachloride as a powerful ionic chlorinating agent, and phosphorus oxychloride as a solvent, the reaction mixture being heated to reflux for a long time (from 12 to 60 h). The limitation of such a procedure rapidly appears because of the small or medium yields obtained (from 4 to 61%), depending on the substrate, considering the importance of reaction time needed.

In continuation of our studies exploring the chemical reactivity of α-trichloromethylated nitrogen containing heterocycles in electron transfer reactions, we tried to improve this chlorination synthesis procedure as far as obtaining the optimal procedure. We first started to work on the progression of this methodology in classical operating conditions, acting on two main parameters: reaction time and quantity of chlorinating agent used. For each substrate, repeating Kato's protocol, several times of reaction were investigated, and so was done for various quantities of $PCl_5$. The minimal required time for the reaction to proceed in a quantitative way is more often situated between 12 and 24 h. With longer times, the yield of the reaction decreases because of the highly reactive nature of the refluxed reaction mixture that damages the product previously formed. Optimal $PCl_5$ amount has then been determined. It always has to be superior to the number of hydrogen atoms that have to be substituted by chlorine ones, knowing that each $PCl_5$ molecule is able to liberate a single chlorine atom[9] for the chlorination reaction.

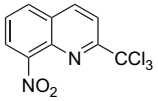
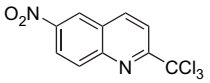
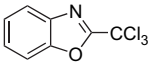
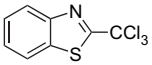
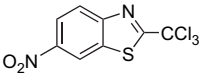
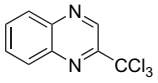
Consequently, in order to trichlorinate our substrates, the use of 4 equiv of $PCl_5$ usually provides the best yields, whereas some substrates require one more for being maximally transformed. Then, we decided to realize the same synthesis with a microwave assisted protocol using a microwave power of 800 W and studying the two same operating parameters. The global comparison between classical and microwave assisted conditions was then done, permitting to demonstrate the consequent contribution of the microwave technology in this synthetic approach (Scheme 3). Table 1 summarizes our optimal results in both conditions. It appears that in the microwave assisted reactions, times were massively reduced, and that the reaction yields were slightly increased or have, at least, remained constant.




**Scheme 3**.

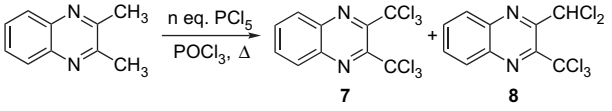
This single trichlorination reaction studied, we evaluated the possibility of performing a double trichlorination reaction in similar conditions, using 2,3-dimethylquinoxaline as a substrate (Scheme 4). Once more, we realized a parallel

**Table 1**. Optimal synthetic conditions and corresponding yields of monotrichlorination reactions

| Compound number | Product | *n* equiv of $PCl_5$ | Classical conditions[a] | | MW conditions[b] | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%) | Time (min) | Yield (%) |
| **1** |  | 4 | 12 | 89 | 5 | 98 |
| **2** |  | 5 | 24 | 61 | 20 | 83 |
| **3** |  | 4 | 12 | 74 | 20 | 75 |
| **4** |  | 4 | 12 | 81 | 30 | 86 |
| **5** |  | 4 | 12 | 84 | 10 | 89 |
| **6** |  | 5 | 1.5 | 75 | 15 | 84 |

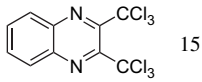
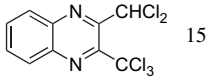
[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

optimization work on both classical and microwave assisted conditions. We synthesized the expected product 2,3-bis(trichloromethyl)quinoxaline **7**, but with lower yields compared to the products obtained with monomethylated substrates. Steric hindrance most probably explains this result, especially when we consider that the main product is 2-dichloromethyl-3-trichloromethylquinoxaline **8**. Here, the $PCl_5$ equivalent number has to be quite elevated so as to compete with steric limitations. Our optimal results are presented in Table 2.



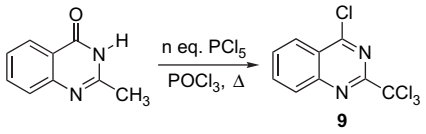

**Scheme 4**.

**Table 2**. Optimal synthetic conditions and corresponding yields of double trichlorination reaction

| Compound number | Product | *n* equiv of $PCl_5$ | Classical conditions[a] | | MW conditions[b] | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%) | Time (min) | Yield (%) |
| **7** |  | 15 | 24 | 35 | 30 | 30 |
| **8** |  | 15 | 24 | 50 | 30 | 60 |

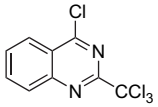
[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

Dehoff[12] and Smith[13] showed that the chlorination of 2-methylquinazolin-4-one with $PCl_5$ and $PCl_3$ logically affects the carbonyl group of the lactam ring, forming the aromatic tetrachlorinated product 4-chloro-2-trichloromethylquinazoline **9** with a maximum yield of 53%. We realized Kato's reaction on this substrate (Scheme 5), and optimized it. Table 3 presents the optimal results that we obtained in both operating conditions. Even without the use of microwaves, the yield of the reaction has been increased.



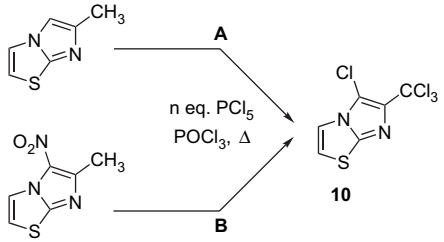

**Scheme 5**.

**Table 3**. Optimal synthetic conditions and corresponding yields for the synthesis of (**9**)

| Compound number | Product | *n* equiv of $PCl_5$ | Classical conditions[a] | | MW conditions[b] | |
|---|---|---|---|---|---|---|
| | | | Time (h) | Yield (%) | Time (min) | Yield (%) |
| **9** |  | 6 | 24 | 76 | 15 | 75 |

[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

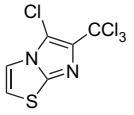
Finally, we developed this chlorination reaction on the imidazo[2,1-*b*]thiazole nucleus. As described in Scheme 6, 6-methylimidazothiazole (case A) and 6-methyl-5-nitroimidazothiazole (case B) were used as substrates for optimizing the trichlorination reaction in both classical and microwave operating conditions. Starting with two distinct substrates, the reaction product is the same compound: 5-chloro-6-trichloromethylimidazo[2,1-*b*]thiazole **10**.




**Scheme 6**.

In case A, the chlorination of the methyl group is associated to the chlorination of the 5-position. In case B, the same methyl trichlorination is accompanied with the substitution of the nitro group by a chlorine atom. Such behavior for a nitro group was already noted by Kato[10] who performed the same substitution on 2-methyl-3-nitroquinoline derivatives. Table 4 presents our optimal results for the two distinct synthesis access to **10** with both traditional and microwave assisted methodologies.

**Table 4**. Optimal operating conditions and corresponding yields for the formation of (**10**)

| Compound number | Product | Method | *n* equiv of $PCl_5$ | Classical conditions[a] | | MW conditions[b] | |
|---|---|---|---|---|---|---|---|
| | | | | Time (h) | Yield (%) | Time (min) | Yield (%) |
| **10** |  | **A** | 5 | 24 | 86 | 10 | 85 |
| | | **B** | 5 | 24 | 89 | 10 | 88 |

[a] Reaction mixture heated to reflux of $POCl_3$.
[b] Reaction mixture heated to reflux of $POCl_3$ under 800 W microwave irradiation.

## 3. Conclusion

The application of microwave assisted reaction to the chlorination protocol described by Kato proved to be a very efficient methodology in order to synthesize α-trichloromethylated nitrogen containing heterocycles. This very simple procedure provides high yields in a minimal time of reaction. Then, different types of chemical reactivity for the trichloromethyl group offer synthetic possibilities such as nucleophilic and polynucleophilic substitutions, vinyl chloride access and present a real pharmaceutical interest as the main synthetic pathway to trifluoromethyl compounds, very numerous among the therapeutic arsenal.

## 4. Experimental

### 4.1. General

Microwave assisted reactions were done in a multimode microwave oven ETHOS Synth Lab Station (Ethos start, Milestone Inc.). Melting points were determined with a B-540 Büchi melting point apparatus. $^1H$ NMR (200 MHz) and $^{13}C$ NMR (50 MHz) spectra were recorded on a Brüker ARX 200 spectrometer in $CDCl_3$ solution at the Faculté de Pharmacie de Marseille. $^1H$ and $^{13}C$ NMR chemical shifts ($\delta$) are reported in parts per million with respect to $CDCl_3$ 7.26 ppm ($^1H$) and 77.16 ppm ($^{13}C$). Elemental analyses were carried out at the Centre de Microanalyses de la Faculté des Sciences et Techniques de Saint-Jérôme. The following adsorbent was used for flash column chromatography: silica gel 60 (Merck, particle size 0.063–0.200 mm, 70–230 mesh ASTM). TLC were performed on 5 cm×10 cm aluminum plates coated with silica gel 60F-254 (Merck) in appropriate solvent.

### 4.2. Experimental procedure

2-Trichloromethylquinoxaline (**6**) was described previously.[14]

**4.2.1. General trichlorination procedure in classical operating conditions.** The required equivalent number of phosphorus pentachloride and twice as much equivalents of phosphorus oxychloride were added to the substrate at 0 °C. The mixture was then heated to reflux and stirred for the adapted time, depending on the substrate. After cooling, the mixture was alkalinized with a saturated sodium carbonate solution and extracted with chloroform. Purification was

conducted by flash chromatography on a silica gel column eluting with dichloromethane–petroleum ether (1:1).

**4.2.2. General microwave assisted trichlorination reaction.** The required equivalent number of phosphorus pentachloride and twice as much equivalents of phosphorus oxychloride were added to the substrate at 0 °C. The mixture was placed in the microwave oven irradiating with 800 W, heating to reflux for the adapted time, depending on the substrate. After cooling, the mixture was alkalinized with a saturated sodium carbonate solution and extracted with chloroform. Purification was conducted by flash chromatography on a silica gel column eluting with dichloromethane–petroleum ether (1:1). Recrystallization wasn't necessary for compounds **1**, **2**, **7–10**, which were pure enough for elementary analysis.

**4.2.3. 8-Nitro-2-trichloromethylquinoline (1).** Pale yellow crystals, mp 127 °C. $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 7.71 (1H, dd, $J$=8.0 and 7.8 Hz, $H_6$), 8.10 (2H, m, $H_5$, $H_7$), 8.18 (1H, d, $J$=8.8 Hz, $H_4$), 8.43 (1H, d, $J$=8.8 Hz, $H_3$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 97.1 (C), 119.4 (CH), 124.8 (CH), 127.2 (CH), 128.4 (C), 131.4 (CH), 136.7 (C), 138.3 (CH), 148.2 (C), 159.0 (C). Anal. Calcd for $C_{10}H_5Cl_3N_2O_2$ (291.5): C, 41.20; H, 1.73; N, 9.61. Found: C, 41.55; H, 1.67; N, 9.99.

**4.2.4. 6-Nitro-2-trichloromethylquinoline (2).** Pale yellow crystals, mp 152 °C. $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 8.24 (1H, d, $J$=8.9 Hz, $H_4$), 8.35 (1H, d, $J$=9.3 Hz, $H_8$), 8.53 (1H, d, $J$=8.9 Hz, $H_3$), 8.58 (1H, dd, $J$=9.3 and 2.5 Hz, $H_7$), 8.85 (1H, d, $J$=2.5 Hz, $H_5$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 97.2 (C), 119.5 (CH), 123.8 (CH), 123.9 (CH), 126.8 (C), 132.1 (CH), 139.9 (CH), 146.8 (C), 147.9 (C), 160.5 (C). Anal. Calcd for $C_{10}H_5Cl_3N_2O_2$ (291.5): C, 41.20; H, 1.73; N, 9.61. Found: C, 41.70; H, 1.71; N, 9.84.

**4.2.5. 2-Trichloromethylbenzoxazole (3).** Colorless crystals, mp 61 °C (lit.[15]: 60 °C). $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 7.47 (2H, m, $H_5$, $H_6$), 7.62 (1H, m, $H_4$), 7.86 (1H, m, $H_7$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 86.0 (C), 111.4 (CH), 121.7 (CH), 125.7 (CH), 127.5 (CH), 139.9 (C), 151.5 (C), 160.0 (C).

**4.2.6. 2-Trichloromethylbenzothiazole (4).** Yellow crystals, mp 38 °C (lit.[15]: 37 °C). $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 7.54 (2H, m, $H_5$, $H_6$), 7.91 (1H, m, $H_4$), 8.15 (1H, m, $H_7$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 91.3 (C), 121.7 (CH), 124.8 (CH), 127.1 (CH), 127.2 (CH), 136.5 (C), 157.1 (C), 169.5 (C).

**4.2.7. 6-Nitro-2-trichloromethylbenzothiazole (5).** Yellow crystals, mp 110 °C (lit.[6]: 113 °C). $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 8.26 (1H, d, $J$=9.1 Hz, $H_4$), 8.45 (1H, dd, $J$=9.1 and 2.3 Hz, $H_5$), 8.88 (1H, d, $J$=2.3 Hz, $H_7$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 90.3 (C), 118.5 (CH), 122.5 (CH), 125.4 (CH), 136.7 (C), 146.1 (C), 155.6 (C), 174.8 (C).

**4.2.8. 2,3-Bis(trichloromethyl)quinoxaline (7).** Colorless crystals, mp 176 °C. $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 7.95 (2H, m, $H_6$, $H_7$), 8.22 (2H, m, $H_5$, $H_8$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 96.8 (2C), 128.9 (2CH), 133.1 (2CH), 138.8 (2C), 146.6 (2C). Anal. Calcd for $C_{10}H_4Cl_6N_2$ (364.9): C, 32.92; H, 1.10; N, 7.68. Found C, 32.99; H, 1.08; N, 7.68.

**4.2.9. 2-Dichloromethyl-3-trichloromethylquinoxaline (8).** Colorless crystals, mp 160 °C. $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 7.81 (1H, s, $CHCl_2$), 7.93 (2H, m, $H_6$, $H_7$), 8.21 (1H, m, $H_8$), 8.30 (1H, m, $H_5$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 67.1 (CH), 95.7 (C), 129.0 (CH), 129.8 (CH), 132.6 (CH), 132.7 (CH), 138.8 (C), 142.4 (C), 145.6 (C), 149.2 (C). Anal. Calcd for $C_{10}H_5Cl_5N_2$ (330.5): C, 36.35; H, 1.53; N, 8.48. Found C, 36.23; H, 1.49; N, 8.47.

**4.2.10. 4-Chloro-2-trichloromethylquinazoline (9).** White powder, mp 127 °C (lit.[12,13]). $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 7.86 (1H, m, $H_6$), 8.08 (1H, m, $H_7$), 8.22 (1H, dd, $J$=8.5 and 0.5 Hz, $H_5$), 8.36 (1H, dd, $J$=8.4 and 0.6 Hz, $H_8$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 95.9 (C), 122.9 (C), 126.0 (CH), 129.7 (CH), 130.6 (CH), 135.9 (CH), 150.2 (C), 159.9 (C), 164.0 (C).

**4.2.11. 5-Chloro-6-trichloromethylimidazo[2,1-*b*]thiazole (10).** Colorless crystals, mp 84 °C. $^1$H NMR (200 MHz; $CDCl_3$): $\delta$ 7.02 (1H, d, $J$=4.5 Hz, $H_2$), 7.40 (1H, d, $J$=4.5 Hz, $H_3$). $^{13}$C NMR (50 MHz; $CDCl_3$): $\delta$ 90.2 (C), 107.7 (C), 115.6 (CH), 116.6 (CH), 142.1 (C), 145.5 (C). Anal. Calcd for $C_6H_2Cl_4SN_2$ (276.0): C, 26.11; H, 0.73; N, 10.15. Found: C, 26.28; H, 0.72; N, 9.84.

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# Synthesis and stability of 1,1-dialkyl-1*H*-azulenium cations

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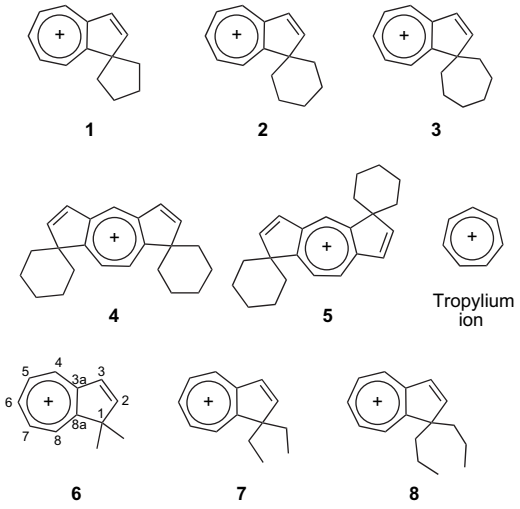
**Abstract**—Starting from trimethylsilyl enol ether of 1-acetyl-1,3,5-cycloheptatriene, the title 1,1-dimethyl-, 1,1-diethyl-, and 1,1-dipropyl-1*H*-azulenium cations **6–8** were synthesized in five steps. The order of p$K_R$+ values of these cations was found to be **7**>**8**>**6**. A comparison of the values between 1,1-dialkyl- and 1,1-spiroalkylated 1*H*-azulenium cations with the same number of carbon atoms at the 1-position provided the results of **7**>**1** and **8**<**3**. The cation **8** shows a relatively lower p$K_R$+ value to those of **3** and **7** probably due to its slightly bulkier propyl groups from which solvation stabilization of **8** under the conditions suffers. An intermolecular charge-transfer interaction between the cations and dibenzo-24-crown-8 was also studied.


## 1. Introduction

We previously reported the synthesis and some crystal structures of various 1,1-spiroalkylated 1*H*-azulenium cations **1**–**5**.[1,2] Their p$K_R$+ values were in a range of 9.9–13.2, which are far greater than that of the tropylium cation. The order of the stability of mono-spiroalkylated cations increases with the number of carbon atoms of the carbocycle at the 1-position, as **3**>**2**>**1** and the reluctance against electrochemical reduction showed a similar tendency.[1] The enhanced thermodynamic stability is attributed to a hybrid stabilization of the inductive and σ–π conjugation effects of the carbocycle and the π–π conjugation of the double bond at the 2- and 3-positions. Since the degree of the π–π conjugative effects is the same in a series of the cations, the order of the stability of mono-spiroalkylated cations should mainly meet the degree of the effects of the substituents at the 1-position; the cation having more carbon atoms in the substituents at the 1-position should be more stable. Herein, we describe the synthesis of 1*H*-azulenium cations **6–8** substituted simply by linear alkyl groups and also their stability, which does not come up to the order of the number of carbon atoms in the alkyl groups.




## 2. Results and discussion

### 2.1. Synthesis and physical properties of 1,1-dialkyl-1*H*-azulenium cations 6–8

The title cations were synthesized by the method, which we had developed for the spiroalkylated cation **3**[3] (Scheme 1). The Mukaiyama aldol reaction[4] of the trimethylsilyl enol ether **9** with the ketones in the presence of titanium tetrachloride and the subsequent Nazarov cyclization[5,6] provided the azulenones **13–15** in moderate yields. Since the yield of the keto-alcohol **12** was slightly less than those of others, the Noyori–Mukaiyama aldol reaction[7] was also applied for **9**

*Keywords*: Carbocations; p$K_R$+ values; Tropylium ions; Nazarov cyclizations; Intermolecular charge-transfer interaction.
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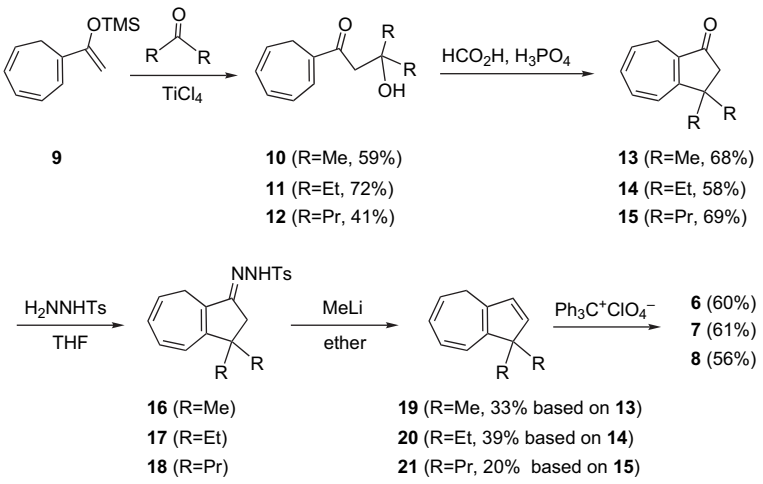
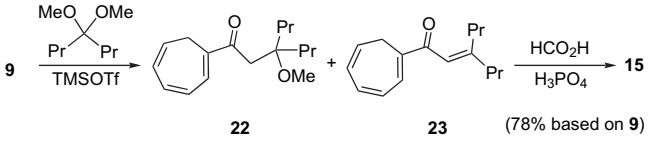



**Scheme 1**.

with 4,4-dimethoxyheptane. The reaction gave a mixture of two products, **22** and **23** (Scheme 2). Separation of the products by column chromatography resulted in isolation of only **23**. So far, **22** has not been isolated, though its existence in the mixture was confirmed by its NMR spectrum. Without purification, this mixture was converted by the Nazarov cyclization into **15** in 78% yield based on **9**. The azulenones **13**–**15** were transformed into the 1,4-dihydroazulenes **19**–**21** via the tosylhydrazone **16**–**18** by the Shapiro reaction.[8] The final hydride abstraction with trityl perchlorate ($Ph_3C^+ClO_4^-$) produced the desired cations **6**–**8**. Their structures were fully characterized by spectroscopic and combustion analyses. The results of H–H COSY, HMQC, and HMBC experiments covered the assignments of both proton and carbon signals indicated in Section 5 except the carbon signals for the 6- and 7-positions of **6**. Their UV spectra showed three bands at 224–231, 264–271, and 358–363 nm as seen in the spectra of **1**–**3** (Table 1; Figs. 1 and 2).




**Scheme 2**.

**Table 1**. UV absorption maxima in acetonitrile of **1**, **2**, **3**, **6**, **7**, and **8**

| Compounds | $\lambda_{max}$ in nm (log $\varepsilon$) |
|---|---|
| **1** | 230 (4.31), 272 (4.44), 364 (4.00) |
| **2** | 230 (4.26), 272 (4.33), 367 (4.07) |
| **3** | 227 (4.29), 268 (4.34), 362 (4.03) |
| **6** | 222 (4.33), 264 (4.43), 358 (4.09) |
| **7** | 228 (4.15), 268 (4.18), 362 (3.94) |
| **8** | 231 (4.29), 271 (4.35), 363 (4.08) |

## 2.2. Thermodynamic stability and reduction potentials of 1,1-dialkyl-1*H*-azulenium cations

Assuming equilibrium between a carbocation and its corresponding alcohol (Eq. 1), the p$K_R$+ value can be determined,[9] which indicates thermodynamic stability for the carbocation.

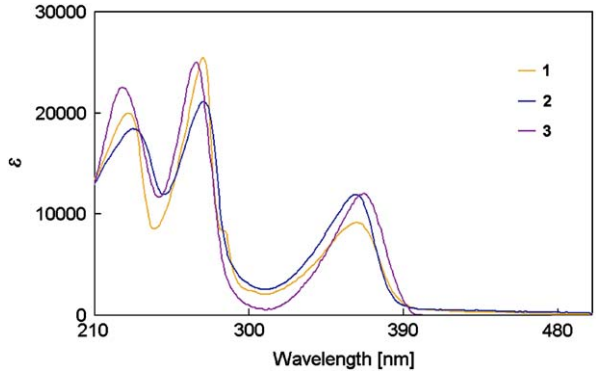



**Figure 1**. UV spectra of the cations **1**–**3** in acetonitrile.

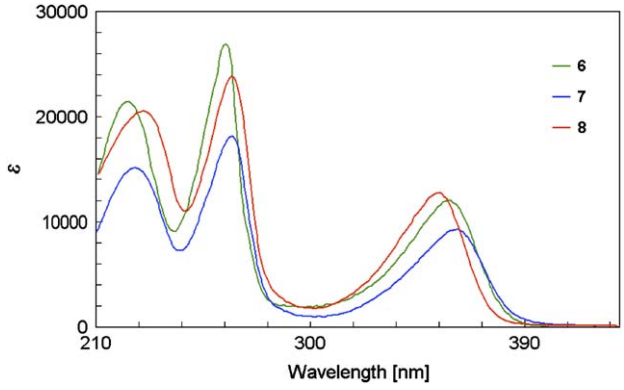



**Figure 2**. UV spectra of the cations **6**–**8** in acetonitrile.

$$R^+ + H_2O \rightleftharpoons ROH + H^+ \quad (1)$$

The p$K_R$+ values of **6**, **7**, and **8** obtained by the UV method in 50% aqueous acetonitrile solutions were 8.6, 10.1, and 9.2, respectively (Table 2). The thermodynamic stability of these cations is comparable to those of the cations **1**–**3** and

**Table 2**. The p$K_R$+ values and reduction potentials of **1**, **2**, **3**, **6**, **7**, and **8**

| Compounds | p$K_R$+ values[a] | Reduction potentials (V vs SCE)[b] |
|---|---|---|
| **1** | 9.9 | −0.41 |
| **2** | 10.0 | −0.46 |
| **3** | 10.4 | −0.54 |
| **6** | 8.6 | −0.38 |
| **7** | 10.1 | −0.45 |
| **8** | 9.2 | −0.46 |

[a] For measurements, see Section 5.
[b] Irreversible.

1,2-bicyclo[2.2.2]octanotropylium cation (**24**, p$K_R$+ 8.8)[10] and is greater than that (p$K_R$+ 3.88)[11] of the tropylium cations. The order of the stability (**7**>**8**>**6**) is not that expected from the number of carbon atoms in the alkyl groups. Since two propyl groups located at the 1-position of the cation **8** are slightly hydrophobic and bulky to show steric hindrance, the solvation stabilization in the aqueous acetonitrile solution of the cation **8** must suffer.[12] In other words, the degree of the inductive and conjugative effects of the propyl group in **8** cannot be adequately evaluated from this p$K_R$+ value. On the other hand, tropylium ions in general show irreversible potentials by electrochemical reduction (Fig. 3). The reduction potentials of tropylium ions indicate their reluctance for the reduction and provide another empirical stability parameter for carbocations.[13] Reduction potentials for **6**–**8** measured by cyclic voltammetry in an acetonitrile solution with tetrabutylammonium perchlorate as a supporting electrolyte are shown in Table 2.

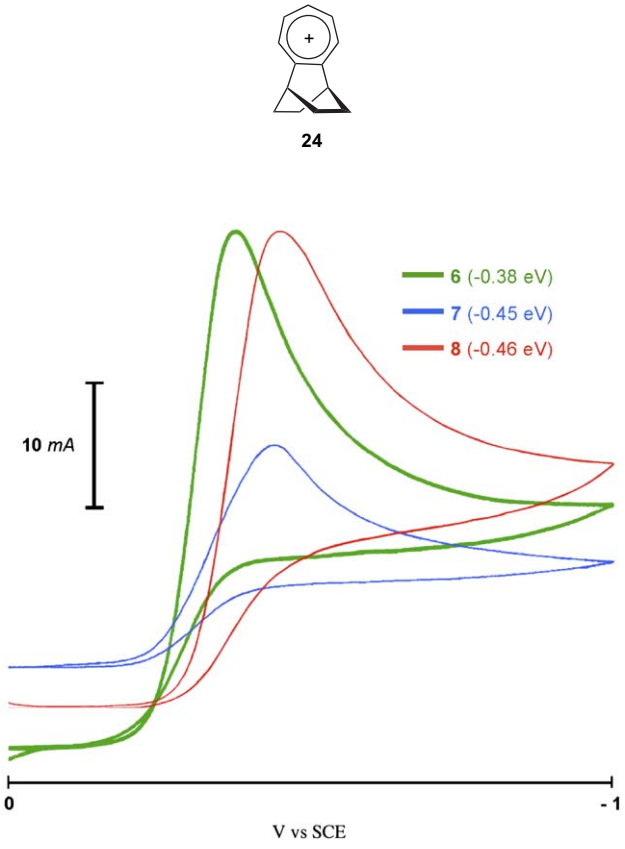



**Figure 3**. Cyclic voltammograms of the cations **6**–**8** in an acetonitrile solution containing 0.1 M tetrabutylammonium perchlorate.

Although the potentials of **6**–**8** decrease with increasing number of carbon atoms in the substituents, the value of **8** is comparable to that of **7**, suggesting that stabilization by inductive and σ–π conjugative effects of the propyl groups in **8** is the same as that of the ethyl groups in **7**. This is in contrast to the result in the case of 1,1-spiroalkyl-1*H*-azulenium cations **1**–**3**. Specially, it is most clear when the cations with the same number of carbon atoms in the substituents at the 1-position between two series of 1,1-dialkyl- and 1,1-spiroalkyl cations are compared; **7** shows slightly greater stability than **1** based not only on the p$K_R$+ values but also on reduction potentials, though stability of **8** is less than that of **3**. Therefore, it is apparent that stabilization by inductive and σ–π conjugative effects of the alkyl group in the 1,1-dialkyl system is almost saturated up to the number of six carbon atoms.

## 3. Intermolecular charge-transfer interaction of the 1,1-substituted 1*H*-azulenium cations with dibenzo-24-crown-8

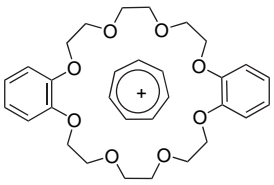
The tropylium cation as an acceptor shows intermolecular charge-transfer (ICT) interactions with n-donors of halide anions[14] and π-donors of aromatic hydrocarbons.[15] Benzene-substituted crown ethers are known to serve also as a π-donor and show ICT absorptions with tropylium cations.[16] As a typical example, the tropylium cation and dibenzo-24-crown-8 yielded the 1:1 inclusion complex **25**.[17] We also are interested in whether the 1,1-substituted 1*H*-azulenium cations interact with dibenzo-24-crown-8 or not. In order to examine such possibility, measurements of $^1$H NMR and UV–vis spectra in the presence of the crown ether were carried out. The difference between the average chemical shifts of the cationic protons in the presence and absence of the crown ether is quite small as shown in Table 3. The acetonitrile solutions containing a 1:1 mixture of the cation and the crown ether indicated clear ICT bands around 500–700 nm. However, attempts to isolate inclusion complexes have met with little success so far. These results suggest that the interaction between the azulenium cations and the benzene ring of the crown ether occurs not in the way of the cationic part sandwiched between two benzene rings of the crown ether like **25** but the cationic part with one benzene ring at the outside of the crown molecule, probably due to larger molecular sizes of these azulenium cations than that of the tropylium cation. Further study for evaluating the associate constant for complexes and interaction using

**Table 3**. The change of average chemical shifts of the cations **1**, **2**, **3**, **6**, **7**, and **8** in the presence of dibenzo-24-crown-8 and ICT absorption bands

| Compounds | Change of the shift[a] $\delta$ (ppm) | ICT absorption wavelength (nm)[b] |
|---|---|---|
| **1** | +0.031 | 599, 646 |
| **2** | +0.025 | 650, 715sh |
| **3** | +0.016 | 554, 667 |
| **6** | +0.04 | 655 |
| **7** | +0.01 | 520sh |
| **8** | +0.006 | 509sh |
| Tropylium ion | +0.11 | 425[c] |

[a] The average shifts of the seven-membered ring protons of a 1:1 mixture in $CDCl_3$ solutions.
[b] Measured in acetonitrile.
[c] Taken from Ref. 16.

crown ethers with a larger core size is the focus of current investigations.



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## 4. Summary

We have synthesized and characterized the 1,1-dialkyl-1*H*-azulenium cations **6**–**8** whose stability was discussed based on their p$K_R$+ values and reduction potentials. The p$K_R$+ value of the cation **8** is smaller relative to those of **1**, **2**, **3**, and **7**. This can be ascribed to its restrained solvation stabilization due to its slightly bulkier substituents. Comparison of reduction potentials of various 1*H*-azulenium cations suggests that stabilization by inductive and σ–π conjugative effects shows saturation up to the number of six carbon atoms in the alkyl group in the 1,1-dialkyl-1*H*-azulenium cations.

## 5. Experimental

### 5.1. General

Melting points were measured on a Yanaco MP-3 and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum RX I spectrometer. UV spectra were measured on a Shimadzu UV-1600 spectrometer. $^1$H and $^{13}$C NMR were recorded with tetramethylsilane as an internal standard on JEOL α400 spectrometer. Mass spectra were measured on a JMS-700 mass spectrometer. Cyclic voltammograms were recorded on a Yanako P1100 instrument. Column chromatography was done with either Merck Kieselgel 60 Art 7734 or Wako activated alumina. Ether and THF were purified by distillation from sodium and benzophenone under argon atmosphere. An ether solution of methyl lithium was purchased from Kanto Chem. Co. and was titrated before use. Titanium tetrachloride was purchased from Wako Chem. and was used without purification. Dibenzo-24-crown-8 was purchased from Tokyo Kasei Industry. The syntheses of 1-(trimethylsiloxyvinyl)-1,3,5-cycloheptatriene **9** from 1-acetyl-1,3,5-cycloheptatriene and 3,3-dimethyl-1,2,3,8-tetrahydroazulenone **14** via **10** from **9** were previously reported.[3] Trityl perchlorate was prepared by the method of Dauben et al.[18]

**5.1.1. Synthesis of 3,3-diethyl- and 3,3-dipropyl-1,2,3,8-tetrahydroazulenones (14 and 15) by the Mukaiyama aldol method.** A solution of 2.06 g (10.0 mmol) of the silyl enol ether **9** in 30 ml of dichloromethane was added dropwise to a solution of 1.30 ml (11.0 mmol) of titanium chloride and 3.20 ml (30.0 mmol) of 3-pentanone in 20 ml of dichloromethane at 0 °C under nitrogen atmosphere. After being stirred for 3 h, the reaction mixture was poured into water. The aqueous layer was extracted with dichloromethane (50 ml×2). The combined organic layer was washed with a saturated $NaHCO_3$ aqueous solution and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography ($SiO_2$, hexane–ethyl acetate (9:1) as eluent) to give 1.58 g (72% yield) of **11** as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 0.86 (t, *J*=7.6 Hz, 6H), 1.53 (m, 4H), 2.63 (d, *J*=7.1 Hz, 2H), 2.83 (s, 2H), 4.15 (br s, 1H), 5.58 (dt, *J*=9.4, 7.1 Hz, 1H), 6.29 (dd, *J*=9.4, 5.6 Hz, 1H), 6.71 (dd, *J*=11.2, 5.9 Hz, 1H), 6.88 (dd, *J*=11.2, 5.9 Hz, 1H), 7.12 (d, *J*=5.9 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) δ 8.1, 25.2, 31.3, 43.6, 74.4, 125.8, 127.3, 129.1, 131.9, 133.1, 136.5, 201.8 ppm; IR (KBr) $\nu_{max}$=1647s, 732s cm$^{-1}$; MS (20 eV) *m*/*z* (rel int) 220 (M$^+$, 2), 202 (18), 134 (18), 119 (93), 91 (100), 65 (25), 57 (28). Found: 220.1463. Calcd for $C_{14}H_{20}O_2$: M, 220.1445.

A mixture of 1.35 g (6.52 mmol) of **11** in formic acid (7.5 ml) and phosphoric acid (7.5 ml) was heated at 90 °C for 4 h. Then the resulted dark brown mixture was poured into water and extracted with ether (50 ml×3). The combined organic layer was washed with a saturated $NaHCO_3$ aqueous solution and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography ($SiO_2$, hexane–ethyl acetate (9:1) as eluent) to give 700 mg (58% yield) of **14** as a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 0.68 (t, *J*=6.1 Hz, 6H), 1.61 (m, 4H), 2.29 (s, 2H), 2.68 (d, *J*=6.5 Hz, 2H), 5.65 (dt, *J*=9.9, 6.5 Hz, 1H), 6.13 (dd, *J*=9.9, 5.9 Hz, 1H), 6.63 (d, *J*=11.3 Hz, 1H), 6.80 (dd, *J*=11.3, 5.9 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) δ 8.5, 21.5, 31.4, 44.3, 46.6, 125.4, 127.2, 127.9, 133.5, 136.7, 168.5, 206.0 ppm; IR (KBr) $\nu_{max}$= 2963s, 1692s cm$^{-1}$; MS (70 eV) *m*/*z* (rel int) 202 (M$^+$, 80), 173 (32), 145 (100), 131 (39), 118 (58), 105 (22), 91 (45). Found: 202.1358. Calcd for $C_{14}H_{18}O$: M, 202.1373.

Similarly **15** was obtained via **12**. Compound **12**: a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 0.89 (t, *J*=7.2 Hz, 6H), 1.23–1.52 (m, 8H), 2.64 (d, *J*=7.3 Hz, 2H), 2.83 (s, 2H), 5.59 (dt, *J*=9.3, 7.2 Hz, 1H), 6.29 (dd, *J*=9.3, 5.6 Hz, 1H), 6.70 (dd, *J*=11.2, 6.0 Hz, 1H), 6.89 (dd, *J*=11.2, 5.6 Hz, 1H), 7.10 (d, *J*=6.0 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) δ 14.6, 17.1, 25.2, 41.9, 44.4, 74.1, 125.8, 127.3, 129.0, 131.9, 133.0, 136.5, 201.8 ppm; IR (KBr) $\nu_{max}$=3480br m, 2933s, 1650s, 1603s, 1408s, 1384s, 1200s, 1170s, 717s cm$^{-1}$; MS (20 eV) *m*/*z* (rel int) 230 (M$^+$−$H_2O$, 19), 205 (5), 134 (19), 133 (22), 119 (28), 118 (18), 115 (14), 105 (10), 103 (7), 92 (13), 91 (100), 90 (30), 89 (27).[19] Found: 230.1636. Calcd for $C_{16}H_{22}O$: M, 230.1671. Compound **15**: a pale yellow oil. $^1$H NMR ($CDCl_3$) δ 0.83–0.91 (m, 2H), 0.85 (t, *J*=7.2 Hz, 6H), 1.09–1.19 (m, 2H), 1.44 (td, *J*=12.8, 4.1 Hz, 2H), 1.57 (td, *J*=12.8, 4.1 Hz, 2H), 2.32 (s, 2H), 2.66 (d, *J*=6.5 Hz, 2H), 5.65 (dt, *J*=9.9, 7.2 Hz, 1H), 6.13 (dd, *J*=9.9, 6.0 Hz, 1H), 6.64 (d, *J*=11.4 Hz, 1H), 6.78 (dd, *J*=11.4, 6.0 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) δ 14.6, 17.7, 21.6, 41.7, 45.7, 46.1, 125.6, 127.4, 128.1, 133.0, 136.8, 169.4, 206.4 ppm; IR (KBr) $\nu_{max}$=2957s, 2929s, 1692s, 1272s cm$^{-1}$; MS (70 eV) *m*/*z* (rel int) 231 (M$^+$+1, 19), 230 (M$^+$, 100), 224 (21), 188 (31), 187 (40), 167 (15), 159 (81), 149 (50), 145 (84). Found: 230.1674. Calcd for $C_{16}H_{22}O$: M, 230.1671.

**5.1.2. Synthesis of 3,3-dipropyl-1,2,3,8-tetrahydroazulenone (21) by the Noyori–Mukaiyama aldol method.** To a solution of 5.15 g (25.0 mmol) of the silyl enol ether **9**

and 4.41 g (27.5 mmol) of 4,4-dimethoxyheptane in 125 ml of dichloromethane at −78 °C under nitrogen atmosphere was added 0.45 ml (2.5 mmol) of trimethylsilyl triflate. After being stirred at the same temperature for 19 h, the reaction mixture was poured into water. The aqueous layer was extracted with dichloromethane (50 ml×2). The combined organic layer was washed with a saturated $NaHCO_3$ aqueous solution and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography ($SiO_2$, hexane–ethyl acetate (96:4) as eluent) to give 5.98 g of a mixture of **22** and **23** as a pale yellow oil. This mixture was dissolved in formic acid (40 ml) and phosphoric acid (40 ml) and was heated at 90 °C for 4 h. The resulted dark brown mixture was poured into ice-water (100 ml) and extracted with ether (100 ml×3). The combined organic layer was washed with a saturated $NaHCO_3$ aqueous solution and brine, and then dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography ($SiO_2$, hexane–ethyl acetate (9:1) as eluent) to give 4.48 g (78% yield based on **9**) of **15** as a pale yellow oil.

Purification of a mixture of **22** and **23** by column chromatography gave **23** as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.94 (t, $J$=7.3 Hz, 6H), 1.45–1.55 (m, 4H), 2.14 (t, $J$=7.6 Hz, 2H), 2.42 (t, $J$=7.9 Hz, 2H), 2.67 (d, $J$=7.2 Hz, 2H), 5.59 (dt, $J$=8.9, 7.2 Hz, 1H), 6.26 (dd, $J$=9.3, 5.6 Hz, 1H), 6.41 (s, 1H), 6.68 (dd, $J$=11.1, 6.0 Hz, 1H), 6.81 (dd, $J$=11.1, 5.6 Hz, 1H), 7.05 (d, $J$=6.0 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 14.4, 21.0, 21.9, 25.9, 34.7, 40.5, 120.8, 125.4, 127.0, 129.3, 131.3, 139.9, 135.2, 161.4, 191.5 ppm; UV ($CH_3OH$) $\lambda_{max}$=291 (log $\varepsilon$=3.91), 318sh (3.78) nm; IR (KBr) $\nu_{max}$=2957s, 2929s, 1692s, 1272s cm$^{-1}$; MS (70 eV) *m/z* (rel int) 230 ($M^+$, 100), 201 (29), 187 (45), 159 (22), 145 (78), 139 (48), 119 (26), 91 (78). Found: 230.1670. Calcd for $C_{16}H_{22}O$: M, 230.1671.

**5.1.3. Synthesis of 1,1-dimethyl-, 1,1-diethyl-, and 1,1-dipropyl-1,4-dihydroazulenes (19, 20, and 21).** A suspension of **14** (0.895 g, 4.43 mmol) of tosylhydrazide in 5 ml of dry THF was stirred at 40 °C for 72 h. The solids formed were collected by filtration and washed well with ether to give 0.848 g of **16** (56% yield) as a white powder. Analytical samples of **16** were obtained by recrystallization from hexane–dichloromethane.

Compound **16**: colorless microcrystals, mp 197–198 °C. Found: C, 66.39; H, 6.48; N, 8.25%. Calcd for $C_{19}H_{22}N_2O_2S$: C, 66.64; H, 6.47; N, 8.18%.

To a suspension of 1.00 g (2.92 mmol) of **16** in 20 ml of dry ether at 0 °C under nitrogen atmosphere was added 50 ml of methyl lithium solution (0.8 M ether solution, 40 mmol) slowly through a syringe. After the addition, the mixture was stirred for 12 h. The mixture was quenched by adding water carefully and was poured into a mixture of ether and ice-water. The aqueous layer was extracted with ether (50 ml×2). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography ($SiO_2$, hexane as eluent) to give 273 mg (59% yield) of **19** as a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 1.14 (s, 6H), 2.69 (d, $J$=6.4 Hz, 2H), 5.35 (dt, $J$=9.6, 6.8 Hz, 1H), 6.08 (dd, $J$=9.6, 6.0 Hz, 1H), 6.08 (d, $J$=5.6 Hz, 1H), 6.37 (d, $J$=5.6 Hz, 1H), 6.39 (dd, $J$=10.8, 6.0 Hz, 1H), 6.56 (d, $J$=10.8 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 22.6, 27.9, 51.8, 120.7, 125.2, 127.37, 127.40, 130.6, 132.8, 148.6, 149.2 ppm; IR (KBr) $\nu_{max}$=2925s, 732s cm$^{-1}$; MS (70 eV) *m/z* (rel int) 158 ($M^+$, 35), 143 (100), 128 (74), 115 (18), 91 (23), 77 (21), 58 (22). Found: 158.1049. Calcd for $C_{12}H_{14}$: M, 158.0960.

Similarly, **14** and **15** were transformed to **20** without isolating **17** in 31% yield based on **14** and to **21**.

Compound **20**: a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.51 (t, $J$=7.3 Hz, 6H), 1.52 (dq, $J$=11.4, 7.3 Hz, 2H), 1.73 (dq, $J$=11.4, 7.3 Hz, 2H), 2.68 (d, $J$=6.6 Hz, 2H), 5.34 (dt, $J$=9.6, 6.6 Hz, 1H), 6.06 (dd, $J$=9.8, 5.9 Hz, 1H), 6.17 (d, $J$=5.4 Hz, 1H), 6.22 (d, $J$=5.4 Hz, 1H), 6.38 (dd, $J$=11.0, 5.6 Hz, 1H), 6.46 (d, $J$=11.0 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 8.7, 27.8, 29.0, 60.4, 120.4, 125.5, 127.1, 128.7, 133.0, 135.0, 144.9, 145.4 ppm; IR (KBr) $\nu_{max}$=2964s, 2931s, 729s cm$^{-1}$; MS (70 eV) *m/z* (rel int) 186 ($M^+$, 19), 171 (27), 157 (69), 141 (55), 129 (100), 115 (43), 105 (24), 91 (46), 77 (23), 57 (63). Found: 186.1437. Calcd for $C_{14}H_{18}$: M, 186.1409.

Compound **18**: creamy white solids, mp 139–141 °C. Found: C, 69.32; H, 7.71; N, 6.92%. Calcd for $C_{23}H_{30}N_2O_2S$: C, 69.31; H, 7.59; N, 7.03%.

Compound **21**: a pale yellow oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.75 (t, $J$=6.8 Hz, 6H), 0.78–0.89 (m, 2H), 0.90–1.05 (m, 2H), 1.44 (m, 2H), 1.66 (m, 2H), 2.67 (d, $J$=6.4 Hz, 2H), 5.33 (dt, $J$=9.8, 6.4 Hz, 1H), 6.06 (dd, $J$=9.8, 6.0 Hz, 1H), 6.13 (d, $J$=5.4 Hz, 1H), 6.27 (d, $J$=5.4 Hz, 1H), 6.36 (dd, $J$=11.0, 6.0 Hz, 1H), 6.49 (d, $J$=11.0 Hz, 1H) ppm; $^{13}$C NMR ($CDCl_3$) $\delta$ 14.7, 17.4, 27.8, 38.7, 59.8, 120.4, 125.6, 127.1, 127.2, 132.4, 134.5, 145.8, 146.3 ppm; IR (KBr) $\nu_{max}$= 2955s, 2929s, 2870s, 731s cm$^{-1}$; MS (70 eV) *m/z* (rel int) 214 ($M^+$, 32), 213 (53), 185 (32), 171 (39), 155 (31), 143 (49), 142 (32), 131 (21), 129 (100), 128 (60), 117 (36), 115 (49). Found: 214.1650. Calcd for $C_{16}H_{22}$: M, 214.1721.

**5.1.4. Synthesis of 1,1-dimethyl-, 1,1-diethyl-, and 1,1-dipropyl-1*H*-azulenium perchlorates (6, 7, and 8).** To a solution of the precursor hydrocarbon (1.00 mmol) in 10 ml of acetonitrile at 0 °C under nitrogen atmosphere was added trityl perchlorate (1.00 mmol) in one portion. The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was dissolved in the least amount of dichloromethane. Ether was added to the solution and solids formed were collected and washed well with cold ether.

Compound **6**: yellow microcrystals, mp 99–100 °C. $^1$H NMR ($CD_3CN$) $\delta$ 1.55 (s, Me), 7.37 (d, $J$=5.2 Hz, H-3), 7.73 (d, $J$=5.2 Hz, H-2), 8.76 (tt, $J$=9.7, 1.4 Hz, H-6), 8.83 (td, $J$=9.7, 1.4 Hz, H-7), 8.91 (td, $J$=9.7, 1.4 Hz, H-5), 9.00 (dd, $J$=9.7, 1.4 Hz, H-4), 9.02 (dd, $J$=9.7, 1.4 Hz, H-8) ppm; $^{13}$C NMR ($CD_3CN$) $\delta$ 21.6 (Me), 57.8 (C-1), 133.4 (C-3), 145.6 (C-4), 146.1 (C-8), 149.7 (C-6 or 7), 149.8 (C-7 or 6), 153.1 (C-5), 167.8 (C-2), 171.0 (C-3a), 180.0 (C-8a) ppm; IR (KBr) $\nu_{max}$=1087s, 626s cm$^{-1}$; MS (70 eV) *m/z* (rel int) 157 ($C_{12}H_{13}^+$, 17), 156 (68), 141 (100),

128 (23), 115 (28). Found: C, 56.20; H, 5.18%. Calcd for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.10%.

Compound **7**: faintly greenish microcrystals, mp 97–99 °C. $^1$H NMR ($CD_3CN$) $\delta$ 0.50 (t, $J$=7.4 Hz, Me), 2.17 (dq, $J$=14.4, 7.4 Hz, one of $CH_2$), 2.32 (dq, $J$=14.4, 7.4 Hz, one of $CH_2$), 7.52 (d, $J$=5.6 Hz, H-3), 7.71 (d, $J$=5.2 Hz, H-2), 8.80 (tt, $J$=10.0, 1.3 Hz, H-6), 8.85 (td, $J$=10.0, 1.3 Hz, H-5), 8.95 (td, $J$=10.0, 1.3 Hz, H-5), 8.99 (dd, $J$=10.0, 1.3 Hz, H-4), 9.02 (dd, $J$=10.0, 1.3 Hz, H-8) ppm; $^{13}$C NMR ($CD_3CN$) $\delta$ 9.0 (Me), 29.7 ($CH_2$), 67.3 (C-1), 136.0 (C-3), 144.6 (C-4), 145.3 (C-8), 149.5 (C-7), 149.7 (C-6), 153.0 (C-5), 165.7 (C-2), 172.5 (C-3a), 178.5 (C-8a) ppm; IR (KBr) $\nu_{max}$=1449s, 1095s, 623s cm$^{-1}$; MS (70 eV) *m*/*z* (rel int) 185 ($C_{14}H_{17}^+$, 88), 171 (21), 169 (30), 157 (78), 141 (100), 129 (95), 128 (56), 115 (41). Found: C, 58.88; H, 5.97%. Calcd for $C_{12}H_{13}ClO_4$: C, 59.06; H, 6.02%.

Compound **8**: faintly brownish microcrystals, mp 148–150 °C. $^1$H NMR ($CD_3CN$) $\delta$ 0.55–0.66 (m, one of H-2′, 2H), 0.73 (t, $J$=7.1 Hz, Me, 6H), 0.96–1.07 (m, one of H-2′, 2H), 2.07 (m, one of H-1′, 2H), 2.32 (m, one of H-1′, 2H), 7.45 (d, $J$=5.4 Hz, H-3), 7.73 (d, $J$=5.4 Hz, H-2), 8.75 (tt, $J$=10.0, 1.5 Hz, H-6), 8.79 (td, $J$=10.0, 1.5 Hz, H-5), 8.90 (td, $J$=10.0, 1.5 Hz, H-5), 8.96 (d-like, H-4 and H-8) ppm; $^{13}$C NMR ($CD_3CN$) $\delta$ 14.4 (C-3′, Me), 18.3 (C-2′, $CH_2$), 38.9 (C-1′, $CH_2$), 66.5 (C-1), 135.3 (C-3), 144.5 (C-4), 145.2 (C-8), 149.3 (C-7), 149.5 (C-6), 152.7 (C-5), 166.1 (C-2), 172.1 (C-3a), 178.9 (C-8a) ppm; IR (KBr) $\nu_{max}$=1490s, 1450s, 1095s, 831s, 623s cm$^{-1}$; MS (70 eV) *m*/*z* (rel int) 213 ($C_{16}H_{21}^+$, 4), 212 (21), 184 (16), 183 (100), 165 (16), 155 (16), 154 (28), 153 (21), 152 (20), 141 (13), 128 (10). Found: C, 61.86; H, 6.81%. Calcd for $C_{16}H_{21}ClO_4$: C, 61.44; H, 6.77%.

### 5.2. Determination of p$K_R$+ values

The UV spectra in various pH of 50% aqueous acetonitrile solutions were measured by exactly the same method of Komatsu et al.[11] Observed absorbance at the longest absorption maxima at 358–363 nm was plotted against pH to give a classical titration curve, whose midpoint was taken as the p$K_R$+.

### 5.3. Cyclic voltammetry

A standard three-electrode cell configuration was employed using a glassy carbon disk working electrode, a Pt wire auxiliary electrode, and an Ag wire as an Ag/Ag$^+$ quasi-reference electrode. The reference electrode was calibrated at the completion of each measurement on a saturated calomel electrode (SCE). Cyclic voltammetry was measured in an acetonitrile solution with tetrabutylammonium perchlorate as a supporting electrolyte and a scan rate of 0.1 V s$^{-1}$ at 25 °C. Under these conditions, ferrocene showed a half wave oxidation potential of +0.40 V versus SCE.

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# Synthesis and kinetic investigation of the selective acidolysis of *para*-substituted *N*-benzyl- or *N*-phenyl-*N*-phenylacetyl-α,α-dialkylglycine cyclohexylamides

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**Abstract**—Several derivatives of *N*-phenylacetyl-*N*-benzyl-α,α-dimethylglycine cyclohexylamide and their α,α-dibenzylglycine analogues were synthesised by a Ugi–Passerini reaction. In addition, a few analogues of the former but having an *N*-phenyl instead of a benzyl group at the nitrogen atom were synthesised. The compounds in each of these three sets differed from each other at position 4 of the *N*-benzyl (and *N*-phenyl) group. These adducts were submitted to acidolysis with TFA to obtain the corresponding free acids, the reactions being monitored by HPLC and data collected for kinetic purposes. The kinetic data were submitted to Hammett uni- and biparametric relationships and the results were analysed in terms of structure–reactivity in connection with the sensitivity of the reaction rates to the electronic contributions of the various substituents at position 4 of the aromatic rings. The results allowed comparison with information obtained in previous investigations and rationalise the contribution of the substituent at the nitrogen atom to the lability of the C-terminal amide bond.


## 1. Introduction

Conformational rigidity increases potency and selectivity of bioactive peptides, improving their bioavailability and enhancing resistance to peptidases.[1] Consequently, design of conformationally constrained peptides is one of the approaches for development of bioactive species with high activity and selectivity towards a specific receptor.[2,3] Owing to steric crowding within the neighbourhood of the α-carbon atom of α,α-dialkylglycines, conformational rigidity can be obtained by inserting one or more residues of these amino acids into the peptide chain. In addition, special conformational features imparted to the peptide backbone by these amino acid residues[4–7] may be used to modulate the activity and selectivity. This can be best achieved by previous parametrisation of these amino acids[8] followed by molecular dynamics simulations of the bioactive peptides[9] as modified at strategic positions by one or more residues of these amino acid units. Once the most promising peptide sequences are predicted, it is necessary to synthesise the selected compounds. In most cases these amino acids are not commercially available and their synthesis is usually difficult due to steric hindrance of the required reactions. Nevertheless, the interest these amino acids have raised in late years led to the recent development of a few interesting and sometimes ingenious approaches for preparation of either symmetric[10–12] or asymmetric compounds.[13,14] Having obtained the required amino acids is not sufficient to reach one's goal, as again steric crowding makes their insertion into a peptide chain even more problematic than the amino acid synthesis; thus, conventional methods of peptide synthesis become unpractical as reflected by the low yields observed in the rare cases where a product is obtained. A promising way to overcome these difficulties would consist in synthesising the α,α-dialkylglycine unit already incorporated into the peptide chain, a route that is in principal offered by the four-component Ugi-Passerini reaction.[16] This is particularly appropriate when no concern for asymmetric induction is required, such as in the case of symmetric α,α-dialkylglycines, which are among the simplest and most widely used structural units in the construction of peptides with a predetermined secondary structure.[15] However, the above strategy is not exempt of difficulties, as it requires that (i) the unwanted alkyl group bound to the nitrogen atom of the dialkylated centre be removed and (ii) the unavoidable racemisation of the amino acid residue that follows the

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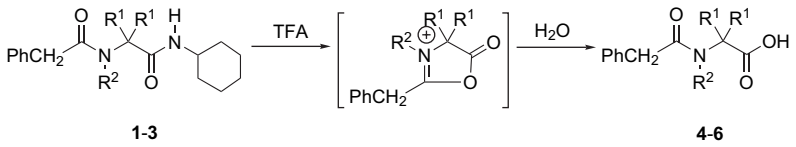



**1a**, **4a** $R^1$ = Me, $R^2$ = 4-MeO-$C_6H_4CH_2$ **2a**, **5a** $R^1$ = Bn, $R^2$ = 4-MeO-$C_6H_4CH_2$ **3a**, **6a** $R^1$ = Me, $R^2$ = 4-MeO-$C_6H_4$
**1b**, **4b** $R^1$ = Me, $R^2$ = 4-Me-$C_6H_4CH_2$ **2b**, **5b** $R^1$ = Bn, $R^2$ = 4-Me-$C_6H_4CH_2$ **3b**, **6b** $R^1$ = Me, $R^2$ = $C_6H_5$
**1c**, **4c** $R^1$ = Me, $R^2$ = $C_6H_5CH_2$ **2c**, **5c** $R^1$ = Bn, $R^2$ = $C_6H_5CH_2$ **3c**, **6c** $R^1$ = Me, $R^2$ = 4-Cl-$C_6H_4$
**1d**, **4d** $R^1$ = Me, $R^2$ = 4-F-$C_6H_4CH_2$ **2d**, **5d** $R^1$ = Bn, $R^2$ = 4-F-$C_6H_4CH_2$ **3d**, **6d** $R^1$ = Me, $R^2$ = 4-CN-$C_6H_4$
**1e**, **4e** $R^1$ = Me, $R^2$ = 4-Cl-$C_6H_4CH_2$ **2e**, **5e** $R^1$ = Bn, $R^2$ = 4-Cl-$C_6H_4CH_2$ **3e**, **6e** $R^1$ = Me, $R^2$ = 4-$NO_2$-$C_6H_4$
**1f**, **4f** $R^1$ = Me, $R^2$ = 4-$CF_3O$-$C_6H_4CH_2$ **2f**, **5f** $R^1$ = Bn, $R^2$ = 4-$CF_3O$-$C_6H_4CH_2$
**1g**, **4g** $R^1$ = Me, $R^2$ = 4-$CF_3$-$C_6H_4CH_2$ **2g**, **5g** $R^1$ = Bn, $R^2$ = 4-$CF_3$-$C_6H_4CH_2$
**1h**, **4h** $R^1$ = Me, $R^2$ = 4-$NO_2$-$C_6H_4CH_2$ **2h**, **5h** $R^1$ = Bn, $R^2$ = 4-$NO_2$-$C_6H_4CH_2$

**Scheme 1**.

newly synthesised unit be overcome. We have shown that the former can be achieved if the unwanted *N*-substituent is methoxybenzyl,[17] and that the latter can be overcome by taking advantage of the lability of the amide bond at the C-terminus of the α,α-dialkyl glycine unit.[18–20] This allows obtaining the amino acid unit at the peptide C-terminus, ready for further elongation of the chain without any risk of racemisation. The above can be achieved by treatment of Ugi–Passerini adduct with trifluoroacetic acid (TFA), but this approach will prove useful only if the double cleavage can be performed under acceptable selectivity and in good yield, which depends on the nature and structure of this adduct. In order to assess the selectivity of the amide bond cleavage, we have further investigated its mechanism and evaluated the effect of the substituent bulk and structure at the N- and C-terminus, and also at the α-carbon atom of the fully substituted amino acid (Scheme 1).[21,23] In order to complete this investigation, we now present the results of a similar evaluation concerning the nature of the alkyl substituent bound to the N-terminal nitrogen atom of Ugi–Passerini adduct.

## 2. Results and discussion

### 2.1. Syntheses

In our previous work it was found that the bulk of the amino acid side chains may affect seriously not only the rate of the acidolyses but also the path of the reactions involved.[20] Compounds with methyl group at the side chain reacted faster and behaved better when compared with the corresponding benzyl analogues where a larger steric effect had to be expected. Thus, for the present investigation we designed one set of compounds with methyl (substrates **1**) and another with benzyl (substrates **2**) at the amino acid side chain, with eight substrates in each set (Scheme 1). As in our previous work $R^2$ was always 4-methoxybenzyl, for these two sets we chose differently substituted benzyl groups (including the nonsubstituted group). In addition, we have also devised a third set of substrates with methyl at the amino acid side chain but in which $R^2$ was a phenyl, substituted or not in position 4 (substrates **3**); in this case only five compounds were envisaged. All the compounds were synthesised by Ugi–Passerini reaction using phenylacetic acid, cyclohexyl isonitrile, the appropriate amine and acetone (compounds **1a**–**1h** and **3a**–**3e**) or dibenzyl ketone (compounds **2a**–**2h**) according to the methodologies described elsewhere (Table 1).[19,20] As shown previously[18,20] and is depicted in Scheme 1, these substrates undergo acidolysis, which proceeds via an oxazolone derivative to yield the corresponding open-chain *N*-acyl-*N*,α,α-trialkylglycine. Thus, each of the above substrates was treated at room temperature with 5% TFA in acetonitrile to give three new sets of compounds (**4**, **5** and **6**) homologous to the previous ones (**1**, **2** and **3**, respectively) and the yields are presented also in Table 1.

**Table 1**. Synthesis of Ugi–Passerini adducts $PhCH_2CO$-N(4-X-$C_6H_4$-$CH_2$)-C($R^1$)$_2$CO-$NHC_6H_{11}$ (**1a**–**1h** and **2a**–**2h**) and $PhCH_2CO$-N(4-X-$C_6H_4$)-C($CH_3$)$_2$CO-$NHC_6H_{11}$ (**3a**–**3e**) and of their cleavage products (**4a**–**4h**, **5a**–**5h** and **6a**–**6e**, respectively)

| X | Compound | | Yield (%) | Compound | | Yield[a] (%) | Compound | | Yield (%) | Compound | | Yield[a] (%) | Compound | | Yield (%) | Compound | | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | No. | | $R^1$ | No. | | $R^1$ | No. | | $R^1$ | No. | | $R^1$ | No. | | $R^1$ | No. | |
| $CH_3O$ | Me | **1a** | 91 | Me | **4a** | 84 | Bn | **2a** | 82 | Bn | **5a** | 68 | Me | **3a** | 92 | Me | **6a** | 98[b] |
| $CH_3$ | Me | **1b** | 90 | Me | **4b** | 89 | Bn | **2b** | 60 | Bn | **5b** | 93 | | | | | | |
| H | Me | **1c** | 71 | Me | **4c** | 76 | Bn | **2c** | 44 | Bn | **5c** | 98 | Me | **3b** | 86 | Me | **6b** | 77[b] |
| F | Me | **1d** | 95 | Me | **4d** | 97 | Bn | **2d** | 85 | Bn | **5d** | 88 | | | | | | |
| Cl | Me | **1e** | 86 | Me | **4e** | 89 | Bn | **2e** | 76 | Bn | **5e** | 85 | Me | **3c** | 71 | Me | **6c** | 66[a] |
| $CF_3O$ | Me | **1f** | 91 | Me | **4f** | 90 | Bn | **2f** | 63 | Bn | **5f** | 92 | | | | | | |
| $CF_3$ | Me | **1g** | 98 | Me | **4g** | 92 | Bn | **2g** | 78 | Bn | **5g** | 95 | | | | | | |
| CN | | | | | | | | | | | | | Me | **3d** | 24 | Me | **6d** | 56[a] |
| $NO_2$ | Me | **1h** | 50 | Me | **4h** | 89 | Bn | **2h** | 47 | Bn | **5h** | 62 | Me | **3e** | 9 | Me | **6e** | 48[c] |

[a] Treatment with TFA in acetonitrile (5%) at room temperature.
[b] Treatment with neat TFA at room temperature.
[c] Treatment with boiling neat TFA.

## 2.2. Acquisition and treatment of kinetic information

As will be discussed below, even in the case of the lower yields obtained in the acidolyses with 5% TFA no signs have been detected for the reagent undergoing any reaction other than acidolytic cleavage of the C-terminal amide bond as depicted in Scheme 1. Thus, each substrate was submitted to acidolysis with 2% TFA under controlled conditions for collection of kinetic data; this was assisted by HPLC to monitor the reagent peak according to the procedure described below in Section 4. As expected,[21–23] an excellent linear relationship between substrate concentration and HPLC peak areas was found, which allowed calculation of reaction rate constants directly from peak areas. All reactions exhibited pseudo-first order behaviour with respect to the amino acid derivative, which is shown by the linear variation of ln *A*, where *A* is an HPLC peak area, as a function of time. As an example, ln *A* versus *t* plots for experiments concerning substrates **1a** at two temperatures (25.00 and 40.00 °C) and **2a** at 25.00 °C are presented in Fig. 1. The observed rate constants, *k*, were calculated by the linear least squares methodology for a straight line. Four to five experiments were performed for each substrate in reactions carried out at 25.00 °C, while only two to three were performed for reactions at other temperatures. The results presented in Tables 2 and 3 are the mean rate constant values (*k*) and their mean deviations (d*k*).

As in all compounds now under investigation $R^2$ is connected to the rest of the molecule through an aromatic moiety, it is appropriate to analyse the kinetic results at the light of a Hammett treatment. For this purpose, the uniparametric correlation $\log k = \log k_o + \rho\sigma$ was applied to all

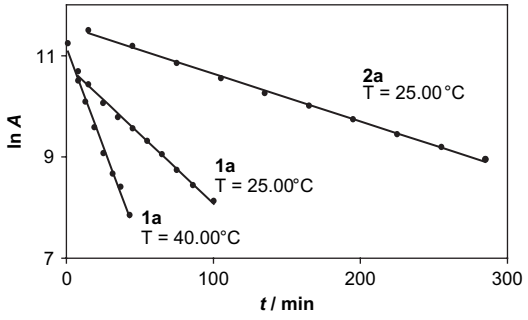



**Figure 1**. Plots of values of ln *A* versus time for acidolysis of compounds **1a** (25.00 and 40.00 °C) and **2a** (25.00 °C).

**Table 3**. Rate constants, *k*, and mean deviations, d*k*, for the acidolysis of $PhCH_2CO\text{-}N(4\text{-}X\text{-}C_6H_4\text{-}CH_2)\text{-}CMe_2CO\text{-}NHC_6H_{11}$ (**1a–1g**) at different temperatures

| X | Compound no. | $(k\pm dk)\times10^4$ ($s^{-1}$) | | | |
|---|---|---|---|---|---|
| | | 20.00 °C | 30.00 °C | 35.00 °C | 40.00 °C |
| $CH_3O$ | **1a** | 2.54±0.05 | 6.23±0.18 | 9.44±0.22 | 12.99±0.48 |
| $CH_3$ | **1b** | 2.20±0.06 | 4.62±0.18 | 6.68±0.25 | 11.99±0.45 |
| H | **1c** | 1.50±0.06 | 3.32±0.09 | 5.13±0.18 | 8.16±0.40 |
| F | **1d** | 1.06±0.03 | 2.35±0.07 | 3.45±0.11 | 5.76±0.23 |
| Cl | **1e** | 0.84±0.02 | 1.84±0.06 | 2.95±0.10 | 4.06±0.16 |
| $CF_3O$ | **1f** | 0.68±0.01 | 1.55±0.04 | 2.20±0.06 | 3.53±0.18 |
| $CF_3$ | **1g** | 0.53±0.02 | 1.14±0.03 | 1.68±0.10 | 2.40±0.08 |

acidolyses, $\sigma$ being the Hammett substituent constant and $\rho$ the reaction constant reflecting the sensitivity of the reaction rate to the total electronic effect of the substituents. The values of Hammett constants for *para*-substituents ($\sigma_p$) used to fit the observed rate constants (*k*) are listed in Table 4;[25] although the number of substituents used in each set of compounds is not large, it is worthwhile to note that they provide a wide range of electronic effects. Table 5 shows the parameters estimated ($a_0$ and $a_1$) for Hammett plots by the least squares methodology for a straight line. The correlation coefficient (*r*) and the standard deviation (*s*) of the fits are also presented together with the standard deviations of the estimated parameters. The confidence levels for the estimated parameters as well as those for the fits obtained in a test-F[24] were always better than 99.99%, except for the reactions with compounds **3a–3e**, which was 99.8%; this difference is most probably due to the small number of compounds (*N*=5) available in the latter case. Fig. 2 shows the corresponding plots. The success obtained in the above treatment of the electronic effect of substituents on the rate of our reactions leads us to investigate the possibility to quantify field/inductive and resonance contributions. For this purpose, we extended our analysis of rate constants

**Table 4**. Hammett constants and their constituent contributions[24]

| Substituent | $\sigma_P$ | $\sigma_R$ | $\sigma_I$ |
|---|---|---|---|
| $CH_3O$ | −0.268 | −0.56 | 0.29 |
| $CH_3$ | −0.170 | −0.18 | 0.01 |
| H | 0.000 | 0 | 0.003 |
| F | 0.063 | −0.39 | 0.45 |
| Cl | 0.227 | −0.19 | 0.42 |
| $CF_3O$ | 0.350 | −0.04 | 0.39 |
| $CF_3$ | 0.540 | 0.16 | 0.38 |
| CN | 0.660 | — | — |
| $NO_2$ | 0.778 | 0.13 | 0.65 |

**Table 2**. Rate constants, *k*, and mean deviations, d*k*, at 25.00 °C for the acidolysis of $PhCH_2CO\text{-}N(4\text{-}X\text{-}C_6H_4\text{-}CH_2)\text{-}C(R^1)_2CO\text{-}NHC_6H_{11}$ (**1a–1h** and **2a–2h**) and $PhCH_2CO\text{-}N(4\text{-}X\text{-}C_6H_4)\text{-}C(CH_3)_2CO\text{–}NHC_6H_{11}$ (**3a–3e**)

| X | Compound | | $(k\pm dk)\times10^4$ $s^{-1}$ | Compound | | $(k\pm dk)\times10^4$ $s^{-1}$ | Compound | | $(k\pm dk)\times10^6$ $s^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|
| | $R^1$ | No. | | $R^1$ | No. | | $R^1$ | No. | |
| $CH_3O$ | Me | **1a** | 4.513±0.051 | Bn | **2a** | 1.567±0.019 | Me | **3a** | 10.14±0.02 |
| $CH_3$ | Me | **1b** | 3.333±0.042 | Bn | **2b** | 1.306±0.034 | | | |
| H | Me | **1c** | 2.530±0.078 | Bn | **2c** | 1.005±0.013 | Me | **3b** | 6.833±0.022 |
| F | Me | **1d** | 1.711±0.017 | Bn | **2d** | 0.692±0.002 | | | |
| Cl | Me | **1e** | 1.417±0.059 | Bn | **2e** | 0.512±0.002 | Me | **3c** | 1.729±0.014 |
| $CF_3O$ | Me | **1f** | 1.190±0.050 | Bn | **2f** | 0.439±0.003 | | | |
| $CF_3$ | Me | **1g** | 0.727±0.004 | Bn | **2g** | 0.322±0.003 | | | |
| CN | | | | | | | Me | **3d** | 0.347±0.018 |
| $NO_2$ | Me | **1h** | 0.497±0.010 | Bn | **2h** | 0.196±0.010 | Me | **3e** | 0.334±0.017 |

**Table 5**. Application of the Hammett equation[a] $\log k = a_0 + a_1\sigma_p$

| Compound | **1a–1h** | **2a–2h** | **3a–3e** | **1a–1g** | | | |
|---|---|---|---|---|---|---|---|
| $T$ (°C) | 25.00 | 25.00 | 25.00 | 20.00 | 30.00 | 35.00 | 40.00 |
| $a_0$ | −3.63±0.02 | −4.05±0.02 | −5.34±0.07 | −3.85±0.02 | −3.50±0.02 | −3.32±0.02 | −3.13±0.02 |
| $a_1$ | −0.91±0.05 | −0.86±0.04 | −1.56±0.15 | −0.89±0.08 | −0.91±0.07 | −0.92±0.07 | −0.96±0.06 |
| N | 8 | 8 | 5 | 7 | 7 | 7 | 7 |
| $r$ | 0.993 | 0.993 | 0.986 | 0.981 | 0.987 | 0.985 | 0.990 |
| $s$ | 0.04 | 0.04 | 0.13 | 0.05 | 0.05 | 0.05 | 0.04 |

[a] Estimated parameters, $a_0$ and $a_1$, number of points, $N$, correlation coefficient, $r$, and standard deviation, $s$.

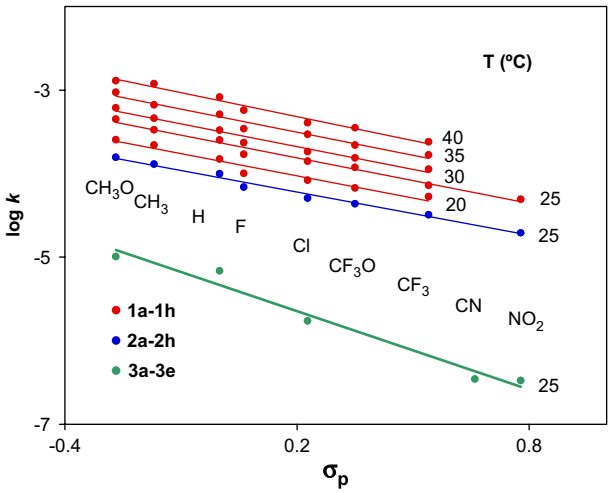



**Figure 2**. Hammett plots ($\log k$ vs $\sigma_p$) for compounds **1a–1h**, **2a–2h** and **3a–3e** at 25.00 °C and **1a–1g** at other temperatures.

taking advantage of a biparametric relationship in order to evaluate these two main part components as follows: $\log k = a_0 + a_1\sigma_R + a_2\sigma_I$ (where $\sigma_R$ and $\sigma_I$ are the resonance constant and the field/inductive constant, respectively).[25] This treatment was applied only to those cases where the number of results available allowed the most meaningful statistical analysis, i.e., compounds **1a–1h** and **2a–2h** at 25.00 °C. The values of the constants used in the regression analysis, $\sigma_R$ and $\sigma_I$, are listed also in Table 4. It should be noted that for the range of the substituents studied these two constants are not collinear and can be used as independent variables since their correlation coefficient is as low as 0.148 ($N$=8). The results of the biparametric equations are presented in Table 6.

### 2.3. Discussion of results

The yields obtained in Ugi–Passerini reaction (Table 1) were usually good to very good, except in the case of nitro derivatives. The behaviour observed with the nitro derivatives is possibly due to the large electron withdrawing effect of the nitro group, which would decrease substantially the nucleophilicity of the amine nitrogen atom when compared with the other substituents. This was so enhanced in the case of nitroanilide **3e** that it could not be obtained in a yield better than 9%. Acidolyses of the dimethylglycine derivatives **1** with 5% TFA were faster than those with the corresponding dibenzylglycine compounds **2** (2.5–4 h for substrates **1a–1g** and 20–27 h for compounds **2a–2e**, respectively). The acidolyses of the nitrobenzyl derivatives were much slower, requiring 26 and 48 h for **1h** and **2h**, respectively. As shown in Table 1, good to very good yields were obtained in the acidolysis of compounds **1b–1g** and **2b–2g**. We have shown[20] that (i) when treated with TFA at low concentration and room temperature the 4-methoxybenzyl group is not cleaved, but (ii) the partial cleavage may occur by prolonged treatment with 5% TFA and (iii) the full cleavage is usually achieved on boiling in neat TFA for 5 min. Thus, full selective cleavage of the amide bond was observed with compound **1a** to give a yield of 91% of the required product. However, as the acidolysis of **2a** was about three times slower than that of **1a**, subsequent partial cleavage of the *N*-methoxybenzyl group took place to allow only 68% of the required product. This did not affect the kinetic measurements not only because these are referred to the disappearance of **2a**, which occurs prior to further cleavage, but also because no secondary peaks were found overlapping with the reagent peak in the chromatograms. When **1b** and **1d** were boiled in neat TFA for 20 min the substituent at $R^2$ was not eliminated, the corresponding *N*-phenylacetyltrialkylglycine being the only product obtained; this differentiates methoxybenzyl group from the remaining compounds investigated. It was already known[26] that the *N*-substituent of *N*,α,α-tribenzylglycine resists to boiling in concentrated aqueous HBr for several hours and that its cleavage requires hydrogenation in hot butanol for 12 h. The reactions of the *N*-phenyl derivatives with 5% TFA at room temperature were so slow (27–168 h for **3a–3d**) that in most cases partial decomposition of the product was observed on completion, thus contributing to lower the final yield. Nevertheless, the acidolysis of compound **3a** was still sufficiently fast to avoid decomposition even when it was treated with neat TFA; so, this gave the best results for compound **3a** and also **3b** (Table 1). However, with the other substrates of this set their reactions with neat TFA were still slow and showed considerable decomposition of the product, the best results being then obtained with 5% TFA at room temperature; in the case of the nitrophenyl derivative (**3e**) boiling in neat TFA for more than 1 h was required for an acceptable progress but a yield of only 48% could be obtained.

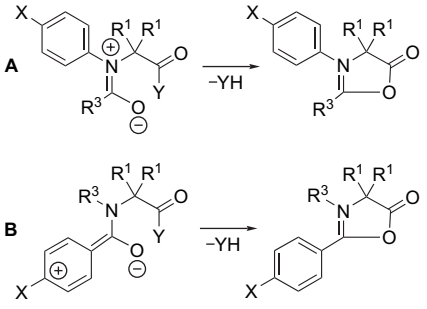
In general, the values of the rate constants for the compounds of *N*-benzyl derivatives of α,α-dimethylglycine **1a–1h** are

**Table 6**. Application of the biparametric Hammett equation[a] $\log k = a_0 + a_1\sigma_R + a_2\sigma_I$ at 25.00 °C ($N$=8 points)

| Compound | $a_0$ | $a_1$ | $a_2$ | $r$ | $s$ |
|---|---|---|---|---|---|
| **1a–1h** | −3.61±0.04 | −0.86±0.07 | −0.95±0.08 | 0.993 | 0.05 |
| **2a–2h** | −4.00±0.02 | −0.78±0.04 | −0.96±0.05 | 0.996 | 0.03 |

[a] Estimated parameters, $a_0$, $a_1$ and $a_2$, correlation coefficient, $r$, and standard deviation, $s$.

about 2.5 times larger than those for their analogues in the α,α-dibenzylglycine series (**2a**–**2h**). This difference must be related to a larger steric contribution of the amino acid side chains ($R^1$) to the reaction rates in the case of compounds **2**. Nevertheless, both sets have approximately the same sensitivity to electronic contributions, which is particularly visible by comparing the values for $a_1$ in the Hammett plots (−0.91 and −0.86 for set **1** and set **2**, respectively, at 25.00 °C; Table 5 and Fig. 2). However, a different behaviour is observed in the case of the *N*-phenyl derivatives of α,α-dimethylglycine **3a**–**3e**, where the rate constants are 40–150 times smaller than those found for similar compounds in set **1**. Now, the reactions are not only much slower but also much more sensitive to the electronic contribution of the substituent at the nitrogen atom than in the above case. This different behaviour becomes evident from the value of $a_1$ in the corresponding Hammett plot (−1.56), which differs significantly from those of the previous sets. The absence of a methylene group between the nitrogen atom and the aromatic ring allows the electronic contribution of the substituent to be passed onto the oxygen atom of the vicinal carbonyl group, thus tuning its nucleophilicity. It is clear that conjugation of the side chain phenyl ring of compounds **3** with the reaction centre contributes to its stabilisation, thus decreasing the nucleophilicity of the oxygen atom to make the reactions slower than with the benzyl derivatives. In their investigation of the effect of the substituent on the rate of acidolysis under similar conditions of various *para*-substituted *N*-benzoyl derivatives of *N*,α,α-trimethylglycine, Creighton et al.[18] have found that the value is −1.335. This suggests that the nucleophilicity of the oxygen atom is more sensitive to the electronic contribution of the substituent at the nitrogen atom (Scheme 2A) than that at the *N*-carbonyl carbon atom (Scheme 2B). This may be interpreted as resulting from the additional interaction in our case between the substituent and the nucleophilic oxygen atom through the formation of an N–C double bond during the cyclisation process. The results presented in Table 5 and Figure 2 for compounds **1** at different temperatures show a slope varying, although not much but steadily, with temperature, in agreement with what one would expect from the properties of Hammett reaction constant. Fluorine derivatives **1d** and **2d** are the less well behaved compounds; in fact, in the plots obtained at different temperatures they show systematic deviations to the same side of the lines (Fig. 2).




**Scheme 2**.

The biparametric relationships presented above for compounds **1a**–**1h** and **2a**–**2h** at 25.00 °C are excellent, the

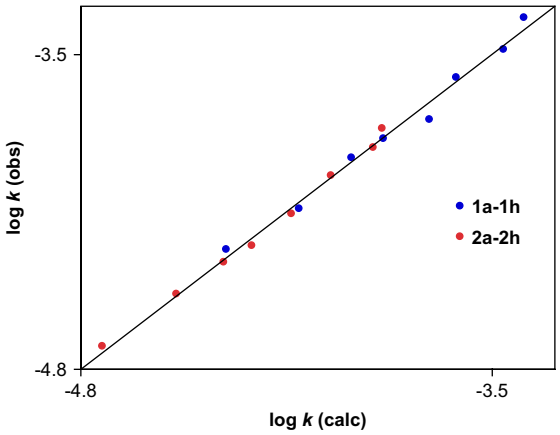



**Figure 3**. Plot of observed log *k* values for acidolysis of compounds **1a**–**1g** against those calculated with $\log k = -3.61 - 0.86\sigma_R - 0.95\sigma_I$ and of compounds **2a**–**2g** against those calculated with $\log k = -4.00 - 0.78\sigma_R - 0.96\sigma_I$.

significance of the estimated parameters and of the fit obtained by the test-F were always better than 99.99%. In order to further demonstrate the validity of these correlations, the values observed for log *k* were plotted against those calculated by the equations, as shown in Fig. 3. The 16 points (eight for **1a**–**1h** and eight for **2a**–**2h**) fall very closely to the bisectrix of perfect correlation. The successful decomposition of substituent electronic effects places the discussion of field/inductive and resonance components in numerical terms. Since in our case $a_1$ and $a_2$ have a similar magnitude (Table 6), one might conclude that, as an average, both effects contribute significantly to the reactivity. Now, fluorine derivative **1d** is again less well behaved. It can be seen in Table 4 and Fig. 4 that the field/inductive constant and resonance constant can be very different from each other for every substituent. Fluorine, where these two constants are large, have opposite signs and are almost of the same size is the exception; in this case the resonance contribution can almost cancel the field/inductive contribution if the reaction under consideration is equally sensitive to both, as has already been discussed by others.[27] However, if in our case the sensitivities concerning the fluorine derivatives are different, these compounds should diverge from the average, which might explain the deviant behaviour.

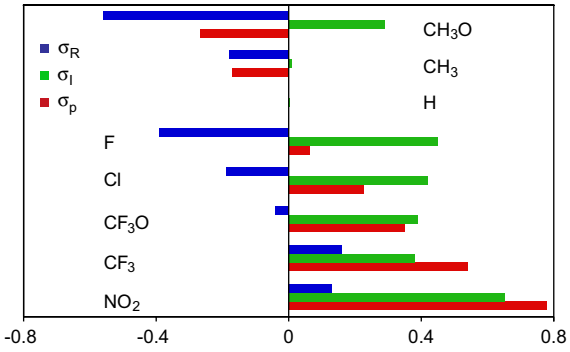



**Figure 4**. Plot of Hammett constant ($\sigma_p$), field/inductive constant ($\sigma_I$) and resonance constant ($\sigma_R$) for the different substituents.

## 3. Conclusions

The kinetic results obtained in this investigation show that the reaction rate constants differ sufficiently from compound to compound to allow their interpretation in terms of structure–reactivity considerations. The sensitivity of the measured reaction rates to the nature (electronic contribution) of the substituent at the nitrogen atom of the anilides **3a**–**3e** is larger than that reported[19] for the *N*-acyl group and this may be related to the formation of C–N double bond required for cyclisation and consequent cleavage of the C-terminal amide bond, as depicted in Scheme 2. *N*-Benzyl derivatives of either α,α-dimethyl- or α,α-dibenzylglycine (**1a**–**1h** and **2a**–**2h**, respectively) exhibit a lesser sensitivity, which is in agreement with the existence of a methylene group between the nitrogen atom and the phenyl ring. Similarly to what we have previously found, α,α-dimethylglycine derivatives react much faster than the corresponding α,α-dibenzylglycines. However, these two sets of compounds show a very similar behaviour in what concerns sensitivity to the electronic contribution of the substituent $R^2$ to acidolysis and to its main components (resonance and field/inductive effect). Although acidolytic cleavage of the C-terminal amide bond of α,α-dialkylglycine derivatives requires an alkyl/aryl substituent at the amino acid nitrogen atom,[19–23] it occurs independent of the size of the electronic contribution, which contributes only to the rate of acidolysis. This suggests that such requirement is essentially related to steric effect and not so much to a polar effect, possibly by assisting the molecules to assume a bent conformation and facilitating internal nucleophilic attack in support of what we had already suggested.[21] Our results showed that anilides substituted with electron withdrawing groups such as *N*-(4-chlorophenyl) and *N*-(4-cyanophenyl) exhibit a comparatively high resistance of the C-terminal amide bond of α,α-dialkylglycine amides to acidolysis. This suggests that either of these groups would seem appropriate to impart useful conformational restrictions in combination with α,α-dialkylglycine peptides while preventing unwanted cleavage of the C-terminal peptide bond of the amino acid residue bearing the two side chains. Finally, it is noteworthy that while the 4-methoxybenzyl group can be cleaved from Ugi–Passerini substrate together with the C-terminal amide bond if sufficient forcing conditions are used (boiling with neat TFA), all the other 4-substituted benzyl groups tested do not. Thus, when cleavage of the *N*-alkyl group from Ugi–Passerini adducts is required, only 4-methoxybenzyl compounds suit this purpose, which was the group we have used with success in our previous work.

## 4. Experimental

### 4.1. Syntheses

Tri-distilled and de-ionised water was used in HPLC experiments. Methanol and acetone were dried by standard procedures. All other solvents and reagents were used as obtained from commercial sources. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60 $F_{254}$) and spots were visualised under UV light or by exposure to vaporised iodine. Preparative chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded at 25 °C in ~5% solutions on a Varian Unity Plus-300 spectrometer; all shifts are given in parts per million using $Me_4Si$=0; *J*-values are given in hertz, and assignments were made by comparison of chemical shifts, peak multiplicity and *J*-values. $^{13}$C NMR spectra were recorded with the same instrument at 75.4 MHz and using the solvent peak as internal reference; assignments were carried out using DEPT 135, HMBC, HMQC and NOE techniques. Elemental analyses were preformed on a Leco CHNS 932 instrument. HPLC measurements were carried out with a Jasco PU-980 intelligent HPLC Pump, a Shimadzu SPD-6AV UV–vis Spectrophotometric Detector and a Shimadzu C-R6A Chromatopac Printer. A reverse phase LiChrospher 100 RP-18 (5 m) column was used throughout the work. Temperature stability was maintained throughout the kinetic work with a HAAKE Circulator DL30 thermostatic bath, the temperatures being set with the aid of Precision thermometers allowing an accuracy of 0.01 °C.

**4.1.1. General method for the synthesis of Ugi–Passerini adducts (1, 2 and 3).** For the preparation of the α,α-dimethylglycine derivatives, a 0.5 M solution of the required amine in dry acetone containing anhydrous sodium sulfate (0.12 g cm$^{-3}$) was prepared and stirred for 15 min; then, 1 equiv of a 2 M solution of phenylacetic acid in dry methanol was added and the mixture was stirred for further 15 min. Finally, 1 equiv of cyclohexyl isocyanide was also added and the mixture was stirred at room temperature for 1–4 weeks in the dark and under nitrogen. To the suspension thus obtained dichloromethane was added to dissolve the product that meanwhile had precipitated and the sodium sulfate was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography using the following eluent sequence: dichloromethane/*n*-hexane 2:1, dichloromethane, dichloromethane/methanol 200:1, 100:1 and 50:1. For the preparation of α,α-dibenzylglycine derivatives, to a 1 M solution of 1,3-diphenylpropanone in dry methanol containing anhydrous sodium sulfate (0.12 g cm$^{-3}$) 1 equiv of the required amine was added. After stirring for 45–60 min, 1 equiv of cyclohexyl isocyanide was mixed and the preparation was continued as above.

**4.1.1.1. *N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine cyclohexylamide (1a).** The reaction was carried out on a 0.05-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1a** (19.17 g, 91%) as a white solid, mp 168.9–169.8 °C (lit.[20] 168.4–169.8 °C). $^1$H NMR (300 MHz, $CDCl_3$): 1.08–1.21 (3H, m, $C_6H_{11}$), 1.42 (6H, s, 2×$CH_3$), 1.64–1.73 (5H, m, $C_6H_{11}$), 1.95 (2H, m, $C_6H_{11}$), 3.68 (2H, s, $CH_2CO$), 3.71–3.80 (1H, m, $C_6H_{11}$-*H*1), 3.82 (3H, s, $OCH_3$), 4.53 (2H, s, $NCH_2$), 5.50 (1H, d, *J*=8.1 Hz, N*H*), 6.94 (2H, d, *J*=8.7 Hz, $NCH_2$Ph-*H*3,5), 7.21–7.31 (5H, m, $COCH_2Ph$), 7.38 (2H, d, *J*=9.0 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.21 (2×$CH_3$), 24.81 ($C_6H_{11}$-*C*3,5), 25.56 ($C_6H_{11}$-*C*4), 32.87 ($C_6H_{11}$-*C*2,6), 42.05 (*C*$H_2$CO), 47.06 (*C*$H_2$N), 48.25 ($C_6H_{11}$-*C*1), 55.18 ($OCH_3$), 62.36 (*C*$^\alpha$), 114.21 ($NCH_2$Ph-*C*2,6), 126.71 ($COCH_2$Ph-*C*4), 127.08 ($NCH_2$Ph-*C*3,5), 128.39 ($COCH_2$Ph-*C*2,6), 128.62 ($COCH_2$Ph-*C*3,5),

130.23 ($NCH_2$Ph-*C*4), 134.86 ($COCH_2$Ph-*C*1), 158.74 ($NCH_2$Ph-*C*4), 171.74 (*C*$OCH_2$), 172.65 (*C*ONH). Anal. Calcd for $C_{26}H_{34}N_2O_3$: C, 73.90; H, 8.11; N, 6.63. Found: C, 73.98; H, 8.08; N, 6.69.

**4.1.1.2. *N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dimethylglycine cyclohexylamide (1b).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1b** (3.68 g, 90%) as a white solid, mp 157.5–158.7 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.03–1.21 (3H, m, $C_6H_{11}$), 1.29–1.39 (2H, m, $C_6H_{11}$), 1.42 (6H, s, 2×C$H_3$), 1.57–1.72 (3H, m, $C_6H_{11}$), 1.94 (2H, m, $C_6H_{11}$), 2.36 (3H, s, Ph-C$H_3$), 3.67 (2H, s, C$H_2$CO), 3.70–3.81 (1H, m, $C_6H_{11}$-*H*1), 4.55 (2H, s, NC$H_2$), 5.52 (1H, d, *J*=8.1 Hz, N*H*), 7.19–7.44 (9H, m, $COCH_2$*Ph*+$NCH_2$*Ph*); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 20.93 (Ph-$CH_3$), 24.22 (2×$CH_3$), 24.21 (2×$CH_3$), 24.80 ($C_6H_{11}$-*C*3,5), 25.56 ($C_6H_{11}$-*C*4), 32.85 ($C_6H_{11}$-*C*2,6), 42.06 (*C*$H_2$CO), 47.45 (*C*$H_2$N), 48.22 ($C_6H_{11}$-*C*1), 62.40 (*C*$^{\alpha}$), 125.84 ($NCH_2$Ph-*C*2,6), 126.71 ($COCH_2$Ph-*C*4), 128.39 ($COCH_2$Ph-*C*2,6), 128.62 ($COCH_2$Ph-*C*3,5), 129.50 ($NCH_2$Ph-*C*3,5), 134.82 ($COCH_2$Ph-*C*1), 135.29 ($NCH_2$Ph-*C*1), 136.88 ($NCH_2$Ph-*C*4), 171.77 (*C*$OCH_2$), 173.75 (*C*ONH). Anal. Calcd for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.98; H, 8.14; N, 7.03.

**4.1.1.3. *N*-Phenylacetyl-*N*-benzyl-α,α-dimethylglycine cyclohexylamide (1c).** The reaction was carried out on a 0.015-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1c** (4.06 g, 71%) as a white solid, mp 161.1–162.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.04–1.22 (3H, m, $C_6H_{11}$), 1.29–1.42 (3H, m, $C_6H_{11}$), 1.43 (6H, s, 2×C$H_3$), 1.67–1.74 (2H, m, $C_6H_{11}$), 1.96 (2H, m, $C_6H_{11}$), 3.67 (2H, s, C$H_2$CO), 3.72–3.82 (1H, m, $C_6H_{11}$-*H*1), 4.59 (2H, s, NC$H_2$), 5.52 (1H, d, *J*=7.8 Hz, N*H*), 7.21–7.34 (6H, m, $COCH_2$*Ph*+$NCH_2$Ph-*H*4), 7.41 (2H, t, *J*=7.5 Hz, $NCH_2$Ph-*H*3,5), 7.48 (2H, d, *J*=7.5 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.22 (2×*C*$H_3$), 24.84 ($C_6H_{11}$-*C*3,5), 25.56 ($C_6H_{11}$-*C*4), 32.90 ($C_6H_{11}$-*C*2,6), 42.07 (*C*$H_2$CO), 47.60 (*C*$H_2$N), 48.29 ($C_6H_{11}$-*C*1), 62.39 (*C*$^{\alpha}$), 125.91 ($NCH_2$Ph-*C*2,6), 126.76 ($COCH_2$Ph-*C*4), 127.23 ($NCH_2$Ph-*C*4), 128.39 ($COCH_2$Ph-*C*2,6), 128.67 ($COCH_2$Ph-*C*3,5), 128.86 ($NCH_2$Ph-*C*3,5), 134.77 ($COCH_2$Ph-*C*1), 138.40 ($NCH_2$Ph-*C*1), 171.82 (*C*$OCH_2$), 173.78 (*C*ONH). Anal. Calcd for $C_{25}H_{32}N_2O_2$: C, 76.50; H, 8.22; N, 7.14. Found: C, 76.44; H, 8.11; N, 7.19.

**4.1.1.4. *N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dimethylglycine cyclohexylamide (1d).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1d** (3.90 g, 95%) as a white solid, mp 162.5–163.5 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.06–1.22 (3H, m, $C_6H_{11}$), 1.29–1.40 (2H, m, $C_6H_{11}$) 1.42 (6H, s, 2×C$H_3$), 1.58–1.74 (3H, m, $C_6H_{11}$), 1.97 (2H, m, $C_6H_{11}$), 3.61 (2H, s, C$H_2$CO), 3.71–3.84 (1H, m, $C_6H_{11}$-*H*1), 4.53 (2H, s, NC$H_2$), 5.51 (1H, d, *J*=8.1 Hz, N*H*), 7.07 (2H, t, *J*=8.7 Hz, $NCH_2$Ph-*H*3,5), 7.18–7.32 (5H, m, $COCH_2$*Ph*), 7.49 (2H, dd, *J*=5.4, 9.0 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.17 (2×*C*$H_3$), 24.88 ($C_6H_{11}$-*C*3,5), 25.57 ($C_6H_{11}$-*C*4), 32.94 ($C_6H_{11}$-*C*2,6), 42.06 (*C*$H_2$CO), 46.80 (*C*$H_2$N), 48.39 ($C_6H_{11}$-*C*1), 62.29 (*C*$^{\alpha}$), 115.70 (d, $J_{C-F}$=21.3 Hz, $NCH_2$Ph-*C*3,5), 126.81 ($COCH_2$Ph-*C*4), 127.56 (d, $J_{C-F}$= 8.1 Hz, $NCH_2$Ph-*C*2,6), 128.33 ($COCH_2$Ph-*C*2,6), 128.32 ($COCH_2$Ph-*C*3,5), 134.13 (d, $J_{C-F}$=3.2 Hz, $NCH_2$Ph-*C*1), 134.70 ($COCH_2$Ph-*C*1), 161.93 (d, $J_{C-F}$=245.6 Hz, $NCH_2$Ph-*C*4), 171.77 (*C*$OCH_2$), 173.80 (*C*ONH). Anal. Calcd for $C_{25}FH_{31}N_2O_2$: C, 73.14; H, 7.61; N, 6.82. Found: C, 73.10; H, 7.67; N, 6.86.

**4.1.1.5. *N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dimethylglycine cyclohexylamide (1e).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1e** (3.69 g, 86%) as a white solid, mp 140.4–141.5 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.07–1.22 (3H, m, $C_6H_{11}$), 1.30–1.39 (2H, m, $C_6H_{11}$), 1.41 (6H, s, 2×C$H_3$), 1.59–1.74 (3H, m, $C_6H_{11}$), 1.96–1.99 (2H, m, $C_6H_{11}$), 3.60 (2H, s, C$H_2$CO), 3.75–3.80 (1H, m, $C_6H_{11}$-*H*1), 4.52 (2H, s, NC$H_2$), 5.51 (1H, d, *J*=7.8 Hz, N*H*), 7.17–7.29 (5H, m, $COCH_2$-*Ph*), 7.35 (2H, d, *J*=8.4 Hz, $NCH_2$Ph-*H*3,5), 7.47 (2H, d, *J*=8.4 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.14 (2×*C*$H_3$), 24.86 ($C_6H_{11}$-*C*3,5), 25.54 ($C_6H_{11}$-*C*4), 32.82 ($C_6H_{11}$-*C*2,6), 42.05 (*C*$H_2$CO), 46.87 (*C*$H_2$N), 48.39 ($C_6H_{11}$-*C*1), 62.26 (*C*$^{\alpha}$), 126.82 ($COCH_2$Ph-*C*4), 127.36 ($NCH_2$Ph-*C*2,6), 128.30 ($COCH_2$Ph-*C*2,6), 128.72 ($COCH_2$Ph-*C*3,5), 128.96 ($NCH_2$Ph-*C*3,5), 132.95 ($NCH_2$Ph-*C*4), 134.60 ($COCH_2$Ph-*C*1), 137.03 ($NCH_2$Ph-*C*1), 171.76 (*C*$OCH_2$), 173.73 (*C*ONH). Anal. Calcd for $C_{25}ClH_{31}N_2O_2$: C, 70.32; H, 7.32; N, 6.52. Found: C, 70.15; H, 7.29; N, 6.66.

**4.1.1.6. *N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dimethylglycine cyclohexylamide (1f).** The reaction was carried out on a 0.006-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1f** (2.61 g, 91%) as a white solid, mp 143.2–144.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.08–1.23 (3H, m, $C_6H_{11}$), 1.32–1.36 (2H, m, $C_6H_{11}$), 1.43 (6H, s, 2×C$H_3$), 1.60–1.74 (3H, m, $C_6H_{11}$), 1.98 (2H, m, $C_6H_{11}$), 3.61 (2H, s, C$H_2$CO), 3.74–3.84 (1H, m, $C_6H_{11}$-*H*1), 4.56 (2H, s, NC$H_2$), 5.52 (1H, d, *J*=8.1 Hz, N*H*), 7.17–7.32 (7H, m, $COCH_2$*Ph*+$NCH_2$Ph-*H*3,5), 7.59 (2H, d, *J*=8.4 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.14 (2×*C*$H_3$), 24.86 ($C_6H_{11}$-*C*3,5), 25.54 ($C_6H_{11}$-*C*4), 32.93 ($C_6H_{11}$-*C*2,6), 42.06 (*C*$H_2$CO), 46.75 (*C*$H_2$N), 48.42 ($C_6H_{11}$-*C*1), 62.26 (*C*$^{\alpha}$), 120.37 (q, $J_{C-F}$= 257.4 Hz, O*C*$F_3$), 121.31 ($NCH_2$Ph-*C*3,5), 126.82 ($COCH_2$Ph-*C*4), 127.35 ($NCH_2$Ph-*C*2,6), 128.30 ($COCH_2$Ph-*C*2,6), 128.72 ($COCH_2$Ph-*C*3,5), 134.57 ($COCH_2$Ph-*C*1), 137.25 ($NCH_2$Ph-*C*1), 148.25 (q, $J_{C-F}$=1.8 Hz, $NCH_2$Ph-*C*4), 171.76 (*C*$OCH_2$), 173.77 (*C*ONH). Anal. Calcd for $C_{26}F_3H_{31}N_2O_3$: C, 65.53; H, 6.56; N, 5.88. Found: C, 65.49; H, 6.42; N, 5.91.

**4.1.1.7. *N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dimethylglycine cyclohexylamide (1g).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **1g** (4.51 g, 98%) as a white solid, mp 126.9–128.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.09–1.23 (3H, m, $C_6H_{11}$),

1.31–1.40 (2H, m, $C_6H_{11}$) 1.43 (6H, s, 2×$CH_3$) 1.59–1.75 (3H, m, $C_6H_{11}$), 1.99 (2H, m, $C_6H_{11}$), 3.58 (2H, s, $CH_2CO$), 3.73–3.85 (1H, m, $C_6H_{11}$-*H*1), 4.60 (2H, s, $NCH_2$), 5.53 (1H, d, *J*=8.1 Hz, N*H*), 7.17–7.32 (5H, m, $COCH_2Ph$), 7.67 (4H, dt, *J*=8.4, 14.4 Hz, $NCH_2Ph$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 24.16 (2×$CH_3$), 24.90 ($C_6H_{11}$-*C*3,5), 25.57 ($C_6H_{11}$-*C*4), 32.97 ($C_6H_{11}$-*C*2,6), 42.13 ($CH_2CO$), 47.11 ($CH_2N$), 48.48 ($C_6H_{11}$-*C*1), 62.29 ($C^{\alpha}$), 124.02 (q, $J_{C-F}$=272.1 Hz, $CF_3$), 125.81 (q, $J_{C-F}$=3.7 Hz, $NCH_2Ph$-*C*3,5), 126.34 ($NCH_2Ph$-*C*2,6), 126.90 ($COCH_2Ph$-*C*4), 128.30 ($COCH_2Ph$-*C*2,6), 128.79 ($COCH_2Ph$-*C*3,5), 129.55 (q, $J_{C-F}$=32.5 Hz, $NCH_2Ph$-*C*4), 134.49 ($COCH_2Ph$-*C*1), 142.79 ($NCH_2Ph$-*C*1), 171.80 ($COCH_2$), 173.73 (*C*ONH). Anal. Calcd for $C_{26}F_3H_{31}N_2O_2$: C, 67.81; H, 6.78; N, 6.08. Found: C, 67.72; H, 6.84; N, 5.92.

**4.1.1.8. *N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dimethylglycine cyclohexylamide (1h).** The reaction was carried out on a 0.005-molar scale, starting with 4-nitrobenzylamine hydrochloride (3 equiv, 5.658 g), which was neutralised with triethylamine (2.9 equiv, 4.01 ml) in dry diethyl ether (30 ml) at room temperature and under stirring for 90 min. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the residue was dissolved in freshly distilled acetone (25 ml) and used according to the general procedure described above. The final product was purified by column chromatography and recrystallised from ethyl acetate to yield **1h** (1.09 g, 50%) as a pale yellow solid, mp 141.8–143.0 °C. $^1H$ NMR (300 MHz, $CDCl_3$): 1.10–1.24 (3H, m, $C_6H_{11}$), 1.31–1.40 (2H, m, $C_6H_{11}$), 1.42 (6H, s, 2×$CH_3$), 1.60–1.75 (3H, m, $C_6H_{11}$), 1.99 (2H, m, $C_6H_{11}$), 3.55 (2H, s, $CH_2CO$), 3.77–3.80 (1H, m, $C_6H_{11}$-*H*1), 4.62 (2H, s, $NCH_2$), 5.55 (1H, d, *J*=7.8 Hz, N*H*), 7.14 (2H, d, *J*=6.3 Hz, $COCH_2Ph$-*H*2,6), 7.22–7.28 (3H, m, $COCH_2Ph$-*H*3,4,5), 7.80 (2H, d, *J*=8.7 Hz, $NCH_2Ph$-*H*2,6), 8.22 (2H, d, *J*=9.0 Hz, $NCH_2Ph$-*H*3,5); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 24.08 (2×$CH_3$), 24.88 ($C_6H_{11}$-*C*3,5), 25.52 ($C_6H_{11}$-*C*4), 32.94 ($C_6H_{11}$-*C*2,6), 42.13 ($CH_2CO$), 46.95 ($CH_2N$), 48.54 ($C_6H_{11}$-*C*1), 62.23 ($C^{\alpha}$), 124.03 ($NCH_2Ph$-*C*3,5), 126.91 ($NCH_2Ph$-*C*2,6), 126.91 ($COCH_2Ph$-*C*4), 128.20 ($COCH_2Ph$-*C*2,6), 128.81 ($COCH_2Ph$-*C*3,5), 134.22 ($COCH_2Ph$-*C*1), 146.32 ($NCH_2Ph$-*C*1), 147.17 ($NCH_2Ph$-*C*4), 171.65 ($COCH_2$), 173.68 (*C*ONH). Anal. Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.49; H, 7.07; N, 9.61.

**4.1.1.9. *N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine cyclohexylamide (2a).** The reaction was carried out on a 0.05-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2a** (18.78 g, 82%) as a white solid, mp 129.0–130.1 °C (lit.[20] 87.3–87.9 °C). $^1H$ NMR (300 MHz, $CDCl_3$): 0.84–1.07 (3H, m, $C_6H_{11}$), 1.19–1.29 (2H, m, $C_6H_{11}$), 1.57–1.61 (5H, m, $C_6H_{11}$), 2.93 (2H, d, *J*=12.0 Hz, $CCH_2Ph$), 3.34 (2H, br d, *J*=10.8 Hz, $CCH_2Ph$), 3.48–3.52 (1H, m, $C_6H_{11}$-*H*1), 3.55 (2H, s, $COCH_2$), 3.68 (2H, br s, $NCH_2$), 3.80 (3H, s, $OCH_3$), 5.05 (1H, d, *J*=7.5 Hz, N*H*), 6.93 (2H, d, *J*=8.7 Hz, $NCH_2Ph$-*H*3,5), 7.12–7.25 (10H, m, 2×$CCH_2Ph$), 7.32–7.38 (5H, m, $COCH_2Ph$), 7.65 (2H, d, *J*=8.4 Hz, $NCH_2Ph$-*H*2,6); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 24.86 ($C_6H_{11}$-*C*3,5), 25.56 ($C_6H_{11}$-*C*4), 32.57 ($C_6H_{11}$-*C*2,6), 36.05 (2×$CCH_2Ph$), 42.08 ($CH_2CO$), 47.25 ($CH_2N$), 48.39 ($C_6H_{11}$-*C*1), 55.17 ($OCH_3$), 69.15 ($C^{\alpha}$), 114.17 ($NCH_2Ph$-*C*3,5), 126.85, 126.88 (2×$CCH_2Ph$-*C*4+$COCH_2Ph$-*C*4), 127.07 ($NCH_2Ph$-*C*2,6), 128.11 (2×$CCH_2Ph$-*C*3,5), 128.54 ($COCH_2Ph$-*C*3,5), 129.49 ($COCH_2Ph$-*C*2,6), 130.97 (2×$CCH_2Ph$-*C*2,6+$NCH_2Ph$-*C*1), 134.71 ($COCH_2Ph$-*C*1), 135.33 (2×$CCH_2Ph$-*C*1), 158.47 ($NCH_2Ph$-*C*4), 170.86 (*C*ONH), 172.64 ($COCH_2$). Anal. Calcd for $C_{38}H_{42}N_2O_3$: C, 79.41; H, 7.37; N, 4.87. Found: C, 79.07; H, 6.94; N, 4.94.

**4.1.1.10. *N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dibenzylglycine cyclohexylamide (2b).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2b** (3.36 g, 60%) as a white solid, mp 201.8–202.9 °C. $^1H$ NMR (300 MHz, $CDCl_3$): 0.86–1.12 (3H, m, $C_6H_{11}$), 1.27–1.35 (2H, m, $C_6H_{11}$), 1.54–1.63 (5H, m, $C_6H_{11}$), 2.35 (3H, s, $CH_3Ph$), 2.94 (2H, d, *J*=12.0 Hz, $CCH_2Ph$), 3.35 (2H, br d, *J*=11.7 Hz, $CCH_2Ph$), 3.52–3.56 (1H, m, $C_6H_{11}$-*H*1), 3.56 (2H, s, $COCH_2$), 3.72 (2H, br s, $NCH_2$), 5.07 (1H, d, *J*=7.5 Hz, N*H*), 7.16–7.26 (12H, m, $NCH_2Ph$-*H*3,5+2×$CCH_2Ph$), 7.33 (5H, m, $COCH_2Ph$), 7.62 (2H, d, *J*=7.8 Hz, $NCH_2Ph$-*H*2,6); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 20.99 ($CH_3Ph$), 24.84 ($C_6H_{11}$-*C*3,5), 25.55 ($C_6H_{11}$-*C*4), 32.56 ($C_6H_{11}$-*C*2,6), 36.07 (2×$CCH_2Ph$), 42.08 ($CH_2CO$), 47.60 ($CH_2N$), 48.35 ($C_6H_{11}$-*C*1), 69.13 ($C^{\alpha}$), 125.84 ($NCH_2Ph$-*C*2,6), 126.85 (2×$CCH_2Ph$-*C*4+$COCH_2Ph$-*C*4), 128.08 (2×$CCH_2Ph$-*C*3,5), 128.52 ($COCH_2Ph$-*C*3,5), 129.48 ($COCH_2Ph$-*C*2,6+$NCH_2Ph$-*C*3,5), 130.95 (2×$CCH_2Ph$-*C*2,6), 134.68 ($COCH_2Ph$-*C*1), 135.33 (2×$CCH_2Ph$-*C*1), 136.00 ($NCH_2Ph$-*C*1), 136.37 ($NCH_2Ph$-*C*4), 170.78 (*C*ONH), 172.63 ($COCH_2$). Anal. Calcd for $C_{38}H_{40}N_2O_2$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.84; H, 7.41; N, 5.15.

**4.1.1.11. *N*-Phenylacetyl-*N*-benzyl-α,α-dibenzylglycine cyclohexylamide (2c).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2c** (2.40 g, 44%) as a white crystals, mp 206.5–207.4 °C. $^1H$ NMR (300 MHz, $CDCl_3$): 0.66–1.16 (3H, m, $C_6H_{11}$), 1.21–1.42 (2H, m, $C_6H_{11}$), 1.50–1.82 (5H, m, $C_6H_{11}$), 2.94 (2H, d, *J*=11.7 Hz, $CCH_2Ph$), 3.34 (2H, br d, *J*=10.5 Hz, $CCH_2Ph$), 3.54 (3H, s, $COCH_2$+$C_6H_{11}$-*H*1), 3.74 (2H, br s, $NCH_2$), 5.05 (1H, d, *J*=7.5 Hz, N*H*), 7.12–7.23 (11H, m, 2×$CCH_2Ph$+$NCH_2Ph$-*H*4), 7.35–7.42 (7H, m, $NCH_2Ph$-*H*3,5+$COCH_2Ph$), 7.75 (2H, d, *J*=9.0 Hz, $NCH_2Ph$-*H*2,6); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 24.85 ($C_6H_{11}$-*C*3,5), 25.54 ($C_6H_{11}$-*C*4), 32.55 ($C_6H_{11}$-*C*2,6), 36.12 (2×$CCH_2Ph$), 42.09 ($CH_2CO$), 47.73 ($CH_2N$), 48.38 ($C_6H_{11}$-*C*1), 69.10 ($C^{\alpha}$), 125.92 ($NCH_2Ph$-*C*2,6), 126.83, 126.89 (2×$CCH_2Ph$-*C*4+$NCH_2Ph$-*C*4+$COCH_2Ph$-*C*4), 128.12 (2×$CH_2Ph$-*C*3,5), 128.56 ($NCH_2Ph$-*C*3,5), 128.79 ($COCH_2Ph$-*C*3,5), 129.46 ($COCH_2Ph$-*C*2,6), 130.94 (2×$CH_2Ph$-*C*2,6), 134.58 ($COCH_2Ph$-*C*1), 135.25 (2×$CCH_2Ph$-*C*1), 139.05 ($NCH_2Ph$-*C*1), 170.79 (*C*ONH), 172.65 ($COCH_2$). Anal. Calcd for $C_{37}H_{40}N_2O_2$: C, 81.58; H, 7.40; N, 5.14. Found: C, 81.56; H, 7.27; N, 5.27.

**4.1.1.12. *N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dibenzylglycine cyclohexylamide (2d).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above

and recrystallised from ethyl acetate to yield **2d** (4.80 g, 85%) as a white solid, mp 190.9–192.2 °C. $^1$H NMR (300 MHz, $CDCl_3$): 0.85–1.11 (3H, m, $C_6H_{11}$), 1.22–1.35 (2H, m, $C_6H_{11}$), 1.53–1.62 (5H, m, $C_6H_{11}$), 2.91 (2H, d, $J$=12.0 Hz, $CCH_2$Ph), 3.34 (2H, br d, $J$=10.8 Hz, $CCH_2$Ph), 3.51 (2H, s, $COCH_2$), 3.49–3.58 (1H, m, $C_6H_{11}$-*H*1), 3.72 (2H, br s, $NCH_2$), 5.04 (1H, d, $J$=7.5 Hz, N*H*), 7.08 (2H, t, $J$=8.7 Hz, $NCH_2$Ph-*H*3,5), 7.13–7.29 (10H, m, 2×$CCH_2Ph$), 7.33–7.37 (5H, m, $COCH_2Ph$), 7.75 (2H, dd, $J$=5.4, 8.4 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.81 ($C_6H_{11}$-*C*3,5), 25.52 ($C_6H_{11}$-*C*4), 32.52 ($C_6H_{11}$-*C*2,6), 36.00 (2×$CCH_2$Ph), 42.07 ($CH_2CO$), 47.12 ($CH_2N$), 48.23 ($C_6H_{11}$-*C*1), 69.13 ($C^{\alpha}$), 115.58 (d, $J_{C-F}$= 21.3 Hz, $NCH_2$Ph-*C*3,5), 126.90, 126.94 (2×$CCH_2$Ph-*C*4+ $COCH_2$Ph-*C*4), 127.58 (d, $J_{C-F}$=7.8 Hz, $NCH_2$Ph-*C*2,6), 128.14 (2×$CCH_2$Ph-*C*3,5), 128.56 ($COCH_2$Ph-*C*3,5), 129.40 ($COCH_2$Ph-*C*2,6), 130.91 (2×$CCH_2$Ph-*C*2,6), 134.47 ($COCH_2$Ph-*C*1), 134.70 (d, $J_{C-F}$=2.9 Hz, $NCH_2$Ph-*C*1), 135.15 (2×$CCH_2$Ph-*C*1), 161.79 (d, $J_{C-F}$=245.0 Hz, $NCH_2$Ph-*C*4), 170.84 (*C*ONH), 172.51 ($COCH_2$). Anal. Calcd for $C_{37}FH_{39}N_2O_2$: C, 78.97; H, 6.99; N, 4.98. Found: C, 79.11; H, 6.68; N, 4.94.

**4.1.1.13. *N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dibenzylglycine cyclohexylamide (2e).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2e** (4.37 g, 76%) as a beige solid, mp 180.6–181.5 °C. $^1$H NMR (300 MHz, $CDCl_3$): 0.84–1.07 (3H, m, $C_6H_{11}$), 1.20–1.30 (2H, m, $C_6H_{11}$), 1.53–1.62 (5H, m, $C_6H_{11}$), 2.90 (2H, d, $J$=12.0 Hz, $CCH_2$Ph), 3.33 (2H, br d, $J$=10.8 Hz, $CCH_2$Ph), 3.48–3.55 (1H, m, $C_6H_{11}$-*H*1), 3.50 (2H, s, $COCH_2$), 3.69 (2H, br s, $NCH_2$), 5.02 (1H, d, $J$=7.5 Hz, N*H*), 7.13–7.26 (10H, m, 2×$CCH_2Ph$), 7.30–7.37 (7H, m, $COCH_2Ph$+ $NCH_2$Ph-*H*3,5), 7.72 (2H, d, $J$=8.4 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.83 ($C_6H_{11}$-*C*3,5), 25.52 ($C_6H_{11}$-*C*4), 32.53 ($C_6H_{11}$-*C*2,6), 35.97 (2×$CCH_2$Ph), 42.11 ($CH_2CO$), 47.19 ($CH_2N$), 48.44 ($C_6H_{11}$-*C*1), 69.11 ($C^{\alpha}$), 126.95, 127.00 (2×$CCH_2$Ph-*C*4+$COCH_2$Ph-*C*4), 127.45 ($NCH_2$Ph-*C*2,6), 128.17 (2×$CCH_2$Ph-*C*3,5), 128.61 ($NCH_2$Ph-*C*3,5), 128.91 ($COCH_2$Ph-*C*3,5), 129.39 ($COCH_2$Ph-*C*2,6), 130.91 (2×$CCH_2$Ph-*C*2,6), 132.66 ($NCH_2$Ph-*C*4), 134.38 ($COCH_2$Ph-*C*1), 135.08 (2× $CCH_2$Ph-*C*1), 137.66 ($NCH_2$Ph-*C*1), 170.81 (*C*ONH), 172.49 ($COCH_2$). Anal. Calcd for $C_{37}ClH_{39}N_2O_2$: C, 76.73; H, 6.79; N, 4.84. Found: C, 76.73; H, 6.73; N, 4.90.

**4.1.1.14. *N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dibenzylglycine cyclohexylamide (2f).** The reaction was carried out on a 0.0056-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2f** (2.23 g, 63%) as a white solid, mp 169.0–170.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 0.85–1.11 (3H, m, $C_6H_{11}$), 1.22–1.35 (2H, m, $C_6H_{11}$), 1.54–1.63 (5H, m, $C_6H_{11}$), 2.91 (2H, d, $J$=11.7 Hz, $CCH_2$Ph), 3.35 (2H, br d, $J$=10.8 Hz, $CCH_2$Ph), 3.48–3.59 (1H, m, $C_6H_{11}$-*H*1), 3.51 (2H, s, $COCH_2$), 3.75 (2H, br s, $NCH_2$), 5.04 (1H, d, $J$=7.5 Hz, N*H*), 7.14–7.27 (12H, m, 2×$CCH_2Ph$+$NCH_2$Ph-*H*3,5), 7.31–7.38 (5H, m, $COCH_2Ph$), 7.81 (2H, d, $J$=9.0 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.84 ($C_6H_{11}$-*C*3,5), 25.53 ($C_6H_{11}$-*C*4), 32.53 ($C_6H_{11}$-*C*2,6), 36.09 (2×$CCH_2$Ph), 42.07 ($CH_2CO$), 47.16 ($CH_2N$), 48.49 ($C_6H_{11}$-*C*1), 69.14 ($C^{\alpha}$), 120.41 (q, $J_{C-F}$=257.1 Hz, $OCF_3$), 121.21 ($NCH_2$Ph-*C*3,5), 126.98, 127.01 (2×$CCH_2$Ph-*C*4+$COCH_2$Ph-*C*4), 128.44 ($NCH_2$Ph-*C*2,6), 128.19 (2× $CCH_2$Ph-*C*3,5), 128.62 ($COCH_2$Ph-*C*3,5), 129.40 ($COCH_2$Ph-*C*2,6), 130.92 (2×$CCH_2$Ph-*C*2,6), 134.33 ($COCH_2$Ph-*C*1), 135.07 (2×$CCH_2$Ph-*C*1), 137.79 ($NCH_2$Ph-*C*1), 148.11 (q, $J_{C-F}$=1.8 Hz, $NCH_2$Ph-*C*4), 170.86 (*C*ONH), 172.50 ($COCH_2$). Anal. Calcd for $C_{38}F_3H_{39}N_2O_3$: C, 72.59; H, 6.25; N, 4.46. Found: C, 72.72; H, 5.89; N, 4.53.

**4.1.1.15. *N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dibenzylglycine cyclohexylamide (2g).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **2g** (4.79 g, 78%) as a white solid, mp 213.5–214.5 °C. $^1$H NMR (300 MHz, $CDCl_3$): 0.87–1.12 (3H, m, $C_6H_{11}$), 1.24–1.36 (2H, m, $C_6H_{11}$), 1.59 (5H, m, $C_6H_{11}$), 2.89 (2H, d, $J$=11.7 Hz, $CCH_2$Ph), 3.34 (2H, br s, $CCH_2$Ph), 3.50 (2H, s, $COCH_2$), 3.52–3.60 (1H, m, $C_6H_{11}$-*H*1), 3.80 (2H, br s, $NCH_2$), 5.05 (1H, d, $J$=7.5 Hz, N*H*), 7.14–7.30 (10H, m, 2×$CCCH_2Ph$), 7.31–7.38 (5H, m, $COCH_2Ph$), 7.65 (2H, d, $J$=8.1 Hz, $NCH_2$Ph-*H*3,5), 7.92 (2H, d, $J$=8.1 Hz, $NCH_2$Ph-*H*2,6); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.81 ($C_6H_{11}$-*C*3,5), 25.48 ($C_6H_{11}$-*C*4), 32.49 ($C_6H_{11}$-*C*2,6), 36.01 (2×$CCH_2$Ph), 42.15 ($CH_2CO$), 47.45 ($CH_2N$), 48.46 ($C_6H_{11}$-*C*1), 69.11 ($C^{\alpha}$), 124.07 (q, $J_{C-F}$=272.0 Hz, $CF_3$), 125.68 (q, $J_{C-F}$=3.8 Hz, $NCH_2$Ph-*C*3,5), 126.39 ($NCH_2$Ph-*C*2,6), 126.98, 127.01 (2×$CCH_2$Ph-*C*4+$COCH_2$Ph-*C*4), 128.17 (2×$CCH_2$Ph-*C*3,5), 128.61 ($COCH_2$Ph-*C*3,5), 129.33 ($COCH_2$Ph-*C*2,6), 129.20 (q, $J_{C-F}$=32.5 Hz, $NCH_2$Ph-*C*4), 130.87 (2×$CCH_2$Ph-*C*2,6), 134.17 ($COCH_2$Ph-*C*1), 134.96 (2×$CCH_2$Ph-*C*1), 143.32 ($NCH_2$Ph-*C*1), 170.79 (*C*ONH), 172.41 ($COCH_2$). Anal. Calcd for $C_{38}F_3H_{39}N_2O_2$: C, 74.49; H, 6.42; N, 4.57. Found: C, 74.46; H, 6.07; N, 4.63.

**4.1.1.16. *N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dibenzylglycine cyclohexylamide (2h).** The reaction was carried out on a 0.003-molar scale, starting with 4-nitrobenzylamine hydrochloride (1.3 equiv, 2.45 g), which was neutralised with triethylamine (1.2 equiv, 1.66 ml) in dry diethyl ether (20 ml) at room temperature and under stirring for 90 min. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the residue was dissolved in dry MeOH (5 ml) and used according to the general procedure described above. The final product was purified by column chromatography and recrystallised from ethyl acetate to yield **2h** (0.84 g, 47%) as a pale yellow solid, mp 211.8–212.8 °C. $^1$H NMR (300 MHz, $CDCl_3$): 0.88–1.11 (3H, m, $C_6H_{11}$), 1.24–1.35 (2H, m, $C_6H_{11}$), 1.53–1.63 (5H, m, $C_6H_{11}$), 2.87 (2H, d, $J$=11.7 Hz, $CCH_2$Ph), 3.34 (2H, br s, $CCH_2$Ph), 3.48 (2H, s, $COCH_2$), 3.52–3.58 (1H, m, $C_6H_{11}$-*H*1), 3.82 (2H, br s, $NCH_2$), 5.04 (1H, d, $J$=7.8 Hz, N*H*), 7.17–7.25 (10H, m, 2×$CCH_2Ph$), 7.30–7.38 (5H, m, $COCH_2Ph$), 8.00 (2H, d, $J$=8.1 Hz, $NCH_2$Ph-*H*2,6), 8.24 (2H, d, $J$=8.7 Hz, $NCH_2$Ph-*H*3,5); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.80 ($C_6H_{11}$-*C*3,5), 25.49 ($C_6H_{11}$-*C*4), 32.48 ($C_6H_{11}$-*C*2,6), 35.93 (2×$CCH_2$Ph), 42.22 ($CH_2CO$), 47.46 ($CH_2N$), 48.54 ($C_6H_{11}$-*C*1), 69.15($C^{\alpha}$), 124.01 ($NCH_2$Ph-*C*3,5), 127.02, 127.12 (2×$CCH_2$Ph-*C*4+$NCH_2$Ph-*C*2,6+$COCH_2$Ph-*C*4), 128.25 (2×$CCH_2$Ph-*C*3,5), 128.70 ($COCH_2$Ph-*C*3,5), 129.28 ($COCH_2$Ph-*C*2,6), 130.85

(2×$CCH_2$Ph-*C*2,6), 133.91 ($COCH_2$Ph-*C*1), 134.80 (2×$CCH_2$Ph-*C*1), 146.85 ($NCH_2$Ph-*C*4), 147.06 ($NCH_2$Ph-*C*1), 170.78 (*C*ONH), 172.27 (*C*$OCH_2$). Anal. Calcd for $C_{37}H_{39}N_3O_4$: C, 75.36; H, 6.67; N, 7.13. Found: C, 75.05; H, 6.60; N, 6.92.

**4.1.1.17. *N*-Phenylacetyl-*N*-(4-methoxyphenyl)-α,α-dimethylglycine cyclohexylamide (3a).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from diethyl ether to yield **3a** (3.77 g, 92%) as a white crystals, mp 105.7–106.8 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.06–1.21 (3H, m, $C_6H_{11}$), 1.31 (6H, s, 2×$CH_3$), 1.37–1.39 (2H, m, $C_6H_{11}$), 1.58–1.72 (3H, m, $C_6H_{11}$), 1.93 (2H, m, $C_6H_{11}$), 3.33 (2H, s, $CH_2$), 3.69–3.81 (1H, m, $C_6H_{11}$-*H*1), 3.84 (3H, s, $OCH_3$), 5.64 (1H, d, *J*=8.1 Hz, N*H*), 6.86 (2H, d, *J*=9.0 Hz, NPh-*H*3,5), 6.99 (2H, m, $CH_2$Ph-*H*2,6), 7.06 (2H, d, *J*=8.7 Hz, NPh-*H*2,6), 7.20 (3H, m, $CH_2$Ph-*H*3,4,5); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.75 ($C_6H_{11}$-*C*3,5), 25.29 (2×$CH_3$), 25.51 ($C_6H_{11}$-*C*4), 32.75 ($C_6H_{11}$-*C*2,6), 42.59 ($CH_2$), 48.30 ($C_6H_{11}$-*C*1), 55.33 ($OCH_3$), 62.61 ($C^{\alpha}$), 113.99 (NPh-*C*3,5), 126.35 ($CH_2$Ph-*C*4), 128.11 ($CH_2$Ph-*C*3,5), 128.83 ($CH_2$Ph-*C*2,6), 131.27 (NPh-*C*2,6), 132.33 (NPh-*C*1), 135.23 ($CH_2$Ph-*C*1), 159.21 (NPh-*C*4), 171.23 (*C*ON), 173.71 (*C*ONH). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found: C, 73.24; H, 7.91; N, 6.97.

**4.1.1.18. *N*-Phenylacetyl-*N*-phenyl-α,α-dimethylglycine cyclohexylamide (3b).** The reaction was carried out on a 0.02-molar scale and the crude product was purified by column chromatography as described above and recrystallised from diethyl ether to yield **3b** (6.53 g, 86%) as a white crystals, mp 127.2–128.3 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.03–1.23 (3H, m, $C_6H_{11}$), 1.34 (6H, s, 2×$CH_3$), 1.35–1.40 (2H, m, $C_6H_{11}$), 1.66–1.71 (3H, m, $C_6H_{11}$), 1.94 (2H, m, $C_6H_{11}$), 3.33 (2H, s, $CH_2$), 3.70–3.83 (1H, m, $C_6H_{11}$-*H*1), 5.66 (1H, d, *J*=7.5 Hz, N*H*), 6.98 (2H, m, $CH_2$Ph-*H*2,6), 7.16–7.22 (5H, m, NPh-*H*2,6+$CH_2$Ph-*H*3,4,5), 7.39 (3H, m, NPh-*H*3,4,5); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.78 ($C_6H_{11}$-*C*3,5), 25.37 (2×$CH_3$), 25.55 ($C_6H_{11}$-*C*4), 32.79 ($C_6H_{11}$-*C*2,6), 42.69 ($CH_2$), 48.36 ($C_6H_{11}$-*C*1), 62.56 ($C^{\alpha}$), 126.41 ($CH_2$Ph-*C*4), 128.16 ($CH_2$Ph-*C*3,5), 128.46 (NPh-*C*4), 128.84 ($CH_2$Ph-*C*2,6), 129.03 (NPh-*C*3,5), 130.43 (NPh-*C*2,6), 135.16 ($CH_2$Ph-*C*1), 139.67 (NPh-*C*1), 170.83 (*C*ON), 173.62 (*C*ONH). Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.17; H, 7.90; N, 7.51.

**4.1.1.19. *N*-Phenylacetyl-*N*-(4-chlorophenyl)-α,α-dimethylglycine cyclohexylamide (3c).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **3c** (2.93 g, 71%) as a white crystals, mp 118.9–119.7 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.05–1.22 (3H, m, $C_6H_{11}$), 1.31 (6H, s, 2×$CH_3$), 1.34–1.43 (2H, m, $C_6H_{11}$), 1.57–1.73 (3H, m, $C_6H_{11}$), 1.95 (2H, m, $C_6H_{11}$), 3.32 (2H, s, $CH_2$), 3.71–3.80 (1H, m, $C_6H_{11}$-*H*1), 5.63 (1H, d, *J*=7.8 Hz, N*H*), 6.96 (2H, m, $CH_2$Ph-*H*2,6), 7.11 (2H, d, *J*=8.7 Hz, NPh-*H*2,6), 7.18–7.21 (3H, m, $CH_2$Ph-*H*3,4,5), 7.31 (2H, d, *J*=8.4 Hz, NPh-*H*3,5); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.82 ($C_6H_{11}$-*C*3,5), 25.48 (2×$CH_3$), 25.56 ($C_6H_{11}$-*C*4), 32.85 ($C_6H_{11}$-*C*2,6), 42.83 ($CH_2$), 48.54 ($C_6H_{11}$-*C*1), 62.54 ($C^{\alpha}$), 126.54 ($CH_2$Ph-*C*4), 128.28 ($CH_2$Ph-*C*3,5), 128.76 ($CH_2$Ph-*C*2,6), 129.17 (NPh-*C*3,5), 131.87 (NPh-*C*2,6), 134.42 (NPh-*C*4), 134.93 ($CH_2$Ph-*C*1), 138.35 (NPh-*C*1), 170.74 (*C*ON), 173.50 (*C*ONH). Anal. Calcd for $C_{24}ClH_{29}N_2O_2$: C, 69.80; H, 7.08; N, 6.75. Found: C, 69.58; H, 7.07; N, 6.81.

**4.1.1.20. *N*-Phenylacetyl-*N*-(4-cyanofenyl)-α,α-dimethylglycine cyclohexylamide (3d).** The reaction was carried out on a 0.01-molar scale and the crude product was purified by column chromatography as described above and recrystallised from ethyl acetate to yield **3d** (0.96 g, 24%) as a white crystals, mp 166.0–167.1 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.08–1.21 (3H, m, $C_6H_{11}$), 1.32 (6H, s, 2×$CH_3$), 1.34–1.42 (2H, m, $C_6H_{11}$), 1.59–1.74 (3H, m, $C_6H_{11}$), 1.96 (2H, m, $C_6H_{11}$), 3.29 (2H, s, $CH_2$), 3.70–3.82 (1H, m, $C_6H_{11}$-*H*1), 5.65 (1H, d, *J*=7.8 Hz, N*H*), 6.90 (2H, m, $CH_2$Ph-*H*2,6), 7.16–7.20 (3H, m, $CH_2$Ph-*H*3,4,5), 7.34 (2H, d, *J*=8.1 Hz, NPh-*H*2,6), 7.62 (2H, d, *J*=8.4 Hz, NPh-*H*3,5); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.79 ($C_6H_{11}$-*C*3,5), 25.49 (2×$CH_3$), 25.54 ($C_6H_{11}$-*C*4), 32.81 ($C_6H_{11}$-*C*2,6), 43.09 ($CH_2$), 48.68 ($C_6H_{11}$-*C*1), 62.60 ($C^{\alpha}$), 112.46 (NPh-*C*4), 117.82 (NPh-*C*N), 126.68 ($CH_2$Ph-*C*4), 128.37 ($CH_2$Ph-*C*3,5), 128.55 ($CH_2$Ph-*C*2,6), 131.77 (NPh-*C*2,6), 132.76 (NPh-*C*3,5), 134.46 ($CH_2$Ph-*C*1), 143.99 (NPh-*C*1), 170.15 (*C*ON), 173.22 (*C*ONH). Anal. Calcd for $C_{25}H_{29}N_3O_2$: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.26; H, 7.22; N, 10.38.

**4.1.1.21. *N*-Phenylacetyl-*N*-(4-nitrophenyl)-α,α-dimethylglycine cyclohexylamide (3e).** The reaction was carried out on a 0.04-molar scale and the crude product was purified by column chromatography as described above and recrystallised from diethyl ether to yield **3e** (1.47 g, 9%) as a yellow crystals, mp 100.9–101.9 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.11–1.24 (3H, m, $C_6H_{11}$), 1.36 (6H, s, 2×$CH_3$), 1.42–1.46 (2H, m, $C_6H_{11}$), 1.58–1.76 (3H, m, $C_6H_{11}$), 2.00 (2H, m, $C_6H_{11}$), 3.33 (2H, s, $CH_2$), 3.74–3.85 (1H, m, $C_6H_{11}$-*H*1), 5.64 (1H, d, *J*=7.8 Hz, N*H*), 6.93 (2H, m, $CH_2$Ph-*H*2,6), 7.20–7.22 (3H, m, $CH_2$Ph-*H*3,4,5), 7.41 (2H, d, *J*=9.0 Hz, NPh-*H*2,6), 8.20 (2H, d, *J*=9.0 Hz, NPh-*H*3,5); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.86 ($C_6H_{11}$-*C*3,5), 25.56 ($C_6H_{11}$-*C*4), 25.64 (2×$CH_3$), 32.90 ($C_6H_{11}$-*C*2,6), 43.19 ($CH_2$), 48.79 ($C_6H_{11}$-*C*1), 62.68 ($C^{\alpha}$), 124.14 (NPh-*C*3,5), 126.80 ($CH_2$Ph-*C*4), 128.47 ($CH_2$Ph-*C*3,5), 128.61 ($CH_2$Ph-*C*2,6), 131.93 (NPh-*C*2,6), 134.45 ($CH_2$Ph-*C*1), 145.82 (NPh-*C*4), 147.41 (NPh-*C*1), 170.14 (*C*ON), 173.27 (*C*ONH). Anal. Calcd for $C_{24}H_{29}N_3O_4$: C, 68.06; H, 6.90; N, 9.92. Found: C, 67.98; H, 6.88; N, 9.85.

**4.1.2. General method for the preparative acidolysis of Ugi–Passerini adducts (4, 5 and 6).** Compounds **1a–1h**, **2a–2h** and **3a–3d** (0.20 or 0.25 g, depending on the solubility) were dissolved in 25 ml of 5% TFA in dry acetonitrile and the solutions were kept at room temperature until TLC (dichloromethane/MeOH, 25:1) showed no more starting material (2–168 h). The solvent was concentrated under reduced pressure at 30 °C and the pH of the residue was adjusted to 3 by treatment with 2 M aqueous NaOH. The mixture was stirred overnight and the resulting suspension was extracted into chloroform (3×15 ml). The combined organic layers were washed with water (2×20 ml) and dried

over anhydrous $MgSO_4$; this was filtered off and the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by column chromatography and/or recrystallisation; in the former case the desired fraction was evaporated to dryness to give the corresponding compound (**4**, **5** and **6**).

**4.1.2.1. *N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dimethylglycine (4a).** The reaction was carried out with compound **1a** (0.20 g) and the product was purified by recrystallisation from ethyl acetate to yield **4a** (140 mg, 84%) as a white solid, mp 201.1–202.1 °C (lit.[20] 168.6–169.2 °C). $^1$H NMR (300 MHz, DMSO-$d_6$): 1.27 (6H, s, 2×C$H_3$), 3.57 (2H, s, C$H_2$CO), 3.76 (3H, s, OC$H_3$), 4.59 (2H, s, NC$H_2$), 6.94 (2H, d, $J$=8.7 Hz, NCH$_2$Ph-*H*3,5), 7.11–14 (2H, m, COCH$_2$Ph-*H*2,6), 7.17–7.29 (3H, m, COCH$_2$Ph-*H*3,4,5), 7.36 (2H, d, $J$=8.7 Hz, NCH$_2$Ph-*H*2,6), 12.02 (1H, br s, OH); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 23.33 (2×CH$_3$), 40.34 (*C*H$_2$CO), 46.12 (*C*H$_2$N), 55.06 (O*C*H$_3$), 60.69 (*C*$^{\alpha}$), 113.99 (NCH$_2$Ph-*C*3,5), 126.40 (COCH$_2$Ph-*C*4), 127.03 (NCH$_2$Ph-*C*2,6), 128.27 (COCH$_2$Ph-*C*3,5), 128.92 (COCH$_2$Ph-*C*2,6), 130.92 (NCH$_2$Ph-*C*1), 135.58 (COCH$_2$Ph-*C*1), 158.20 (NCH$_2$Ph-*C*4), 170.78 (*C*OCH$_2$), 175.20 (*C*OOH). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.87; H, 6.82; N, 4.21.

**4.1.2.2. *N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dimethylglycine (4b).** The reaction was carried out with compound **1b** (0.21 g) and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **4b** (152 mg, 89%) as a white solid, mp 160.7–161.7 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.46 (6H, s, 2×C$H_3$), 2.39 (3H, s, Ph-C$H_3$), 3.70 (2H, s, C$H_2$CO), 4.57 (2H, s, NC$H_2$), 7.21–7.35 (9H, m, COCH$_2$*Ph*+NCH$_2$*Ph*), 9.81 (1H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 21.01 (Ph-CH$_3$), 23.50 (2×CH$_3$), 41.36 (*C*H$_2$CO), 47.12 (*C*H$_2$N), 61.40 (*C*$^{\alpha}$), 125.76 (NCH$_2$Ph-*C*2,6), 126.76 (COCH$_2$Ph-*C*4), 128.57 (COCH$_2$Ph-*C*2,6), 128.63 (COCH$_2$Ph-*C*3,5), 129.56 (NCH$_2$Ph-*C*3,5), 134.54 (COCH$_2$Ph-*C*1), 134.86 (NCH$_2$Ph-*C*1), 136.92 (NCH$_2$Ph-*C*4), 172.11 (*C*OCH$_2$), 179.05 (*C*OOH). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.64; H, 7.01; N, 4.41. Compound **4b** was also obtained, in 79% yield, when 0.25 g of **1b** was submitted to the forcing reaction conditions described below for the preparation of **6e**.

**4.1.2.3. *N*-Phenylacetyl-*N*-benzyl-α,α-dimethylglycine (4c).** The reaction was carried out with compound **1c** (0.20 g) and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **4c** (121 mg, 76%) as a white solid, mp 196.9–197.9 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.47 (6H, s, 2×C$H_3$), 3.69 (2H, s, C$H_2$CO), 4.61 (2H, s, NC$H_2$), 7.21–7.31 (6H, m, COCH$_2$*Ph*+NCH$_2$Ph-*H*4), 7.41–7.45 (4H, m, NCH$_2$Ph-*H*2,3,5,6), 9.41 (1H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 23.50 (2×*C*H$_3$), 41.36 (*C*H$_2$CO), 47.31 (*C*H$_2$N), 61.44 (*C*$^{\alpha}$), 125.79 (NCH$_2$Ph-*C*2,6), 126.78 (COCH$_2$Ph-*C*4), 127.26 (NCH$_2$Ph-*C*4), 128.56 (COCH$_2$Ph-*C*2,6), 128.63 (COCH$_2$Ph-*C*3,5), 128.88 (NCH$_2$Ph-*C*3,5), 134.44 (COCH$_2$Ph-*C*1), 137.93 (NCH$_2$Ph-*C*1), 172.16 (*C*OCH$_2$), 178.99 (*C*OOH). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.35; H, 6.59; N, 4.61.

**4.1.2.4. *N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dimethylglycine (4d).** The reaction was carried out with compound **1d** (0.25 g) and the product was purified by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4d** (191 mg, 97%) as white crystals, mp 191.4–192.2 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.45 (6H, s, 2×C$H_3$), 3.67 (2H, s, C$H_2$CO), 4.56 (2H, s, NC$H_2$), 7.10 (2H, t, $J$=8.7 Hz, NCH$_2$Ph-*H*3,5), 7.18–7.33 (5H, m, COCH$_2$*Ph*), 7.41 (2H, dd, $J$=5.4, 8.4 Hz, NCH$_2$Ph-*H*2,6), 9.43 (1H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 23.47 (2×*C*H$_3$), 41.41 (*C*H$_2$CO), 46.68 (*C*H$_2$N), 61.47 (*C*$^{\alpha}$), 115.81 (d, $J_{C-F}$=21.6 Hz, NCH$_2$Ph-*C*3,5), 126.90 (COCH$_2$Ph-*C*4), 127.41 (d, $J_{C-F}$=7.8 Hz, NCH$_2$Ph-*C*2,6), 128.52 (COCH$_2$Ph-*C*2,6), 128.72 (COCH$_2$Ph-*C*3,5), 133.59 (d, $J_{C-F}$=3.2 Hz, NCH$_2$Ph-*C*1), 134.29 (COCH$_2$Ph-*C*1), 162.01 (d, $J_{C-F}$=245.6 Hz, NCH$_2$Ph-*C*4), 172.15 (*C*OCH$_2$), 178.83 (*C*OOH). Anal. Calcd for $C_{19}FH_{20}NO_3$: C, 69.29; H, 6.12; N, 4.25. Found: C, 69.14; H, 6.10; N, 4.03. Compound **4d** was also obtained, in 66% yield, when 0.25 g of **1d** was submitted to the forcing reaction conditions described below for the preparation of **6e**.

**4.1.2.5. *N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dimethylglycine (4e).** The reaction was carried out with compound **1e** (0.21 g) and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4e** (154 mg, 89%) as a white solid, mp 168.8–169.8 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.44 (6H, s, 2×C$H_3$), 3.65 (2H, s, C$H_2$CO), 4.56 (2H, s, NC$H_2$), 7.18–7.38 (9H, m, COCH$_2$-*Ph*+NCH$_2$Ph-*H*2,3,5,6), 10.01 (1H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 23.43 (2×*C*H$_3$), 41.40 (*C*H$_2$CO), 46.72 (*C*H$_2$N), 61.45 (*C*$^{\alpha}$), 126.90 (COCH$_2$Ph-*C*4), 127.21 (NCH$_2$Ph-*C*2,6), 128.47 (COCH$_2$Ph-*C*2,6), 128.71 (COCH$_2$Ph-*C*3,5), 129.05 (NCH$_2$Ph-*C*3,5), 133.08 (NCH$_2$Ph-*C*4), 134.18 (COCH$_2$Ph-*C*1), 136.49 (NCH$_2$Ph-*C*1), 172.11 (*C*OCH$_2$), 178.81 (*C*OOH). Anal. Calcd for $C_{19}ClH_{20}NO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.68; H, 5.93; N, 4.01.

**4.1.2.6. *N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dimethylglycine (4f).** The reaction was carried out with compound **1f** (0.25 g) and the product was purified by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4f** (153 mg, 90%) as a white solid, mp 149.9–150.7 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.45 (6H, s, 2×C$H_3$), 3.66 (2H, s, C$H_2$CO), 4.59 (2H, s, NC$H_2$), 7.19–7.32 (7H, m, COCH$_2$*Ph*+NCH$_2$Ph-*H*3,5), 7.49 (2H, d, $J$=8.4 Hz, NCH$_2$Ph-*H*2,6), 9.32 (1H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 23.47 (2×*C*H$_3$), 41.47 (*C*H$_2$CO), 46.69 (*C*H$_2$N), 61.49 (*C*$^{\alpha}$), 120.4 (q, $J_{C-F}$=257.1 Hz, O*C*F$_3$), 121.45 (NCH$_2$Ph-*C*3,5), 126.96 (COCH$_2$Ph-*C*4), 127.21 (NCH$_2$Ph-*C*2,6), 128.50 (COCH$_2$Ph-*C*2,6), 128.76 (COCH$_2$Ph-*C*3,5), 134.15 (COCH$_2$Ph-*C*1), 136.71 (NCH$_2$Ph-*C*1), 148.39 (q, $J_{C-F}$=1.9 Hz, NCH$_2$Ph-*C*4), 172.17 (*C*OCH$_2$), 178.80 (*C*OOH). Anal. Calcd for $C_{20}F_3H_{20}NO_4$: C, 60.76; H, 5.10; N, 3.54. Found: C, 60.67; H, 5.36; N, 3.28.

**4.1.2.7. *N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dimethylglycine (4g).** The reaction was carried out with compound **1g** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **4g** (161 mg,

92%) as white crystals, mp 180.9–181.8 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.46 (6H, s, 2×C$H_3$), 3.65 (2H, s, C$H_2$CO), 4.64 (2H, s, NC$H_2$), 7.18 (2H, m, $COCH_2$-*H*2,6), 7.24–7.33 (3H, m, $COCH_2$Ph-*H*3,4,5), 7.60 (2H, d, *J*=8.4 Hz, $NCH_2$Ph-*H*2,6), 7.67 (2H, d, *J*=8.4 Hz, $NCH_2$Ph-*H*3,5), 9.00 (1H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 23.48 (2×*C*$H_3$), 41.54 (*C*$H_2$CO), 47.03 (*C*$H_2$N), 61.54 ($C^{\alpha}$), 124.03 (q, $J_{C-F}$=274.0 Hz, *C*$F_3$), 125.93 (q, $J_{C-F}$=3.7 Hz, $NCH_2$Ph-*C*3,5), 126.20 ($NCH_2$Ph-*C*2,6), 127.02 ($COCH_2$Ph-*C*4), 128.48 ($COCH_2$Ph-*C*2,6), 128.80 ($COCH_2$Ph-*C*3,5), 129.75 (q, $J_{C-F}$=32.5 Hz, $NCH_2$Ph-*C*4), 134.06 ($COCH_2$Ph-*C*1), 142.25 ($NCH_2$Ph-*C*1), 172.17 (*C*$OCH_2$), 178.67 (*C*OOH). Anal. Calcd for $C_{20}F_3H_{20}NO_3$: C, 63.32; H, 5.31; N, 3.69. Found: C, 63.38; H, 5.04; N, 3.62.

**4.1.2.8. *N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dimethylglycine (4h).** The reaction was carried out with compound **1h** (0.20 g) and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **4h** (146 mg, 89%) as pale yellow crystals, mp 194.7–195.8 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.45 (6H, s, 2×C$H_3$), 3.64 (2H, s, C$H_2$CO), 4.68 (2H, s, NC$H_2$), 7.17 (2H, d, *J*=6.6 Hz, $COCH_2$Ph-*H*2,6), 7.22–7.32 (3H, m, $COCH_2$Ph-*H*3,4,5), 7.66 (2H, d, *J*=8.7 Hz, $NCH_2$Ph-*H*2,6), 8.26 (2H, d, *J*=8.7 Hz, $NCH_2$Ph-*H*3,5), 9.03 (1H, br s, OH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 24.44 (2×*C*$H_3$), 41.60 (*C*$H_2$CO), 47.00 (*C*$H_2$N), 61.59 ($C^{\alpha}$), 124.19 ($NCH_2$Ph-*C*3,5), 126.73 ($NCH_2$Ph-*C*2,6), 127.14 ($COCH_2$Ph-*C*4), 128.41 ($COCH_2$Ph-*C*2,6), 128.87 ($COCH_2$Ph-*C*3,5), 133.75 ($COCH_2$Ph-*C*1), 145.65 ($NCH_2$Ph-*C*1), 147.32 ($NCH_2$Ph-*C*4), 172.12 (*C*$OCH_2$), 178.51 (*C*OOH). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.89; H, 5.65; N, 7.59.

**4.1.2.9. *N*-Phenylacetyl-*N*-(4-methoxybenzyl)-α,α-dibenzylglycine (5a).** The reaction was carried out with compound **2a** (0.14 g) and the product was purified by PLC (dichloromethane/MeOH, 15:1) followed by recrystallisation from ethyl acetate to yield **5a** (81 mg, 68%) as a white solid, mp 208.2–209.3 °C (lit.[20] 158.2–159.2 °C). $^1$H NMR (300 MHz, DMSO-$d_6$): 2.77 (2H, d, *J*=12.9 Hz, CC$H_2$Ph), 3.26 (2H, d, *J*=13.2 Hz, CC$H_2$Ph), 3.44 (2H, s, COC$H_2$), 3.72 (3H, s, OC$H_3$), 3.80 (2H, s, NC$H_2$), 6.94 (2H, d, *J*=8.7 Hz, $NCH_2$Ph-*H*3,5), 7.13–7.15 (2H, m, $COCH_2$Ph-*H*2,6), 7.19–7.34 (13H, m, 2×$CCH_2$*Ph*+$COCH_2$Ph-*H*3,4,5), 7.44 (2H, d, *J*=8.7 Hz, $NCH_2$Ph-*H*2,6), 12.34 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 36.22 (2×*C*$CH_2$Ph), 40.50 (*C*$H_2$CO), 47.02 (*C*$H_2$N), 55.03 (O*C*$H_3$), 68.18 ($C^{\alpha}$), 114.04 ($NCH_2$Ph-*C*3,5), 126.54 (2×$CCH_2$Ph-*C*4), 126.75 ($NCH_2$Ph-*C*2,6+$COCH_2$Ph-*C*4), 128.16 (2×$CCH_2$Ph-*C*3,5), 128.19 ($COCH_2$Ph-*C*3,5), 129.59 ($COCH_2$Ph-*C*2,6), 130.74 (2×$CCH_2$Ph-*C*2,6), 130.96 ($NCH_2$Ph-*C*1), 135.04 ($COCH_2$Ph-*C*1), 135.68 (2×$CCH_2$Ph-*C*1), 158.11 ($NCH_2$Ph-*C*4), 171.57 (*C*$OCH_2$), 172.29 (*C*OOH). Anal. Calcd for $C_{32}H_{31}NO_4$: C, 77.87; H, 6.33; N, 2.84. Found: C, 77.44; H, 6.05; N, 2.86.

**4.1.2.10. *N*-Phenylacetyl-*N*-(4-methylbenzyl)-α,α-dibenzylglycine (5b).** The reaction was carried out with compound **2b** (0.25 g) and the product was purified by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **5b** (200 mg, 93%) as a white solid, mp 212.5–213.7 °C. $^1$H NMR (300 MHz, $CDCl_3$): 2.34 (3H, s, C$H_3$Ph), 3.02 (2H, d, *J*=13.2 Hz, CC$H_2$Ph), 3.43 (2H, br d, *J*=12.9 Hz, CC$H_2$Ph), 3.61 (2H, s, COC$H_2$), 3.82 (2H, br s, NC$H_2$), 7.17–7.30 (12H, m, 2×$CCH_2$*Ph*+$NCH_2$Ph-*H*3,5), 7.33–7.44 (7H, m, $COCH_2$*Ph*+$NCH_2$Ph-*H*2,6), 8.45 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 20.98 (*C*$H_3$Ph), 36.13 (2×*C*$CH_2$Ph), 41.31 (*C*$H_2$CO), 48.11 (*C*$H_2$N), 68.88 ($C^{\alpha}$), 125.57 ($NCH_2$Ph-*C*2,6), 127.01 ($COCH_2$Ph-*C*4), 127.06 (2×$CCH_2$Ph-*C*4), 128.40 (2×$CCH_2$Ph-*C*3,5), 128.58 ($COCH_2$Ph-*C*3,5), 129.62 ($NCH_2$Ph-*C*3,5), 129.72 ($COCH_2$Ph-*C*2,6), 130.87 (2×$CCH_2$Ph-*C*2,6), 134.42 ($COCH_2$Ph-*C*1), 135.14 ($NCH_2$Ph-*C*1), 135.37 (2×$CCH_2$Ph-*C*1), 136.68 ($NCH_2$Ph-*C*4), 173.42 (*C*$OCH_2$), 175.66 (*C*OOH). Anal. Calcd for $C_{32}H_{31}NO_3$: C, 80.47; H, 6.54; N, 2.93. Found: C, 80.64; H, 6.64; N, 3.10.

**4.1.2.11. *N*-Phenylacetyl-*N*-benzyl-α,α-dibenzylglycine (5c).** The reaction was carried out with compound **2c** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **5c** (207 mg, 98%) as a white solid, mp 228.6–229.7 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): 2.76 (2H, d, *J*=12.9 Hz, CC$H_2$Ph), 3.26 (2H, d, *J*=12.9 Hz, CC$H_2$Ph), 3.43 (2H, s, COC$H_2$), 3.94 (2H, s, NC$H_2$), 7.13 (2H, br dd, *J*=1.5, 6.6 Hz, $COCH_2$Ph-*H*2,6), 7.23–7.30 (14H, m, 2×$CCH_2$*Ph*+$NCH_2$Ph-*H*4+$COCH_2$Ph-*H*3,4,5), 7.37 (2H, t, *J*=7.8 Hz, $NCH_2$Ph-*C*3,5), 7.53 (2H, d, *J*=7.5 Hz, $NCH_2$Ph-*H*2,6), 12.35 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 36.28 (2×*C*$CH_2$Ph), 40.50 (*C*$H_2$CO), 47.58 (*C*$H_2$N), 68.23 ($C^{\alpha}$), 125.66 ($NCH_2$Ph-*C*2,6), 126.57 ($NCH_2$Ph-*C*4), 126.78, 126.82 (2×$CCH_2$Ph-*C*4+$COCH_2$Ph-*C*4), 128.19 (2×$CH_2$Ph-*C*3,5+$COCH_2$Ph-*C*3,5), 128.63 ($NCH_2$Ph-*C*3,5), 129.60 ($COCH_2$Ph-*C*2,6), 130.75 (2×$CH_2$Ph-*C*2,6), 134.98 ($COCH_2$Ph-*C*1), 135.67 (2×$CCH_2$Ph-*C*1), 139.34 ($NCH_2$Ph-*C*1), 171.61 (*C*$OCH_2$), 172.27 (*C*OOH). Anal. Calcd for $C_{31}H_{29}NO_3$: C, 80.32; H, 6.31; N, 3.02. Found: C, 80.23; H, 6.14; N, 3.14.

**4.1.2.12. *N*-Phenylacetyl-*N*-(4-fluorobenzyl)-α,α-dibenzylglycine (5d).** The reaction was carried out with compound **2d** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **5d** (190 mg, 88%) as a white solid, mp 193.9–195.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 3.01 (2H, d, *J*=13.2 Hz, CC$H_2$Ph), 3.45 (2H, br d, *J*=12.6 Hz, CC$H_2$Ph), 3.60 (2H, s, COC$H_2$), 3.84 (2H, br s, NC$H_2$), 7.08 (2H, t, *J*=9.0 Hz, $NCH_2$Ph-*H*3,5), 7.25–7.33 (10H, m, 2×$CCH_2$*Ph*), 7.35–7.41 (5H, m, $COCH_2$*Ph*), 7.43–7.50 (2H, m, $NCH_2$Ph-*H*2,6), 8.81 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 36.12 (2×*C*$CH_2$Ph), 41.31 (*C*$H_2$CO), 47.68 (*C*$H_2$N), 68.93 ($C^{\alpha}$), 115.84 (d, $J_{C-F}$=21.6 Hz, $NCH_2$Ph-*C*3,5), 127.16 (2×$CCH_2$Ph-*C*4+$COCH_2$Ph-*C*4), 127.28 (d, $J_{C-F}$=7.8 Hz, $NCH_2$Ph-*C*2,6), 128.45 (2×$CCH_2$Ph-*C*3,5), 128.64 ($COCH_2$Ph-*C*3,5), 129.64 ($COCH_2$Ph-*C*2,6), 130.82 (2×$CCH_2$Ph-*C*2,6), 133.82 (d, $J_{C-F}$=3.2 Hz, $NCH_2$Ph-*C*1), 134.12 ($COCH_2$Ph-*C*1), 135.17 (2×$CCH_2$Ph-*C*1), 161.88 (d, $J_{C-F}$=245.6 Hz, $NCH_2$Ph-*C*4), 173.41 (*C*$OCH_2$), 175.62 (*C*OOH). Anal. Calcd for $C_{31}FH_{28}NO_3$: C, 77.32; H, 5.86; N, 2.91. Found: C, 76.97; H, 5.79; N, 2.92.

**4.1.2.13. *N*-Phenylacetyl-*N*-(4-chlorobenzyl)-α,α-dibenzylglycine (5e).** The reaction was carried out with compound **2e** (0.25 g) and the product was purified by

recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **5e** (186 mg, 85%) as a white solid, mp 207.9–209.1 °C. $^1$H NMR (300 MHz, $CDCl_3$): 2.98 (2H, d, $J$=13.2 Hz, CC$H_2$Ph), 3.43 (2H, br d, $J$=12.9 Hz, CC$H_2$Ph), 3.57 (2H, s, COC$H_2$), 3.81 (2H, br s, NC$H_2$), 7.26–7.45 (19H, m, 2×CCH$_2$*Ph*+COCH$_2$*Ph*+NCH$_2$*Ph*), 8.22 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 36.06 (2×C*C*H$_2$Ph), 41.36 (*C*H$_2$CO), 47.74 (*C*H$_2$N), 68.91 ($C^{\alpha}$), 127.11 (NCH$_2$Ph-*C*2,6), 127.17 (2×CCH$_2$Ph-*C*4+COCH$_2$Ph-*C*4), 128.47 (2×CCH$_2$Ph-*C*3,5), 128.67 (NCH$_2$Ph-*C*3,5), 129.12 (COCH$_2$Ph-*C*3,5), 129.63 (COCH$_2$Ph-*C*2,6), 130.82 (2×CCH$_2$Ph-*C*2,6), 132.99 (NCH$_2$Ph-*C*4), 134.03 (COCH$_2$Ph-*C*1), 135.13 (2×CCH$_2$Ph-*C*1), 136.76 (NCH$_2$Ph-*C*1), 173.32 (*C*OCH$_2$), 175.48 (*C*OOH). Anal. Calcd for $C_{31}ClH_{28}NO_3$: C, 74.76; H, 5.67; N, 2.81. Found: C, 74.48; H, 5.84; N, 2.94.

**4.1.2.14. *N*-Phenylacetyl-*N*-(4-trifluoromethoxybenzyl)-α,α-dibenzylglycine (5f).** The reaction was carried out with compound **2f** (0.25 g) and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **5f** (201 mg, 92%) as white crystals, mp 175.4–176.4 °C. $^1$H NMR (300 MHz, $CDCl_3$): 3.00 (2H, d, $J$=12.9 Hz, CC$H_2$Ph), 3.45 (2H, br d, $J$=12.9 Hz, CC$H_2$Ph), 3.59 (2H, s, COC$H_2$), 3.86 (2H, br s, NC$H_2$), 7.22–7.43 (17H, m, 2×CCH$_2$*Ph*+NCH$_2$Ph-*H*3,5+COCH$_2$*Ph*), 7.53 (2H, d, $J$=8.7 Hz, NCH$_2$Ph-*H*2,6), 8.51 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 36.13 (2×C*C*H$_2$Ph), 41.37 (*C*H$_2$CO), 47.71 (*C*H$_2$N), 68.96 ($C^{\alpha}$), 121.46 (NCH$_2$Ph-*C*3,5), 120.41 (q, $J_{C-F}$=257.1 Hz, O*C*F$_3$), 127.12 (NCH$_2$Ph-*C*2,6), 127.20, 127.22 (2×CCH$_2$Ph-*C*4+COCH$_2$Ph-*C*4), 128.49 (2×CCH$_2$Ph-*C*3,5), 128.68 (COCH$_2$Ph-*C*3,5), 129.63 (COCH$_2$Ph-*C*2,6), 130.83 (2×CCH$_2$Ph-*C*2,6), 133.98 (COCH$_2$Ph-*C*1), 135.09 (2×CCH$_2$Ph-*C*1), 136.91 (NCH$_2$Ph-*C*1), 148.28 (q, $J_{C-F}$=1.8 Hz, NCH$_2$Ph-*C*4), 173.41 (*C*OCH$_2$), 175.61 (*C*OOH). Anal. Calcd for $C_{32}F_3H_{28}NO_4\cdot 1/3H_2O$: C, 69.43; H, 5.22; N, 2.53. Found: C, 69.53; H, 5.41; N, 2.58.

**4.1.2.15. *N*-Phenylacetyl-*N*-(4-trifluoromethylbenzyl)-α,α-dibenzylglycine (5g).** The reaction was carried out with compound **2g** (0.25 g) and the product was purified by recrystallisation from ethyl acetate to yield **5g** (207 mg, 95%) as white crystals, mp 201.9–203.0 °C. $^1$H NMR (300 MHz, $CDCl_3$): 2.99 (2H, d, $J$=12.9 Hz, CC$H_2$Ph), 3.45 (2H, br d, $J$=12.6 Hz, CC$H_2$Ph), 3.57 (2H, s, COC$H_2$), 3.91 (2H, br s, NC$H_2$), 7.27–7.42 (15H, m, 2×CCCH$_2$*Ph*+COCH$_2$*Ph*), 7.64 (4H, s, NCH$_2$Ph-*H*2,3,5,6), 8.44 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 36.21 (2×C*C*H$_2$Ph), 41.44 (*C*H$_2$CO), 48.01 (*C*H$_2$N), 68.96 ($C^{\alpha}$), 124.00 (q, $J_{C-F}$=272.0 Hz, *C*F$_3$), 125.96 (q, $J_{C-F}$=3.8 Hz, NCH$_2$Ph-*C*3,5), 126.12 (NCH$_2$Ph-*C*2,6), 127.24 (2×CCH$_2$Ph-*C*4+COCH$_2$Ph-*C*4), 128.51 (2×CCH$_2$Ph-*C*3,5), 128.71 (COCH$_2$Ph-*C*3,5), 129.59 (q, $J_{C-F}$=32.5 Hz, NCH$_2$Ph-*C*4), 129.60 (COCH$_2$Ph-*C*2,6), 130.82 (2×CCH$_2$Ph-*C*2,6), 133.85 (COCH$_2$Ph-*C*1), 135.03 (2×CCH$_2$Ph-*C*1), 142.45 (NCH$_2$Ph-*C*1), 173.33 (*C*OCH$_2$), 175.40 (*C*OOH). Anal. Calcd for $C_{32}F_3H_{28}NO_3\cdot 1/3H_2O$: C, 71.50; H, 5.37; N, 2.61. Found: C, 71.33; H, 5.25; N, 2.55.

**4.1.2.16. *N*-Phenylacetyl-*N*-(4-nitrobenzyl)-α,α-dibenzylglycine (5h).** The reaction was carried out with compound **2h** (0.20 g) and the product was purified by column chromatography (dichloromethane/MeOH, 100:1) followed by recrystallisation from ethyl acetate to yield **5h** (108 mg, 62%) as pale yellow crystals, mp 213.3–214.5 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): 2.73 (2H, d, $J$=12.9 Hz, CC$H_2$Ph), 3.29 (2H, d, $J$=13.2 Hz, CC$H_2$Ph), 3.44 (2H, s, COC$H_2$), 4.15 (2H, br s, NC$H_2$), 7.13 (2H, dd, $J$=1.5, 9.3 Hz, COCH$_2$Ph-*H*2,6), 7.21–7.29 (13H, m, 2×CCH$_2$*Ph*+COCH$_2$Ph-*H*3,4,5), 7.78 (2H, d, $J$=8.7 Hz, NCH$_2$Ph-*H*2,6), 8.21 (2H, d, $J$=9.0 Hz, NCH$_2$Ph-*H*3,5), 12.47 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 36.41 (2×C*C*H$_2$Ph), 40.49 (*C*H$_2$CO), 47.51 (*C*H$_2$N), 68.39 ($C^{\alpha}$), 123.63 (NCH$_2$Ph-*C*3,5), 126.57 (COCH$_2$Ph-*C*4), 126.83 (2×CCH$_2$Ph-*C*4), 127.15 (NCH$_2$Ph-*C*2,6), 128.16 (COCH$_2$Ph-*C*3,5), 128.22 (2×CCH$_2$Ph-*C*3,5), 129.65 (COCH$_2$Ph-*C*2,6), 130.75 (2×CCH$_2$Ph-*C*2,6), 134.76 (COCH$_2$Ph-*C*1), 135.54 (2×CCH$_2$Ph-*C*1), 146.50 (NCH$_2$Ph-*C*4), 147.52 (NCH$_2$Ph-*C*1), 171.68 (*C*OCH$_2$), 172.28 (*C*OOH). Anal. Calcd for $C_{31}H_{28}N_2O_5$: C, 73.21; H, 5.55; N, 5.51. Found: C, 72.91; H, 5.46; N, 5.52.

**4.1.2.17. *N*-Phenylacetyl-*N*-(4-methoxyphenyl)-α,α-dimethylglycine (6a).** The reaction was carried out with compound **3a** (0.38 g) in neat TFA at room temperature and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from ethyl acetate to yield **6a** (0.30 g, 98%) as white crystals, mp 164.2–165.5 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.36 (6H, s, 2×C$H_3$), 3.40 (2H, s, C$H_2$), 3.85 (3H, s, OC$H_3$), 6.87 (2H, d, $J$=9.0 Hz, NPh-*H*3,5), 7.04 (2H, m, CH$_2$Ph-*H*2,6), 7.09 (2H, d, $J$=8.7 Hz, NPh-*H*2,6), 7.20 (3H, m, CH$_2$Ph-*H*3,4,5), 8.91 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.84 (2×*C*H$_3$), 42.08 (*C*H$_2$), 55.43 (O*C*H$_3$), 61.69 ($C^{\alpha}$), 114.17 (NPh-*C*3,5), 126.93 (CH$_2$Ph-*C*4), 128.14 (CH$_2$Ph-*C*3,5), 129.03 (CH$_2$Ph-*C*2,6), 131.26 (NPh-*C*2,6), 131.79 (NPh-*C*1), 135.08 (CH$_2$Ph-*C*1), 159.47 (NPh-*C*4), 171.60 (*C*ON), 179.08 (*C*OOH). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.52; H, 6.43; N, 4.35.

**4.1.2.18. *N*-Phenylacetyl-*N*-phenyl-α,α-dimethylglycine (6b).** The reaction was carried out with compound **3b** (0.25 g) in neat TFA at room temperature and the product was purified by column chromatography (dichloromethane/MeOH, 12:1) followed by recrystallisation from ethyl acetate to yield **6b** (72 mg, 77%) as a white solid, mp 154.8–155.7 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.38 (6H, s, 2×C$H_3$), 3.39 (2H, s, C$H_2$), 7.01 (2H, m, CH$_2$Ph-*H*2,6), 7.19–7.22 (5H, m, NPh-*H*2,6+CH$_2$Ph-*H*3,4,5), 7.39 (3H, m, NPh-*H*3,4,5), 9.38 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.86 (2×*C*H$_3$), 42.13 (*C*H$_2$), 61.58 ($C^{\alpha}$), 126.41 (CH$_2$Ph-*C*4), 128.14 (CH$_2$Ph-*C*3,5), 128.70 (NPh-*C*4), 128.99 (CH$_2$Ph-*C*2,6), 129.14 (NPh-*C*3,5), 130.33 (NPh-*C*2,6), 134.94 (CH$_2$Ph-*C*1), 139.08 (NPh-*C*1), 171.16 (*C*ON), 179.08 (*C*OOH). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.63; H, 6.48; N, 4.65.

**4.1.2.19. *N*-Phenylacetyl-*N*-(4-chlorophenyl)-α,α-dimethylglycine (6c).** The reaction was carried out with compound **3c** (0.21 g) in 5% TFA at room temperature and the product was purified by column chromatography (dichloromethane/MeOH, 25:1) followed by recrystallisation from diethyl ether/petroleum ether (40–60 °C) to yield **6c** (109 mg, 66%) as white crystals, mp 170.4–171.5 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.36 (6H, s, 2×C$H_3$), 3.39 (2H, s,

$CH_2$), 7.00 (2H, m, $CH_2$Ph-*H*2,6), 7.11 (2H, d, *J*=8.4 Hz, NPh-*H*2,6), 7.20–7.22 (3H, m, $CH_2$Ph-*H*3,4,5), 7.35 (2H, d, *J*=8.7 Hz, NPh-*H*3,5), 9.35 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.88 (2×$CH_3$), 42.29 ($CH_2$), 61.65 ($C^{\alpha}$), 126.60 ($CH_2$Ph-*C*4), 128.28 ($CH_2$Ph-*C*3,5), 128.88 ($CH_2$Ph-*C*2,6), 129.36 (NPh-*C*3,5), 131.66 (NPh-*C*2,6), 134.58 ($CH_2$Ph-*C*1), 134.74 (NPh-*C*4), 137.59 (NPh-*C*1), 171.05 (*C*ON), 178.94 (*C*OOH). Anal. Calcd for $C_{18}ClH_{18}NO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.10; H, 5.59; N, 4.33.

**4.1.2.20. *N*-Phenylacetyl-*N*-(4-cyanophenyl)-α,α-dimethylglycine (6d).** The reaction was carried out with compound **3d** (0.20 g) in 5% TFA at room temperature and the product was purified by column chromatography (dichloromethane/MeOH, 50:1) followed by recrystallisation from ethyl acetate to yield **6d** (90 mg, 56%) as a white solid, mp 167.6–168.7 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.37 (6H, s, 2×C$H_3$), 3.37 (2H, s, C$H_2$), 6.93 (2H, m, $CH_2$Ph-*H*2,6), 7.19–7.21 (3H, m, $CH_2$Ph-*H*3,4,5), 7.29 (2H, d, *J*=8.1 Hz, NPh-*H*2,6), 7.66 (2H, d, *J*=8.4 Hz, NPh-*H*3,5), 9.56 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.96 (2×$CH_3$), 42.66 ($CH_2$), 61.91 ($C^{\alpha}$), 112.89 (NPh-*C*4), 117.75 (NPh-*C*N), 126.83 ($CH_2$Ph-*C*4), 128.43 ($CH_2$Ph-*C*3,5), 128.69 ($CH_2$Ph-*C*2,6), 131.52 (NPh-*C*2,6), 133.01 (NPh-*C*3,5), 134.12 ($CH_2$Ph-*C*1), 143.20 (NPh-*C*1), 170.50 (*C*ON), 178.85 (*C*OOH). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.50; H, 5.67; N, 8.65.

**4.1.2.21. *N*-Phenylacetyl-*N*-(4-nitrophenyl)-α,α-dimethylglycine (6e).** Compound **3e** (0.25 g) was dissolved in 5 ml of neat TFA and the solution was refluxed for 1 h. The solvent was concentrated under reduced pressure at 30 °C and the pH of the residue was adjusted to 3 by treatment with 2 M aqueous NaOH. The mixture was stirred overnight and the resulting suspension was extracted into chloroform (3×15 ml). The combined organic layers were washed with water (2×20 ml) and dried over anhydrous $MgSO_4$; this was filtered off and the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by column chromatography (dichloromethane/MeOH, 50:1) followed by recrystallisation from ethyl acetate to yield **6e** (100 mg, 48%) as a yellow solid, mp 193.5–194.6 °C. $^1$H NMR (300 MHz, $CDCl_3$): 1.40 (6H, s, 2×C$H_3$), 3.39 (2H, s, C$H_2$), 6.95 (2H, m, $CH_2$Ph-*H*2,6), 7.20–7.23 (3H, m, $CH_2$Ph-*H*3,4,5), 7.35 (2H, d, *J*=9.0 Hz, NPh-*H*2,6), 8.23 (2H, d, *J*=8.7 Hz, NPh-*H*3,5), 9.22 (1H, br s, O*H*); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 24.95 (2×$CH_3$), 42.68 ($CH_2$), 61.89 ($C^{\alpha}$), 124.39 (NPh-*C*3,5), 126.90 ($CH_2$Ph-*C*4), 128.48 ($CH_2$Ph-*C*3,5), 128.70 ($CH_2$Ph-*C*2,6), 131.62 (NPh-*C*2,6), 134.01 ($CH_2$Ph-*C*1), 144.88 (NPh-*C*4), 147.64 (NPh-*C*1), 170.41 (*C*ON), 178.73 (*C*OOH). Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.99; H, 5.36; N, 8.22.

### 4.2. Kinetic measurements

**4.2.1. General method.** To measure reaction rates with compounds **1a**–**1h** and **3a**–**3e**, 0.02 M solutions in acetonitrile containing 2% of TFA were used; 0.007 M solutions were used for compounds **2a**–**2h**. The reaction mixtures were prepared by dissolving the calculated amount of Ugi–Passerini adduct in 4.5 ml of acetonitrile contained in a dilution flask; this was followed by addition of 0.4 ml of 25% TFA in acetonitrile and adjustment of the volume to 5 ml with acetonitrile. The above operations were carried out with the reaction vessel and all reagent solutions were kept in a thermostatic bath at a temperature stabilised within 0.01 °C of the required value, the same was applied throughout the reaction. At regular intervals of time samples were collected for HPLC monitoring and injected as quickly as possible to minimise errors caused due to temperature fluctuations. A mixture of acetonitrile/water 3:1 (v/v) was used as eluent and in most cases the detection was performed at the wavelength of 260 nm.

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# Synthesis of enantiopure 1-substituted, 1,2-disubstituted, and 1,4,5-trisubstituted imidazoles from 1,2-amino alcohols

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**Abstract**—A highly versatile method for the preparation of enantiopure 1-substituted, 1,2-disubstituted, and 1,4,5-trisubstituted imidazoles was developed by using the cyclocondensation reaction of a 1,2-dicarbonyl compound, an aldehyde, a 1,2-amino alcohol, and ammonium acetate.


## 1. Introduction

Imidazole and its derivatives play an important role in the fields of biology and pharmacology as well as chemistry.[1–5] Imidazole ring systems are frequently found in numerous naturally occurring[1] and synthetic molecules such as fungicides, herbicides,[2] and therapeutic agents.[3] Recently, an interest to these heteroaromatic systems has been further expanded as the precursors of imidazolium-based ionic liquids[4] and *N*-heterocyclic carbenes (NHCs).[5] Among them, imidazole derivatives having a *N*-substituent with stereogenic center(s) have attracted special attention, because of their potential utility in a wide range of fields related to chiral recognition and asymmetric catalysis.[6,7]

Synthetic strategies for the preparation of imidazoles with a stereogenic *N*-substituent are classified into two categories; (i) the alkylation of an imidazole nitrogen with enantiopure electrophiles and (ii) the cyclocondensation of ring fragments, typically the combination of glyoxal, ammonia, an aldehyde, and an enantiopure primary amine. The alkylation method is quite straightforward to access target molecules, because imidazole is commercially available and the N-alkylation of imidazole is a well-established reaction with very low possibility of complicated side reactions. In fact, several methods based on the alkylation approach have been recently reported, in which various enantiopure electrophiles were employed.[8] However, the alkylation method still possesses serious limitations: electrophiles usually used for this reaction, such as alkyl halides, alcohols, and epoxides, are not so easy to obtain in an enantiopure form and in a large amount. In addition, this method is obviously disadvantageous for the preparation of *N*-substituted imidazoles with a stereogenic carbon at the α-position of the imidazole N(1), especially when a bulky substituent is placed on the carbon. The efficiency of N-alkylation is significantly influenced by the steric hindrance of the carbon at which a nucleophilic attack occurs. Furthermore, the stereochemistry of the stereogenic carbon in the electrophile is not necessarily preserved during the reaction.

On the other hand, the cyclocondensation of ring fragments established by Gridnev and Mihaltseva[9a] has been applied for the preparation of various *N*-substituted imidazoles.[9,10] By using an enantiopure amine as a primary amine fragment in this method, imidazoles with a stereogenic *N*-substituent can be prepared in one step. Because stereogenic carbon does not directly participate in the cyclocondensation, there is little risk for the racemization/epimerization of the stereogenic carbon. Furthermore, enantiopure amines are easily available in a large scale. Considering the application of *N*-substituted imidazoles as the building blocks of biologically active compounds, asymmetric catalysts, and chiral ionic liquids, the introduction of a functional group as well as a stereogenic center adjacent to the five-membered ring core would be advantageous from the viewpoints of further derivatization and chiral recognition/induction. Therefore, the development of a novel method for the preparation of 1-substituted imidazoles with a functional group and a stereogenic center on the substituent is an important subject.

In the course of our ongoing studies on the design and synthesis of chiral ionic liquids based on imidazoliums,[11] the

*Keywords*: 1,2-Amino alcohol; Chiral pool; Cyclocondensation; Enantiopure; *N*-Substituted imidazole.
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synthesis of 1-substituted and 1,2-disubstituted imidazoles from 1,2-amino alcohols was highly required. Although there have been a large number of reports on the synthesis of imidazoles by the cyclocondensation of four components (glyoxal, ammonia, an aldehyde, and an amine including enantiopure one), little is concerned with the thorough examination of the optimal conditions for the cyclocondensation of glyoxal, ammonia, an aldehyde, and a 1,2-amino alcohol.[9,10] Here we report an efficient and practical method for the preparation of 1-substituted, 1,2-disubstituted, and 1,4,5-trisubstituted imidazoles with a hydroxy group and a stereogenic center on the substituent.

## 2. Results and discussion

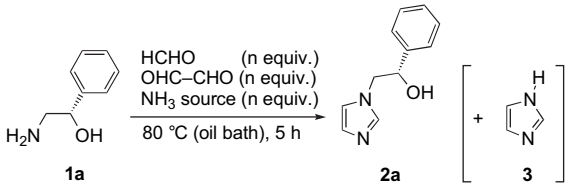
### 2.1. Optimization of the reaction conditions

(*S*)-2-Amino-1-phenylethanol (**1a**) was chosen as an enantiopure primary 1,2-amino alcohol for the study on the reaction conditions, because of its easy availability from (*R*)-mandelic acid and the detectability of the products, developed on a TLC plate, by UV absorption.[12]

For the imidazole formation by cyclocondensation, pH is known to be one of the most crucial factors to determine the yield.[9a,b] Therefore, we at first investigated the effect of an ammonia source on the efficiency of this cyclocondensation; the 1,2-amino alcohol **1a**, glyoxal (40% aqueous solution, 1.0 equiv), formaldehyde (37% aqueous solution, 1.0 equiv) were allowed to react in the presence of ammonia (28% aqueous solution, 1.0 equiv), ammonium chloride, or ammonium acetate in methanol (Table 1, entries 1, 3, and 5). Comparing the yields of the product **2a**, it could be clearly deduced that acidic conditions were favorable for the cyclocondensation. This observation is in good agreement with the result in the report of Gridnev and Mihaltseva.[9a]

Considering the availability of each ring fragment, the first priority should be given to the conversion of the 1,2-amino alcohol unit. Therefore, we then conducted the reactions using excess amounts of the other ring fragments. As shown in Table 1, the amounts of these reagents were another crucial factor to determine the yield of **2a**, especially when ammonium acetate was used as an ammonia source. By increasing the amounts of glyoxal, formaldehyde, and ammonium acetate from 1.0 equiv to 2.0 equiv, the yield of **2a** was significantly improved (entries 5 and 6). However, the yield did not increase any longer by using further excess amounts (4.0 equiv each) of these reagents (entry 7). Contrary to this, when ammonium chloride was employed as an ammonia source, the yield was slightly diminished by using excess amounts of these ring fragments (entry 4). Although the use of the ring fragments in excess resulted in the formation of several undesired by-products, they could be easily removed from the desired product through the work-up process because of their high volatility and/or polarity. Thus, the conditions adopted in entries 3 and 6 (Table 1) seem to be suitable for this cyclocondensation. Worth noting is the fact that the amount of imidazole (**3**) generated through the reaction was surprisingly small, although the ring fragments for the construction of **3** adequately existed under the conditions of entries 2, 4, 6, and 7; when the reactions were conducted under the conditions of these entries, only less than 5% of **3** was generated with respect to **2a**. It means that the 1-substituted imidazole formation is much faster than the imidazole formation.

**Table 1**. Synthesis of 1-substituted imidazole **2a** from (*S*)-2-amino-1-phenylethanol (**1a**)



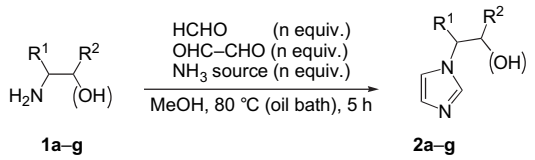

| Entry | $NH_3$ source | *n*/eq. | Solvent | Isolated yield |
|---|---|---|---|---|
| 1 | 28% $NH_3$ aq | 1 | Methanol | 20 |
| 2 | 28% $NH_3$ aq | 2 | Methanol | 44 |
| 3 | $NH_4Cl$ | 1 | Methanol | 69 |
| 4 | $NH_4Cl$ | 2 | Methanol | 63 |
| 5 | $NH_4OAc$ | 1 | Methanol | 53 |
| 6 | $NH_4OAc$ | 2 | Methanol | 71 |
| 7 | $NH_4OAc$ | 4 | Methanol | 72 |
| 8 | $NH_4OAc$ | 2 | Water | 45 |
| 9 | $NH_4OAc$ | 2 | Ethanol | 51 |
| 10 | $NH_4OAc$ | 2 | 2-Propanol | 44 |

In the next stage, we examined the solvent effect for the reaction using ammonium acetate as an ammonia source. The use of water in the place of methanol caused a considerable diminish in the yield of **2a**; a notable amount of precipitates was generated just after the reaction was started, which might arise from hydrophobicity of an intermediate derived from **1a** and glyoxal (Table 1, entry 8). Contrary to this, ethanol and 2-propanol dissolved all of the four components and maintained the homogeneity of the system throughout the reaction, as did methanol. However, the yields observed by using ethanol and 2-propanol were lower than that achieved by using methanol (entries 9 and 10). These observations indicate that the dielectric constant of the reaction medium is also an important factor for the present cyclocondensation; polar solvents are fundamentally favorable as far as the substrate and intermediate are adequately soluble in the reaction media.

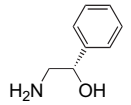
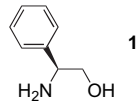
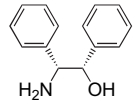
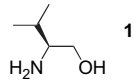
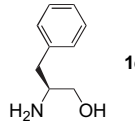
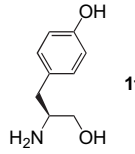
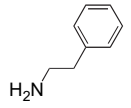
### 2.2. Synthesis of various 1-substituted imidazoles

We then carried out the reactions of various enantiopure 1,2-amino alcohols (Table 2). Under the conditions of entry 4 in Table 1 (method A), the enantiopure 1,2-amino alcohols **1a–f** could be successfully converted to the corresponding *N*-substituted imidazoles without the loss of enantiopurity (entries 1, 3, 5, 7, 9, and 10). The fact that the yield of **2a** (entry 1) was comparable to that of the reaction of 2-phenylethylamine (**1g**) under the same conditions (entry 10) strongly indicates that the hydroxy group in the 1,2-amino alcohols was likely to bring little influence on this reaction. Furthermore, the reaction of (*S*)-tyrosinol (**1f**) afforded the corresponding 1-substituted imidazole **2f** in the yield comparable to those of the other reactions, which clearly shows that this cyclocondensation is tolerant to a phenol moiety (entry 9). Worth noting is the fact that the reaction proceeded efficiently even when a bulky substituent was introduced at the α-position of the amino group (entries 3, 5, and 7). Thus,

**Table 2**. Synthesis of 1-substituted imidazoles **2a–g** from various 1,2-amino alcohols **1a–g**




**1a–g** **2a–g**

| Entry | Primary amine **1** | Method[a] | Isolated yield (%) | ee (%)[b] |
|---|---|---|---|---|
| 1 |  **1a** | A | 71 | >99 |
| 2 | | B | 69 | >99 |
| 3 |  **1b** | A | 65 | >99 |
| 4 | | B | 61 | >99 |
| 5 |  **1c** | A | 65 | >99[c] |
| 6 | | B | 61[d] | >99[c] |
| 7 |  **1d** | A | 69 | >99 |
| 8 | | B | 54[e] | >99 |
| 9 |  **1e** | A | 55 | >99 |
| 10 |  **1f** | A | 63 | n.d. |
| 11 |  **1g** | A | 63 | |

[a] Method A: $n$=2; $NH_3$ source, $NH_4OAc$. Method B: $n$=1; $NH_3$ source, $NH_4Cl$.
[b] Estimated by a chiral HPLC analysis.
[c] Estimated by $^1H$ NMR.
[d] As a mixture with the 1,2-amino alcohol **1c** (**2c**:**1c**=61:19).
[e] As a mixture with imidazole (**3**) (**2d**:**3**=54:5).

a highly convenient and efficient method for the synthesis of imidazoles possessing a stereogenically pure OH-pendant *N*-substituent was established.

The reaction conditions of entry 3 in Table 1 (method B) were also applied to the cyclocondensation of several amino alcohols (**1a–d**: Table 2, entries 2, 4, 6, and 8). The method B realized yields comparable to or slightly lower than those by the method A for the reactions of **1a–c**. However, for the reaction of **1d**, the yield achieved by the method B was obviously lower than that accomplished by the method A. This means that the method A is suitable for the reaction of sterically hindered amino alcohols such as **1d**; ammonium acetate is better than ammonium chloride as the ammonium source. Furthermore, by using ammonium acetate, the reaction can be conducted under almost neutral conditions, which might be advantageous for the reaction of amines bearing a functional group unstable under acidic conditions. Thus, the method A is concluded to be the most favorable for the cyclocondensation.

In order to demonstrate the applicability of this procedure in a large scale, we then conducted the reaction in a multi-gram scale under the same conditions and attempted to isolate the target *N*-substituted imidazoles by a method other than column chromatography. For example, when the reaction of 3.00 g of **1d** (29 mmol) was carried out under the same conditions of the method A, 3.69 g of the corresponding 1-substituted imidazole **2d** (24 mmol, 82% yield) was isolated with satisfactory purity by Kugelrohr distillation (3 mmHg, 170 °C). This preparative method is undoubtedly more efficient, compared with the conventional method reported by Bao et al.;[10b] **2d** was prepared in three reaction steps, all of which required chromatographic purification. On the other hand, for the isolation of less volatile 1-substituted imidazoles such as **2e**, crystallization was found to be effective; when 4.54 g of **1e** (30 mmol) was treated under the same conditions, 2.97 g of **2e** (15 mmol, 50% yield) was isolated by simple crystallization from ethyl acetate/hexane.

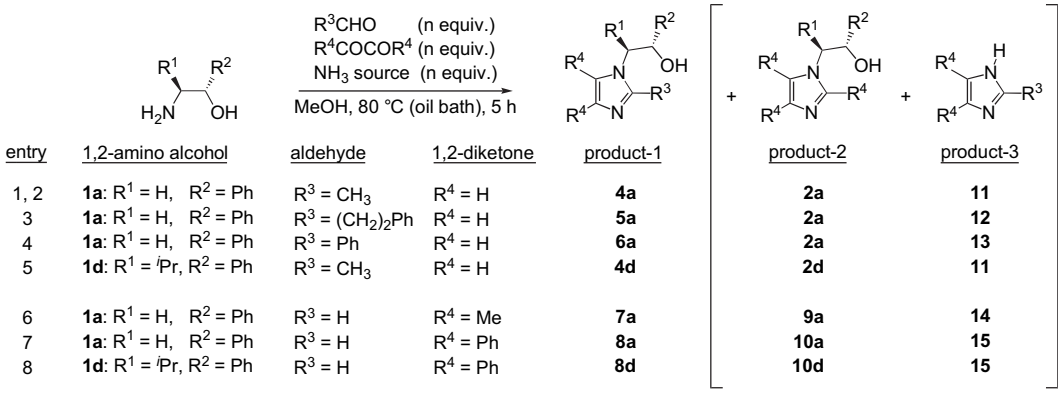
### 2.3. Synthesis of 1,2-disubstituted and 1,4,5-trisubstituted imidazoles

In general, the introduction of a substituent at the C(2) position of 1-substituted imidazoles and 1,3-disubstituted imidazolium salts brings a considerable effect on the properties of the resultant imidazoles/imidazolium salts. Especially in the cases of ionic liquids consisting of 1,3-dialkylimidazolium salts, the alkylation at the C(2) position makes these ionic liquids applicable under basic conditions, because the easy formation of undesired carbene species from 1,3-disubstituted imidazoliums by the action of a base can be prevented.[13] Usually, such a substituent at the C(2) position as well as at the C(4) and/or C(5) positions is introduced by the lithiation of a 1-substituted imidazole, followed by treatment with an electrophile.[14] On the other hand, there has been only a few reports on the preparation of 1,2-disubstituted and 1,4,5-trisubstituted imidazoles by the cyclocondensation, although this route seems to be more convenient compared with conventional methods.[9b,9e–g,15]

With the optimized conditions for the cyclocondensation of a 1,2-amino alcohol, formaldehyde, glyoxal, and an ammonia source in hand, we then attempted to apply the cyclocondensation reaction to the formation of highly substituted imidazoles by replacing formaldehyde and glyoxal with other aldehydes and 1,2-diketones, respectively. At first, we attempted to synthesize 1,2-disubstituted imidazoles by using various aldehydes in the place of formaldehyde (Table 3, entries 1–6).

When **1a**, glyoxal (2.0 equiv), acetaldehyde (2.0 equiv), and ammonium acetate (2.0 equiv) were allowed to react with each other in methanol (method A), the target imidazole **4a** was obtained, as was expected, accompanying the formation of two kinds of by-products, **2a** and **11**, having no substituent at the C(2) and N(1) positions, respectively (Table 3, entry 1). Although such by-products **2a** and **11** were formed,

**Table 3**. Synthesis of 1,2-disubstituted and 1,4,5-trisubstituted imidazoles from (*S*)-2-amino-1-phenylethanol (**1a**) and (*S*)-valinol (**1d**)




| entry | 1,2-amino alcohol | aldehyde | 1,2-diketone | product-1 | product-2 | product-3 |
|---|---|---|---|---|---|---|
| 1, 2 | **1a**: $R^1$ = H, $R^2$ = Ph | $R^3$ = $CH_3$ | $R^4$ = H | **4a** | **2a** | **11** |
| 3 | **1a**: $R^1$ = H, $R^2$ = Ph | $R^3$ = $(CH_2)_2Ph$ | $R^4$ = H | **5a** | **2a** | **12** |
| 4 | **1a**: $R^1$ = H, $R^2$ = Ph | $R^3$ = Ph | $R^4$ = H | **6a** | **2a** | **13** |
| 5 | **1d**: $R^1$ = $^i$Pr, $R^2$ = Ph | $R^3$ = $CH_3$ | $R^4$ = H | **4d** | **2d** | **11** |
| 6 | **1a**: $R^1$ = H, $R^2$ = Ph | $R^3$ = H | $R^4$ = Me | **7a** | **9a** | **14** |
| 7 | **1a**: $R^1$ = H, $R^2$ = Ph | $R^3$ = H | $R^4$ = Ph | **8a** | **10a** | **15** |
| 8 | **1d**: $R^1$ = $^i$Pr, $R^2$ = Ph | $R^3$ = H | $R^4$ = Ph | **8d** | **10d** | **15** |

| Entry | | Method[a] | Ratio of the products[b] (prdct-1:prdct-2:prdct-3) | Yield[c] |
|---|---|---|---|---|
| 1 | **4a** | A | 1.00:0.31:0.17 | 50 (41) |
| 2 | | B | 1.00:0.77:0.18 | 29 (22) |
| 3 | **5a** | A | 1.00:0.58:0.65 | 51 (43) |
| 4 | **6a** | A | 1.00:0.50:0.58 | 48 (40) |
| 5 | **4d** | A | 1.00:1.10:0.69<br>1.00:0.16:0.60[d] | 27 (26)<br>34 (34)[d] |
| 6 | **7a** | A | 1.00:<0.01:<0.01 | 30 (30) |
| 7[e] | **8a** | A | 1.00:<0.01:<0.01 | 83 (83) |
| 8[e] | **8d** | A | 1.00:<0.01:0.07 | 85 (52) |

[a] Method A: $n$=2; $NH_3$ source, $NH_4OAc$. Method B: $n$=1; $NH_3$ source, $NH_4Cl$.
[b] Estimated by $^1$H NMR.
[c] Yield based on $^1$H NMR (in a parenthesis, isolated yield).
[d] Glyoxal (1.0 equiv) was used.
[e] Reaction time, 9 h.

the target 1,2-disubstituted imidazole **4a** was isolated by alumina column chromatography in moderate yield (50% yield by a $^1$H NMR analysis, 41% isolated yield). The cyclocondensation was found to be tolerant to other aldehyde components; the reaction conditions optimized for the formation of **4a** were successfully applied to the reactions involving an aliphatic or aromatic aldehyde, such as 3-phenylpropanal or benzaldehyde, as the C(2) provider, and the corresponding 1,2-disubstituted imidazoles **5a** and **6a** were obtained in yields comparable to that of **4a** (entries 3 and 4).

The formation of **11**–**13** is reasonable, because all of the ring fragments for the formation of **11**–**13** (glyoxal, acetaldehyde, and ammonium acetate) were excessively used. On the other hand, the C(2) of **2a** was most likely provided by formaldehyde or its equivalent, which would be generated in situ from glyoxal under the reaction conditions; the primary amine **1a** should be consumed for the formation of **2a** to diminish the yield of **4a**–**6a**.[16] The same side reaction could be considered to occur during the 1-substituted imidazole formation using formaldehyde (Tables 1 and 2) but might bring little effect on the yield of the target imidazole, because the side reaction afforded the same product. Noteworthy, the pH of the reaction mixture was again found to be an important factor to determine the yield and selectivity of the reaction; when ammonium chloride was used in the place of ammonium acetate, the ratio of the undesired **2a** considerably increased to lower the yield of **4a** (method B, entry 2).

The successful results described above prompted us to apply the cyclocondensation to the formation of 1,4,5-trisubstituted imidazoles, because several 4,5-diaryl-substituted imidazoles have been attracted recent attention as potent inhibitors of p38 MAP kinase.[17] We therefore conducted the cyclocondensation reaction of a 1,2-diketone, ammonium acetate, formaldehyde, and **1a** under the conditions of the method A. To our delight, the reaction proceeded smoothly to afford the target 1,4,5-trisubstituted imidazoles **7a** and **8a** in moderate to good yields (Table 3, entries 6 and 7). Contrary to the case of the reactions using glyoxal, these 1,2-diketones did not act as imidazole C(2) providers; the formation of 1,2,4,5-tetrasubstituted imidazoles **9a** and **10a** was not observed. Furthermore, another kind of possible by-products, 4,5-disubstituted imidazoles (**14** and **15**) were not detected in both of the reactions of the 1,2-diketones.

For the synthetic method to prepare 1,2-disubstituted and 1,4,5-trisubstituted imidazoles thus established, the scope of the primary amine component was investigated. As a primary amine unit, (*S*)-valinol (**1d**) was used in the place of (*S*)-2-amino-1-phenylethanol (**1a**), because **1d** with a sterically congested amino group seemed to be suitable to evaluate the effect of the substituent neighboring an amino group on the efficiency of the reaction. In the cyclocondensation of **1d**, glyoxal (2.0 equiv), acetaldehyde (2.0 equiv), and ammonium acetate (2.0 equiv), the target 1,2-disubstituted imidazole **4d** was obtained, but considerable amounts of the by-products **2d** and **11** were generated to diminish the yield of **4d** (entry 5). The ratio of the by-product lacking a C(2) substituent significantly increased compared with the case of **1d** (entry 1 vs entry 5), most likely because the isopropyl group on **1d** brought an unfavorable effect on the formation of the sterically crowded product possessing a C(2) substituent. However, by reducing the amount of glyoxal from 2.0 equiv to 1.0 equiv, the formation of the undesired by-product **2d** could be efficiently suppressed to improve the yield of **4d**. Contrary to the case of the synthesis of **4d**, the formation of a 1,4,5-trisubstituted imidazole was hardly influenced by a substituent on a primary amine unit; the cyclocondensation of **1d**, benzyl (2.0 equiv), formaldehyde (2.0 equiv), and ammonium acetate (2.0 equiv) proceeded smoothly, and only a small amount of **15** was afforded as a by-product. As a result, the yield of the target 1,4,5-trisubstituted imidazole **8d** was comparable to that of **8a** from **1a** (entry 8).

## 3. Conclusion

We developed a highly versatile method for the preparation of 1-substituted imidazoles by the cyclocondensation of glyoxal, ammonium acetate, formaldehyde, and a 1,2-amino alcohol. The choice of an ammonium source, which gives significant influence on the pH of the reaction mixture, was found to be an important factor to determine the efficiency and selectivity of the reaction. The protocol optimized here was applicable to the transformation of various enantiopure 1,2-amino alcohols, including sterically hindered 1,2-amino alcohols, to the corresponding enantiopure 1-substituted imidazoles with maintaining the enantiopurity. By this method, target imidazoles could be prepared in multi-gram scales and easily isolated in satisfactorily pure forms without resorting column chromatography. Furthermore, the procedure was successfully applied to the synthesis of 1,2-disubstituted and 1,4,5-trisubstituted imidazoles by the proper choice of an aldehyde and a 1,2-dicarbonyl compound. The synthetic procedure established here is expected to contribute to the development of enantiopure imidazole/imidazolium-based molecules, such as bioactive reagents, ionic liquids, NHC ligands, and NHC catalysts.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 operating at 300 and 75 MHz, respectively. IR spectra were recorded on a JASCO model FT/IR-480plus. High-resolution FABMS spectra were recorded on a JEOL JMS-HX110 spectrometer using 3-nitrobenzyl alcohol matrix. Melting points were determined on a Yamato MP-21.

### 4.2. Synthesis and characterization of imidazoles. General procedure

A methanol solution (6 mL) of aqueous glyoxal (40% w/v, 0.87 g, 6.0 mmol) or a 1,2-dicarbonyl compound (6.0 mmol), ammonium acetate (0.46 g, 6.0 mmol), aqueous formaldehyde (36% w/v, 0.50 g, 6.0 mmol) or an aldehyde (6.0 mmol), and a 1,2-amino alcohol (3.0 mmol) was refluxed for 5 h. Unless otherwise noted, the reaction mixture was treated as follows: The reaction mixture was concentrated under reduced pressure. The resultant residue was treated with 2 M aqueous KOH solution (100 mL) and extracted with $CH_2Cl_2$ (4×100 mL). The combined organic

layers were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure.

**4.2.1. Imidazole 2a.** Purified by silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (100:0–95:5, v/v). Mp 147.5–150.5 °C. $[\alpha]_D^{25}$ +45.3 (*c* 1.2, MeOH). IR (KBr): 3120, 2891, 2850, 2788, 1636, 1601, 1513, 1449 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 4.04–4.17 (m, 2H), 4.93 (dd, $J_1$=7.2 Hz, $J_2$=4.5 Hz, 1H), 6.89 (s, 1H), 6.94 (s, 1H), 7.26–7.41 (m, 6H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 54.27, 72.62, 119.60, 125.64, 127.51, 128.05, 128.11, 137.38, 141.55. HRMASS calcd for $[M+H]^+$ $C_{11}H_{13}N_2O$: 189.1028, found: 189.1021. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.24; H, 6.60; N, 14.88.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46×25 cm); eluent, hexane/2-propanol = 85:15, v/v; flow, 1.0 mL/min; (*R*) 21.1 min, (*S*) 23.7 min.

**4.2.2. Imidazole 2b.** Purified by silica gel column chromatography eluted with $CH_2Cl_2$/MeOH (99:1–95:5, v/v). Mp 117.5–120.0 °C. $[\alpha]_D^{25}$ +25.9 (*c* 1.3, MeOH). IR (KBr): 3148, 3108, 3033, 2958, 2925, 2859, 2652, 1984, 1961, 1882, 1812, 1685, 1601, 1583, 1495, 1460, 1451, 1410, 1371 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 4.13–4.25 (m, 2H), 5.27 (dd, $J_1$=7.8 Hz, $J_2$=4.8 Hz, 1H), 6.94–6.96 (m, 2H), 7.15–7.18 (m, 2H), 7.31–7.35 (m, 3H), 7.51 (s, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 63.81, 64.42, 118.77, 127.04, 128.48, 128.53, 129.04, 136.84, 137.53. HRMASS calcd for $[M+H]^+$ $C_{11}H_{13}N_2O$: 189.1028, found: 189.1024. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.00; H, 6.58; N, 14.73.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46×25 cm); eluent, hexane/2-propanol = 80:20, v/v; flow, 1.0 mL/min; (*R*) 9.5 min, (*S*) 12.7 min.

**4.2.3. Imidazole 2c.** Purified by silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (100:0–95:5, v/v) followed by crystallization from EtOAc. Mp 161.5–163.0 °C. $[\alpha]_D^{25}$ −37.6 (*c* 2.1, MeOH). IR (KBr): 3098, 2933, 2841, 1971, 1904, 1832, 1709, 1685, 1636, 1602, 1586, 1508, 1493, 1451, 1397 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 5.23 (d, *J*=6.9 Hz, 1H), 5.41 (d, *J*=6.9 Hz, 1H), 6.89–6.90 (m, 2H), 7.14–7.18 (m, 2H), 7.26–7.31 (m, 5H), 7.34–7.38 (m, 4H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 67.81, 75.14, 118.67, 126.50, 128.28, 128.49, 128.53, 128.62, 128.71, 136.15, 136.75, 141.10. HRMASS calcd for $[M+H]^+$ $C_{17}H_{17}N_2O$: 265.1341, found: 265.1359. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.12; H, 6.12; N, 10.45.

**4.2.4. Imidazole 2d.** Purified by silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (99:1–97:3, v/v). Mp 106.5–111.5 °C. $[\alpha]_D^{25}$ −27.1 (*c* 1.6, MeOH). IR (KBr): 3112, 3090, 2957, 2926, 2856, 2726, 1691, 1599, 1504, 1494 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 0.74 (d, *J*=6.6 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 3H), 2.07–2.14 (m, 1H), 3.64–3.71 (m, 1H), 3.85–3.91 (m, 2H), 6.92 (m, 2H), 7.32 (s, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 19.31, 20.01, 30.01, 62.69, 67.09, 118.15, 128.26, 136.81. HRMASS calcd for $[M+H]^+$ $C_8H_{15}N_2O$: 154.1184, found: 155.1186. Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.19; H, 9.32; N, 18.14.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46×25 cm); eluent, hexane/2-propanol=90:10, v/v; flow, 1.0 mL/min; (*R*) 18.0 min, (*S*) 32.4 min.

**4.2.5. Imidazole 2e.** Purified by silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (99:1–95:5, v/v). Mp 86.0–87.5 °C. $[\alpha]_D^{25}$ −114.7 (*c* 1.1, MeOH). IR (KBr): 3157, 3113, 2962, 2933, 2833, 1963, 1886, 1653, 1604, 1590, 1505 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.99 (dd, $J_1$=13.8 Hz, $J_2$=8.4 Hz, 1H), 3.15 (dd, $J_1$=13.8 Hz, $J_2$=6.5 Hz, 1H), 3.83–3.85 (m, 2H), 4.21–4.26 (m, 1H), 6.89–6.91 (m, 2H), 7.00–7.03 (m 2H), 7.19–7.27 (m, 4H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 38.41, 62.26, 64.21, 117.61, 126.99, 128.59, 128.76, 128.90, 136.47, 137.10. HRMASS calcd for $[M+H]^+$ $C_{12}H_{15}N_2O$: 203.1184, found: 203.1182. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.27; H, 7.20; N, 13.81.

Analytical chiral HPLC: column, CHIRALCEL OD-H (0.46×25 cm); eluent, hexane/2-propanol = 90:10, v/v; flow, 1.0 mL/min; (*R*) 24.5 min, (*S*) 37.2 min.

**4.2.6. Imidazole 2f.** The reaction mixture was concentrated under reduced pressure. The resultant residue was dissolved in water (6 mL), and the aqueous solution was neutralized by the addition of solid $NaHCO_3$ until the pH reached at 7.0–8.0. The resultant mixture was extracted with 1-butanol (6×2 mL), and the organic layers combined were washed with brine (6 mL). The organic solution was concentrated under reduced pressure, and the resultant residue was subjected to silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (90:10, v/v). The separated product was crystallized from $CHCl_3$/MeOH to give **2f**. Mp 175.5–180.5 °C. $[\alpha]_D^{25}$ −133.2 (*c* 1.1, MeOH). IR (KBr): 3142, 3124, 3023, 2931, 2806, 2677, 1614, 1593, 1515, 1504, 1454, 1386, 1373, 1234 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): $\delta$ 2.89 (dd, $J_1$=14.2 Hz, $J_2$=9.3 Hz, 1H), 3.06 (dd, $J_1$=14.2 Hz, $J_2$=5.7 Hz, 1H), 3.77–3.85 (m, 2H), 4.25–4.34 (m, 1H), 6.59–6.64 (m, 2H), 6.82–6.87 (m, 2H), 6.92 (m, 1H), 7.16 (m, 1H), 7.47 (s, 1H). $^{13}C$ NMR ($CD_3OD$): $\delta$ 39.27, 64.36, 65.79, 117.08, 119.85, 129.57, 130.27, 131.76, 139.00, 158.09. HRMASS calcd for $[M+H]^+$ $C_{12}H_{15}N_2O_2$: 219.1134, found: 219.1139. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.87; H, 6.45; N, 12.58.

**4.2.7. Imidazole 2g.** Purified by silica gel (deactivated with 10 wt% water) column chromatography eluted with $CH_2Cl_2$/MeOH (99:1–95:5, v/v) followed by Kugelrohr distillation (3 mmHg, 160 °C). Colorless oil. IR (NaCl): 3111, 3028, 2928, 1672, 1604, 1508, 1455 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): $\delta$ 3.04 (t, *J*=7.2 Hz, 2H), 4.16 (t, *J*=7.2 Hz, 2H), 6.83 (m, 1H), 7.02–7.07 (m, 3H), 7.24–7.32 (m, 4H). $^{13}C$ NMR ($CD_3OD$): $\delta$ 38.14, 48.80, 119.06, 127.28, 128.89, 129.06, 129.69, 137.38, 137.74. HRMASS calcd for $[M+H]^+$ $C_{11}H_{13}N_2$: 173.1078, found: 173.1072.

**4.2.8. Imidazole 4a.** Purified by alumina column chromatography eluted with hexane/$CH_2Cl_2$ (33:67–0:100, v/v). Mp 145.5–150.0 °C. $[\alpha]_D^{25}$ +23.6 (*c* 1.2, MeOH). IR (KBr):

3111, 2846, 1654, 1532, 1505, 1436 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.12 (s, 3H), 3.98–4.01 (m, 2H), 4.90 (t, $J$=5.9 Hz, 1H), 6.72 (d, $J$=1.4 Hz, 1H), 6.81 (d, $J$=1.4 Hz, 1H), 7.26–7.37 (m, 5H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 12.79, 53.80, 73.33, 120.00, 125.99, 126.49, 128.21, 128.72, 141.59, 145.20. HRMASS calcd for $[M+H]^+$ $C_{12}H_{15}N_2O$: 203.1184, found: 203.1180. Anal. Calcd for $C_{12}H_{14}N_2O\cdot 1/6H_2O$: C, 70.21; H, 6.99; N, 13.65. Found: C, 70.08; H, 6.97; N, 13.15.

**4.2.9. Imidazole 4d.** Purified by alumina column chromatography eluted with hexane/$CH_2Cl_2$/MeOH (25:75:0–0:99:1, v/v/v). Viscous oil. $[\alpha]_D^{25}$ −20.4 ($c$ 3.3, MeOH). IR (NaCl): 3156, 2963, 1529, 1498, 1421, 1278, 1147, 1083, 1028, 990, 747, 680 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 0.73 (d, $J$=6.6 Hz, 3H), 1.06 (d, $J$=6.6 Hz, 3H), 1.96–2.08 (m, 1H), 2.35 (s, 3H), 3.68–3.75 (m, 1H), 3.79–3.85 (m, 1H), 3.93–3.97 (m, 1H), 6.83 (d, $J$=1.5 Hz, 1H), 6.85 (d, $J$=1.5 Hz, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.7, 19.9, 20.3, 30.7, 63.4, 65.2, 116.0, 127.3, 145.7. HRMASS calcd for $[M+H]^+$ $C_9H_{17}N_2O$: 169.1341, found: 169.1341.

**4.2.10. Imidazole 5a.** Purified by alumina column chromatography eluted with hexane/$CH_2Cl_2$/MeOH (33:67:0–0:98:2, v/v/v). Viscous oil. $[\alpha]_D^{25}$ +11.7 ($c$ 1.0, MeOH). IR (KBr): 3061, 3027, 2931, 1952, 1881, 1811, 1671, 1603, 1528, 1493, 1453 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.71–2.77 (m, 2H), 2.98 (t, $J$=7.8 Hz, 2H), 3.87–3.90 (m, 2H), 4.76 (t, $J$=5.9 Hz, 2H), 6.84 (d, $J$=1.4 Hz, 1H), 6.91 (d, $J$=1.4 Hz, 1H), 7.09–7.12 (m, 2H), 7.16–7.37 (m, 9H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 28.38, 34.18, 53.14, 72.91, 119.97, 125.90, 126.12, 126.27, 127.95, 128.36, 128.39, 128.51, 141.15, 141.87, 147.75. HRMASS calcd for $[M+H]^+$ $C_{19}H_{21}N_2O$: 293.1654, found: 293.1659.

**4.2.11. Imidazole 6a.** Purified by alumina column chromatography eluted with hexane/$CH_2Cl_2$/MeOH (33:67:0–0:99:1, v/v/v). Mp 152.5–153.5 °C. $[\alpha]_D^{25}$ −3.6 ($c$ 1.0, MeOH). IR (KBr): 3121, 3061, 3031, 2933, 2885, 2835, 2760, 1957, 1896, 1820, 1604, 1577, 1537, 1508, 1492, 1474, 1447, 1425 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 4.15 (d, $J$=6.0 Hz, 2H), 4.86 (t, $J$=6.0 Hz, 1H), 7.01 (d, $J$=1.4 Hz, 1H), 7.08 (d, $J$=1.4 Hz, 1H), 7.14–7.17 (m, 2H), 7.26–7.29 (m, 3H), 7.35–7.43 (m, 5H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 53.89, 73.33, 121.55, 125.88, 127.87, 128.13, 128.48, 128.64, 128.80, 129.28, 130.46, 144.40, 148.04. HRMASS calcd for $[M+H]^+$ $C_{17}H_{17}N_2O$: 265.1341, found: 265.1341. Anal. Calcd for $C_{17}H_{16}N_2O\cdot H_2O$: C, 72.26; H, 6.38; N, 9.92. Found: C, 72.91; H, 5.95; N, 9.91.

**4.2.12. Imidazole 7a.** Purified by silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (100:0–90:10, v/v) followed by aluminum column chromatography eluted with hexane/$CH_2Cl_2$/MeOH (33:67:0–0:98:2, v/v/v). Mp 152.0–156.5 °C. $[\alpha]_D^{25}$ +22.9 ($c$ 1.1, MeOH). IR (KBr): 3119, 3084, 3061, 2977, 2920, 2863, 2789, 2710, 1948, 1877, 1800, 1699, 1653, 1598, 1558, 1541, 1506, 1496, 1451, 1386, 1344 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 2.00 (s, 3H), 2.09 (s, 3H), 3.83–3.99 (m, 2H), 4.87 (dd, $J_1$=8.4 Hz, $J_2$=3.5 Hz, 1H), 7.28–7.42 (m, 5H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 8.82, 12.82, 53.67, 72.78, 121.89, 126.19, 128.25, 128.93, 133.14, 136.13, 141.75. HRMASS calcd for $[M+H]^+$ $C_{13}H_{17}N_2O$: 217.1341, found: 217.1364. Anal. Calcd for $C_{13}H_{16}N_2O\cdot 1/4H_2O$: C, 70.66; H, 7.47; N, 12.68. Found: C, 70.84; H, 7.48; N, 12.54.

**4.2.13. Imidazole 8a.** Purified by silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (100:0–95:5, v/v). Mp 223.0–223.5 °C. $[\alpha]_D^{25}$ +63.2 ($c$ 1.2, $CHCl_3$). IR (KBr): 3117, 3060, 2892, 2847, 2722, 1952, 1896, 1643, 1603, 1508, 1496, 1480, 1444 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ 3.58 (dd, $J_1$=14.1 Hz, $J_2$=2.2 Hz, 1H), 3.74 (dd, $J_1$=14.1 Hz, $J_2$=9.6 Hz, 1H), 4.63 (dd, $J_1$=9.6 Hz, $J_2$=2.2 Hz, 1H), 6.67 (d, $J$=6.9 Hz, 2H), 7.10–7.14 (m, 2H), 7.18–7.42 (m, 11H), 7.81 (s, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 54.04, 72.48, 125.99, 126.76, 127.01, 128.02, 128.27, 128.77, 128.86, 129.08, 130.48, 131.70, 134.87, 137.35, 138.32, 141.63, 144.75. HRMASS calcd for $[M+H]^+$ $C_{23}H_{31}N_2O$: 341.1654, found: 341.1658. Anal. Calcd for $C_{23}H_{30}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.00; H, 6.06; N, 8.08.

**4.2.14. Imidazole 8d.** Purified by silica gel (deactivated with 10 wt % water) column chromatography eluted with $CH_2Cl_2$/MeOH (100:0–99:1, v/v). Mp 161.0–163.0 °C. $[\alpha]_D^{25}$ −55.9 ($c$ 1.8, MeOH). IR (KBr): 3127, 2964, 1894, 1820, 1773, 1602, 1506 $cm^{-1}$. $^1H$ NMR ($CD_3OD$): $\delta$ 0.75 (d, $J$=6.6 Hz, 3H), 0.95 (d, $J$=6.6 Hz, 3H), 2.17–2.29 (m, 1H), 3.56–3.63 (m, 1H), 3.85 (dd, $J_1$=11.7 Hz, $J_2$=3.3 Hz, 1H), 3.97 (dd, $J_1$=11.7 Hz, $J_2$=6.6 Hz, 1H), 7.12–7.22 (m, 3H), 7.30–7.39 (m, 4H), 7.45–7.54 (m, 3H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.95, 32.56, 64.22, 65.76, 128.34, 128.89, 129.93, 130.84, 130.95, 132.23, 132.83, 133.77, 136.49, 137.64, 138.88. HRMASS calcd for $[M+H]^+$ $C_{20}H_{23}N_2O$: 307.1810, found: 307.1806. Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.27; H, 7.34; N, 8.97.

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# Efficient synthesis of carbopeptoid oligomers: insight into mimicry of β-peptide

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**Abstract**—The ready access to a new class of carbohydrate mimetics was demonstrated by the synthesis of tetrameric carbopeptoids, in which glycosidic bonds were replaced with amide linkages. We herein describe the detailed synthetis method of β(1→2)- and β(1→6)-linked carbopeptoids starting from each D-glucosamine and D-glucose derivative. The building blocks were polymerized using BOP reagent and DIEA to form a homooligomer. These produced carbopeptoids are resistant to glycosidases and have interesting biological activity. With conformational analysis by molecular modeling calculation, β(1→2)-linked decamer showed a typical 16-helix form as a mimic of β-peptide. Therefore, our polysaccharide analogues have potential as peptide foldamers.


## 1. Introduction

It has been revealed that carbohydrates are responsible for a variety of diseases and intercellular recognitions, including cell adhesion, viral infection, and cancer metastasis.[1] Due to the rapidly growing importance of carbohydrates in biology, several carbohydrate analogues, including pseudosugars[2] (a cycloalkane instead of sugar ring), C-[3] and S-glycosides,[4] and other mimetics[5–8] have been prepared and their stability against glycosidases has been assessed; however, those analogues have many problems such as synthesis of the unit, deprotection of protective groups, purification and so on. Therefore, new carbohydrate mimetics are still under consideration. We anticipate that if monosaccharides are linked via amide bonds instead of glycosidic bonds, the resulting oligosaccharide analogues may have the same biological activity as the original oligosaccharide because of their similar structure to the oligosaccharide.

Until recently, various amide-linked carbohydrates have been synthesized. One was first demonstrated by Yoshimura et al.[9] in the synthesis of (2→6)-amide-linked disaccharide derivatives: coupling of D-glucosamine and D-mannosamine to 2-amino-2-deoxy-D-mannuronic and D-glucuronic acids such as (i) in Figure 1. Meanwhile, Lehmann et al.[10] also reported a polysaccharide analogue in 1975 in which glycosidic bonds were replaced with amide linkage. This analogue

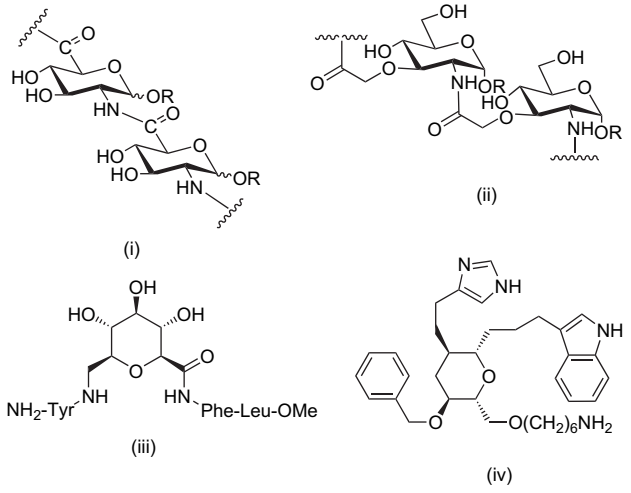


**Figure 1**. Amido-linked carbohydrates.

was later reported and named 'carbopeptoid' by the Nicolaou group[11] in 1995; however, no experiment was reported. Furthermore, the Hoffman-La Roche group reported the synthesis of a tetramer of (i) by a solid-phase-type elongation reaction[12] and of another amide-linked oligosaccharide composed of nor-muramic acid (ii).[13] The application of carbohydrates as amino acid analogues has also recently been reported: von Roedern and Kessler[14] prepared a glucose homologue with both amino and carboxyl groups and incorporated it into a peptide to mimic a proline β-turn residue, as shown in (iii). In a related work, D-glucose has already been used as a scaffold molecule to mimic a cyclic peptide

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such as (iv) by Smith and Nicolaou et al.,[15] while the molecule was not incorporated into the peptide backbone. Furthermore, other sugar-containing amino acids, prepared with both furanose and pyranose residues, were reported.[16–19] Although those compounds have interesting structures, no suggestions of biological activity were shown in the papers.

In work directed toward designing new carbohydrate mimetics, we demonstrated a new kind of carbohydrate analogue, which has the possibility for developing solid-phase synthesis, and also for studying different kinds of new drugs. As shown in Figure 2, in the general structure of our designed amide-linked oligosaccharide analogues (i), the monosaccahride component (ii) has a C-1 carboxylate group, and one of the hydroxy groups is replaced with a protected amino group. Thus, the monosaccharide unit (iii) is regarded as an amino acid derivative, and, therefore, the chain elongation reaction becomes an easy peptide bond formation. The carbohydrate mimetics synthesized are amide-linked tetrasaccharide analogues, in which the monosaccharide residues are linked to each other via the C-1 carbonyl of one sugar to the amino group of another sugar; for example, **1**, a β(1→2)-amide-linked analogue[20] from D-glucosamine, **2**, a β(1→3)-amide-linked analogue[21] from D-glucose, **3**, a β(1→4)-amide-linked analogue[21] from D-galactose, **4**, a β(1→6)-amide-linked analogue[22] from D-glucose, as a new class of carbohydrate mimetics as shown in Figure 3. These analogues are, as expected, resistant to glycosidases (α- and β-glucosidases). We investigated the biological activities of sulfated analogues **18** and **33**, such as anti-HIV activity and inhibition of sialyl Lewis x selectin-mediated cell adhesion. The result revealed that these *O*-sulfated oligomers effectively inhibited HIV infection, sialyl Lewis x-mediated cell adhesion, and heparanase activity in a linkage-specific manner.[21] Therefore, these molecules have potential applications as drugs that block protein–protein interactions and inhibit enzyme catalysis.

Furthermore, our compounds can be assumed as non-natural amino acid analogues with additional functionality on the molecules because of their hydroxyl groups and ring oxygen. Among those analogues, which possess the structural and functional features of both carbohydrates and peptides, our analogues have both a carboxylate group at the anomeric position and an amino group replacing one of the OH groups of the sugar. The structural preferences of our compounds **1**–**4** have been investigated in nuclear magnetic resonance (NMR) and circular dichroism (CD) experiments.[21] As

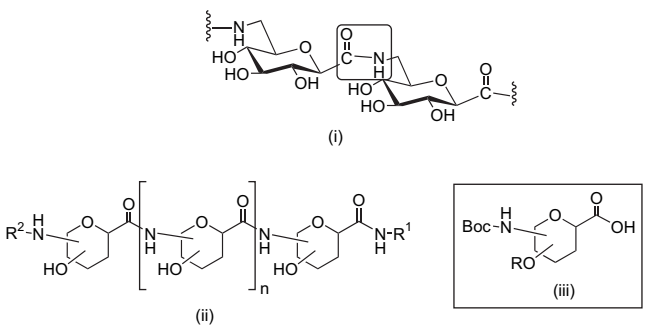
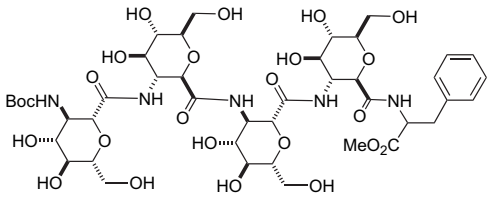
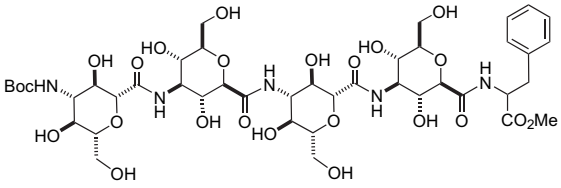
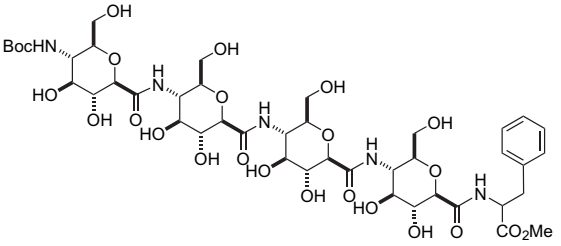



**Figure 2**. The general structure of our designated amido-linked oligosaccharide analogues.



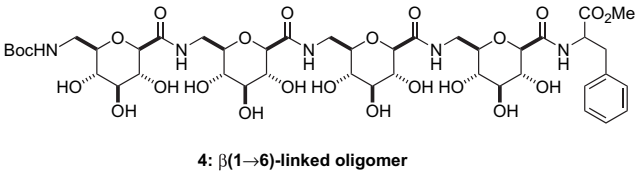




**Figure 3**. A new class of carbohydrate mimetics.

a result, they were found to form rigid secondary structures, in particular the β(1→2)-linked tetramer, which were very likely to form a 14-helical structure. From this information, we predicted that if our glycosamino acid monomer was polymerized, the resulting homooligomer would have the property of a unique folding peptide. The folding of a polypeptide chain into the stable three-dimensional structure of a biologically active protein is still not understood in detail; however, several research groups have recently reported successful atomistic simulations of secondary-structure formation, including the formation of helices of different types, β turns and β sheets of α- and β-peptides.[23–28] Insight into the nature of the folding state has been obtained from various studies simulating the reversible folding of peptides.[29–32] On the basis of this background, we further predicted that the various unique biological activities of our sulfated analogues were due to their three-dimensional structure. Therefore, we examined the additional conformational analysis of our oligomers with computer modeling (molecular dynamics calculations), and explored the application possibility of new physiologically active substances.

We herein report the detailed synthetis method of the tetrameric β(1→2)- and β(1→6)-carbopeptoids. Furthermore, the results of the conformational study of the homooligomer with molecular modeling calculations are reported.

## 2. Results and discussion

As shown in Figure 4, our general synthetic strategy both in the solution phase and in the solid phase is as follows: the monomeric building block (**A**), having a free C-1 carboxylic acid and Boc-protected amino group, couples with **B**, which has a free amino group, in the presence of a peptide coupling reagent to give a coupled product. The coupled product is treated with acid for N-deprotection (removal of *N*-Boc group) to generate another free amino group-carrying compound (**B**) with additional monomeric residue, which is again coupled to the monomeric building block **A**. After the chain elongation sequence is completed, the coupled product is O-deprotected to give the oligomeric analogue (**C**). The tetrameric compound was sulfated by a known method to afford the sulfated analogue (**D**).

Scheme 1 outlines the synthesis of the β(1→2)-linked homo-oligomer **1** starting from D-glucosamine hydrochloride. We first synthesized the known 1-cyano-2-phthalimide derivative (**5**), which was obtained according to the published procedure.[33,34] The C-1 CN group was hydrated with 30%

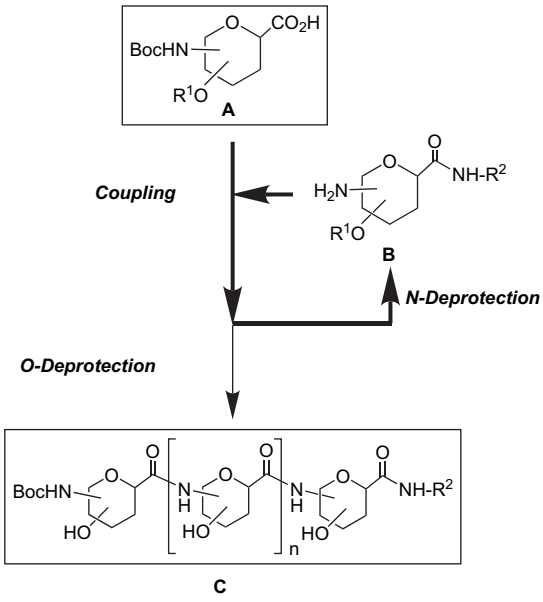
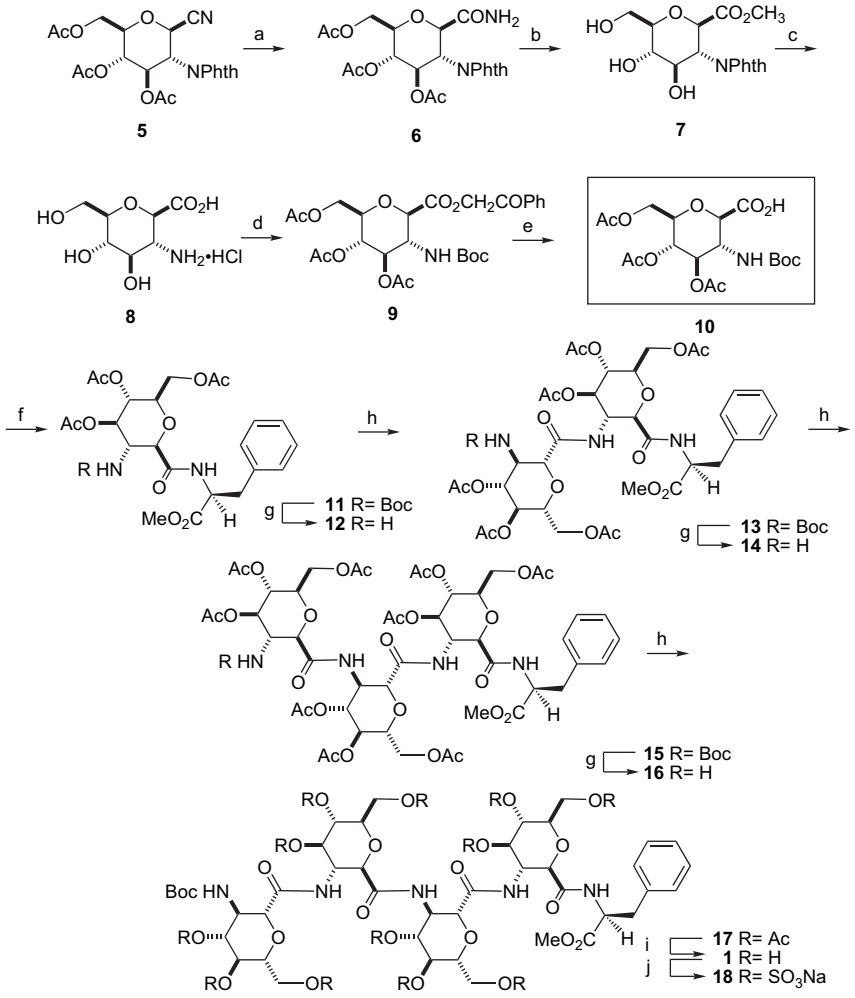



**Figure 4**. General synthetic strategy.



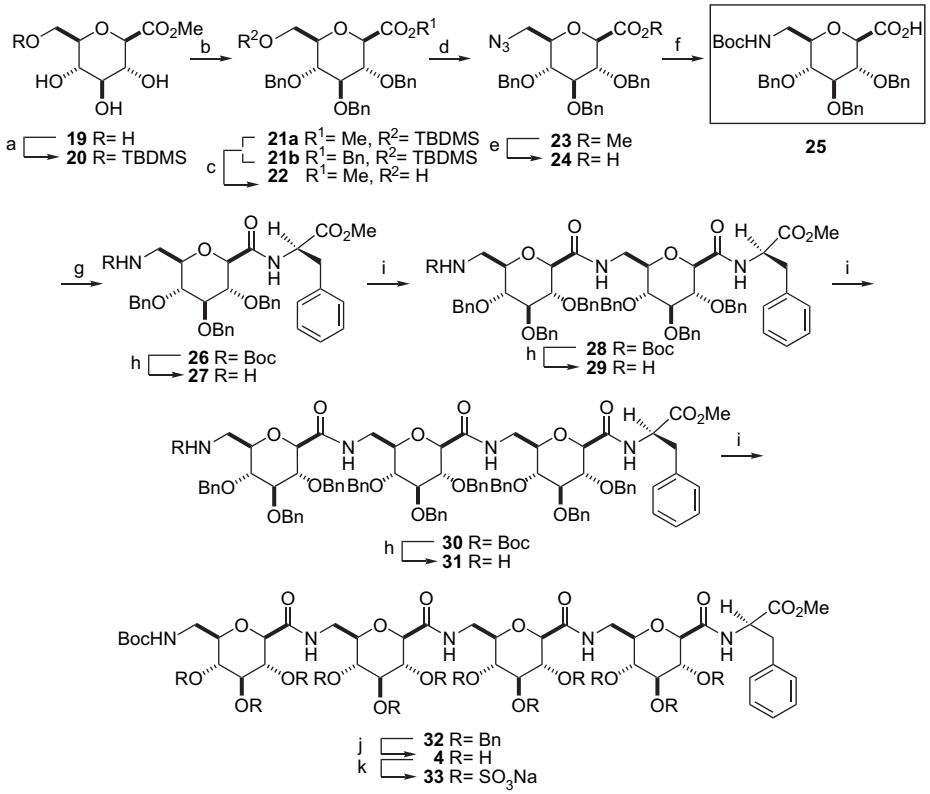

**Scheme 1**. Synthesis of a carbopeptoid tetramer **1**. Reagents and conditions: (a) 30% HBr–AcOH, 3 h, 0 °C to rt, 85%; (b) Dowex 50W-X8 [$H^+$], MeOH, 16 h, 80 °C, 97%; (c) (i) 6 equiv of LiOH, MeOH/$H_2O$ (3:1), 16 h, 60 °C, (ii) 3 N HCl, 3 h, reflux, 95% overall; (d) (i) 2 equiv of BOC-ON, $Et_3N$, dioxane/$H_2O$ (1:1), 12 h, rt, (ii) 2-bromoacetophenone, $Et_3N$, DMF, 4 h, rt, (iii) $Ac_2O$, pyridine, 12 h, rt, 73% overall; (e) $H_2$, Pd/C, AcOEt/EtOH (2:1), 16 h, rt, 90%; (f) L-phenylalanine methyl ester, DEPC, $Et_3N$, 16 h, 0 °C to rt, 86%; (g) 2 N HCl in EtOAc, 3 h, 0 °C to rt, 95%; (h) 1.2 equiv of **10**, BOP, DIEA, DMF, 16 h, rt, 59%; (i) MeONa in MeOH (pH 11), 2 h, rt, 68%; (j) 10 equiv of sulfur trioxide trimethylamine complex, 5 days 50 °C.

HBr–AcOH, then converted to a $CONH_2$ group (**6**) in 85% yield. Hydrolysis of the amide group of **6** with Dowex 50W-X8 [$H^+$] in refluxing MeOH gave methyl ester derivative (**7**) in 97% yield. The removal of acetyl groups and the phthaloyl group was accomplished by successive treatment with aqueous LiOH and 3 N HCl to give an amine derivative (**8**) in 95% overall yield. Protection of the amino group was carried out with BOC-ON,[34] then esterification of the C-1 carboxylate with 2-bromoacetophenone and conventional acetylation of hydroxyl groups afforded **9** in 73% overall yield. Finally, the monomeric component (**10**) was obtained by hydrogenation of **9** in 90% yield.

To form polysaccharide mimetics, the C-terminal group of **10** was first linked to L-phenylalanine methyl ester. C-Terminal modification can be replaced by a polymer support and applied for the solid-phase synthesis of oligo- and polysaccharide mimetics. Coupling of **10** with L-phenylalanine methyl ester using diethylphosphoryl cyanide (DEPC)[35] and $Et_3N$ gave **11** in 86% yield. Removal of the Boc group of **11** with 2 N HCl/EtOAc gave **12** in 95% yield. The elongation reaction of **14** with **10** was accomplished with BOP[36] reagent and diisopropylethylamine (DIEA) in DMF to give the coupling product in 59% yield. Repetition of the same synthetic manipulation: (i) removal of the Boc group and (ii) coupling with the monomeric component (**10**), easily produced the trimer (**15**) and tetramer (**17**). The tetramer (**17**) was *O*-deacetylated with NaOMe in MeOH to give **1** in 68% yield.

Scheme 2 summarizes the synthesis of the β(1→6)-linked homooligomer **4** starting with a known methyl D-*glycero*-D-gulo-hepturonate (**19**), which was reported by Lehmann et al.[10] For the introduction of the 6-amino group, the primary hydroxyl group 6-OH of **19** was selectively silylated with TBDMSCl to afford **20**, and the remaining 2,3,4-trihydroxyl groups of **20** were benzylated with $Ag_2O$ and BnBr in DMF. The benzylation of **20** gave a 1:1 mixture of a methyl ester (**21a**) and the corresponding benzyl ester (**21b**) in 75% yield. Presumably, the basic condition caused an ester-exchange reaction between the $CO_2Me$ and BnOH generated by the hydrolysis of BnBr. The silyl group of **21a** and **21b** was removed under acidic conditions, and the crude product was then treated with MeOH under basic conditions to give **22** in 78% overall yield. Tosylation of the primary OH followed by conversion to azido gave **23** in 81% overall yield. The methyl ester of **23** was hydrolyzed with aqueous LiOH, followed by successive reduction of azido with $H_2$/Lindlar catalyst,[37] and protection of the amino group with $Boc_2O$ to obtain the monomeric building block **25**. The monomeric component **25** was first coupled with phenylalanine using the same method as Scheme 1 in 92% yield. The formation of polysaccharide mimetics **4** was also carried out repeating the same method as Scheme 1.

O-Sulfation of the dimer, trimer, and tetramer of each of the β-amide-linked oligosaccharide analogues **1** and **4** produced the corresponding *O*-sulfated derivatives **18** and **33**.[21] The β(1→2)- (**1**) or β(1→6)-tetramer (**4**) was treated with an




**Scheme 2**. Synthesis of a carbopeptoid tetramer **4**. Reagents and conditions: (a) 1.2 equiv of TBDMSCl, 2.5 equiv of imidazole, DMF, 2 h, 0 °C, 83%; (b) 9 equiv of BnBr, 6 equiv of $Ag_2O$, DMF, 20 h, rt, 75%; (c) (i) AcOH/THF/$H_2O$ (3:1:1), 15 h, rt, (ii) 25% NaOMe, MeOH, 1 h, rt, 78% overall; (d) (i) TsCl, pyridine, 12 h, 0 °C to rt, (ii) 2 equiv of $NaN_3$, DMF, 12 h, 60 °C, 81% overall; (e) 2 equiv of LiOH·$H_2O$, MeOH/THF/$H_2O$ (3:3:1), 3 h, rt, 82%; (f) (i) Lindlar catalyst, $H_2$, MeOH, 3 h, rt, (ii) 1.5 equiv of $Boc_2O$, 2 equiv of LiOH·$H_2O$, MeOH/$H_2O$ (3:1), 12 h, rt, 54% overall; (g) 1.2 equiv of L-phenylalanine methyl ester, 1.5 equiv of DEPC, 3 equiv of $Et_3N$, 16 h, 0 °C to rt, 92%; (h) 2 N HCl in EtOAc, 3 h, 0 °C to rt; (i) 1.2 equiv of **25**, 1.5 equiv of DEPC, 3 equiv of $Et_3N$, 16 h, 0 °C to rt; (j) 10% Pd/C, $H_2$, MeOH, 16 h, rt, 86%; (k) 10 equiv of sulfur trioxide trimethylamine complex, 5 days, 50 °C.

excess amount of $SO_3 \cdot NMe_3$ in anhydrous DMF at 50 °C and the reaction progress was monitored by TLC (disappearance of the starting material and if possible for product formation). However, in this case, we expected high efficiency of a complete O-sulfation, and it was quite impossible to observe the fully *O*-sulfated compound in TLC. Instead, we stopped the reaction by cooling down and separated the product from the reagents with a Sephadex G-15 column eluted with water. Fractions stained with Azure reagent[38] were combined and concentrated to dryness. Then, we lyophilized the fractions and took an NMR. If the reaction was not completed, we observed several peaks corresponding to the methyl ester of **18** or **33**. After stirred at 50 °C for 5 days, we were able to see the single peak for the methyl ester of sulfated compounds. The sulfur content of the sulfated compounds was calculated by elemental analysis.

The β(1→2)- (**1**) and β(1→6)-tetramers (**4**) showed interesting and potent biological activities as mentioned. We anticipated that those activities might relate to their conformation. In our previous study, CD spectroscopy data of a β(1→2)-linked hexamer suggested the possibility of a 14-helical structure.[21] In addition, a β(1→2)-linked oligomer can be particularly assumed as a unique β-peptide with functionality on molecules such as hydroxyl groups and ring oxygen. Therefore, we focused on a β(1→2)-linked oligomer for conformational study among our carbopeptoid oligomers **1**–**4**. Conformational search calculations were performed with the package of MacroModel ver. 8.1 (Schrödinger Inc.) on an SGI workstation. The Monte Carlo Multiple Minimum (MCMM) method and AMBER* force field were used to find the global and local minimum energy conformation. As the initial structure, an extended structure was used. More than 10,000 conformers were optimized. Figure 5 shows the result of conformational analysis of a β(1→2)-linked decamer with a molecular modeling calculation. Interestingly, it revealed that a typical right-handed 16-helix was the most stable conformation. The 16-helix structure was stabilized with a hydrogen bond between oxygen of the C-1 carbonyl group and nitrogen of the C-2 amino group of another unit as shown in Figure 5. Although we examined various calculations, β(1→2)-linked oligomers from dimer to decamer have never had left-handed conformation except tetramers. This finding corresponds to the result of β-amino acid oligomer reported by Gellman et al.[23,24] In the case of the tetramer, one reason why it possessed sinistral structure might be steric hinderance caused by amino acids.

This unique conformation of a β(1→2)-linked oligomer may give various functions such as protein–protein interaction. In an earlier work in this field, Seebach demonstrated that β-peptide hairpins could bind somatostatin receptors with high affinity and specificity.[39,40] Seebach and co-workers,[41] DeGrado and co-workers,[42,43] and Gellman and co-workers[44–46] demonstrated that amphiphathic β-peptides could perform a variety of functions including the inhibition of cholesterol and fat uptake,[41] potent antibacterial activity,[42–45] and RNA binding.[46] Recently, some groups reported the synthesis and investigation of the helical structure of α, β, and γ-peptide including molecular dynamics simulation.[47–51] Some evaluated biological activity, for example, Kritzer et al. studied protein–protein interaction inhibitors, which were made from 14-helical β-peptide.[47] Meanwhile Porter et al. reported structure–activity trends among

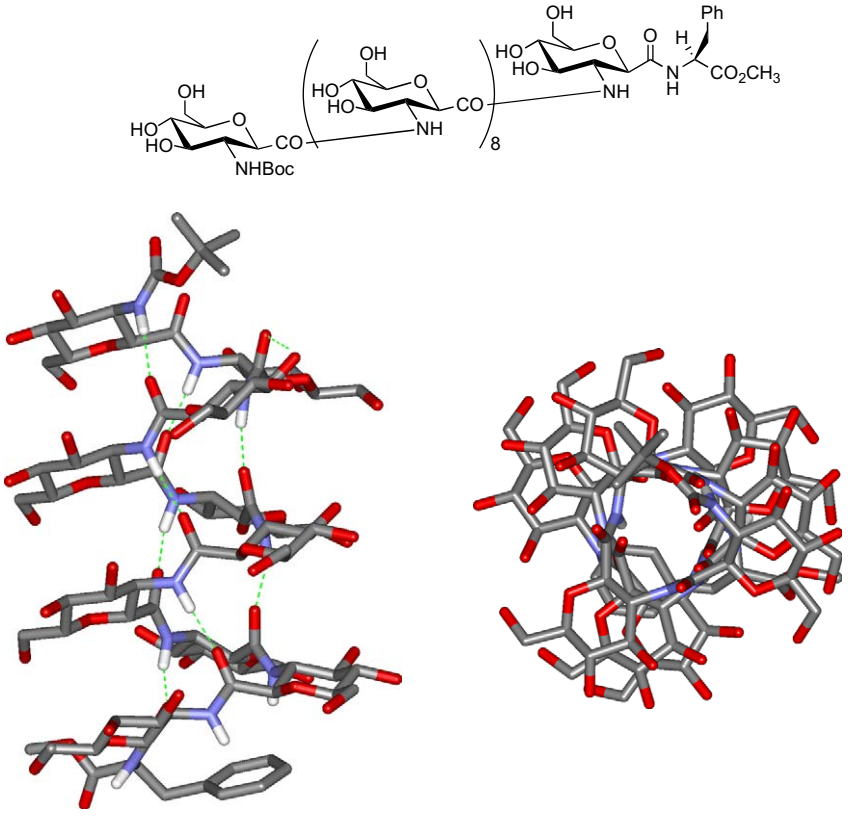



**Figure 5**. Conformational analysis of β(1→2)-amide-linked analogue.

helix-forming β-amino acid oligomers that are intended to mimic α-helical host-defense peptides.[48] Their β-peptide displayed antimicrobial activity. These findings indicate that a β-peptide field is now poised to make significant contributions to chemical biology. Protein–protein interactions are extremely difficult to target; however, the foldamer scaffold may provide a general platform for controlling crucial interactions with high potency and specificity. Unlike the case of reported peptides, our carbopeptoid oligomers have peptide as well as carbohydrate properties, therefore, modification of their hydroxyl groups can be a new methodology for therapeutic agents.

## 3. Conclusion

We have shown the synthetis strategy for a new class of oligomers composed of carbopeptoids, which possess a carboxylate at the anomeric position and an amino group replacing one of the hydroxyl groups of monosaccharide, and this synthesis can be effectively accomplished in a stereo- and regioselective manner. We also examined conformational analysis with molecular modeling and found that the β(1→2)-linked oligomer formed a rigid secondary structure, therefore it had the property of a folding β-peptide. Some *O*-sulfated oligomers effectively inhibited HIV infection, sialyl Lewis x-mediated cell adhesion, and heparanase activity in a linkage-specific manner, as reported in the previous paper. Although further investigation is required to clarify the structure–activity relationships, these findings may lead to the design of a new class of biologically active analogues of peptides or oligosaccharides. Thus, our analogues are especially interesting as tools for mimicking native peptide and protein structures, and may stimulate synthesis work in this field.

## 4. Experimental

### 4.1. General

Unless otherwise indicated, all starting materials were obtained from commercial suppliers and without further purification. All reactions were conducted under Ar atmosphere. When reactions were worked up by extraction with $CH_2Cl_2$, $CHCl_3$, or EtOAc, organic solutions were dried with molecular sieves 4 Å and concentrated with a rotary evaporator. Silica gel column chromatography was performed using Fisher Scientific S704-25 60–200-mesh silica gel. Reactions and chromatography fractions were analyzed using Merck silica gel 60 F-254 TLC plates. $^1$H NMR and $^{13}$C NMR spectra were measured in $CDCl_3$ at 300 and 75 MHz, respectively. Chemical shifts are expressed in parts per million relative to internal $CHCl_3$. *J* values are in Hertz. Melting points were determined in Pyrex capillaries. IR spectra were measured as solutions in the solvent indicated.

**4.1.1. 4,5,7-Tetra-*O*-acetyl-3-phthalimido-D-*glycero*-D-*gluco*-hepturonamide (6).** A suspension of 3-phthalimido-4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*gulo*-heptononitrile (**5**, 2-phthalimido-3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl cyanide; 7.71 g, 17.3 mmol) in 30% (w/w) hydrogen bromide–glacial acetic acid (17 mL) was stirred in a closed vessel for 3 h at room temperature. The resulting solution was then poured into stirred ice and water (200 mL), which was immediately extracted with chloroform (2×200 mL). The extracts were combined, successively washed with saturated aqueous sodium hydrogen carbonate solution (2×100 mL) and water (100 mL), and then processed as described under Section 4.1. Crystallization from chloroform (30 mL)–diethyl ether (120 mL) gave **6** (6.81 g, 14.7 mmol; 85% yield) as heteromorphic crystals, mp 223–226 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.86–7.83 (m, 2H, Phthalimide), 7.75–7.70 (m, 2H, Ph), 6.47 (s, 1H, NH), 5.94 (t, 1H, *J*=9.8 Hz, H-3), 5.69 (s, 1H, NH), 5.16 (t, 1H, *J*=9.7 Hz, H-4), 4.84 (d, 1H, *J*=10.8 Hz, H-1), 4.44 (t, 1H, *J*=10.6 Hz, H-2), 4.33 (dd, 1H, *J*=4.8, 12.4 Hz, H-6a), 4.23 (dd, 1H, *J*=2.1, 12.5 Hz, H-6b), 3.96–3.91 (m, 1H, H-5), 2.13, 2.05, 1.88 (3s, 3H each, 3×C*H*$_3$CO); $^{13}$C NMR (72.5 Hz, $CDCl_3$): δ 170.7, 169.9, 169.4 (3×CH$_3$*C*O), 167.7, 153.9 (CO), 134.1, 123.6 (Ph), 75.7, 72.3, 71.0, 68.7, 61.9, 51.9 (C-1, 2, 3, 4, 5, 6), 13.8, 13.4, 13.1 (3×*C*H$_3$CO); Anal. Calcd for $C_{21}H_{22}O_{10}N_2\cdot 1/2H_2O$: C, 53.52; H, 4.92; N, 5.94. Found: C, 53.32; H, 4.94; N, 5.33.

**4.1.2. (2*R*,3*R*,4*R*,5*S*,6*R*)-Methyl tetrahydro-4,5-dihydroxy-6-(hydroxymethyl)-3-(1,3-dioxoisoindolin-2-yl)-2*H*-pyran-2-carboxylate (7).** The amide (**6**) (12.0 g, 30.0 mmol) and the resin of Dowex 50W-X8 [H$^+$] were combined with sufficient solvent (MeOH) to cover the resin (~50 mL). For slightly soluble amides, the volume of solvent was doubled. Gentle agitation was provided by a magnetic spin bar small enough to prevent powdering of the resin. The flask was tightly stoppered and warmed to the reflux temperature of the solvent for 16 h. The progress of the reaction was monitored by TLC. Removal of the resin by filtration and evaporation of the solvent provided the crude product, which was purified by silica gel column chromatography (1:1–0:1 hexane/EtOAc) to afford **7** (8.80 g, 25.0 mmol; 97%) as a white powder, mp 94–97 °C; $^1$H NMR (300 MHz, $CD_3OD$): δ 7.90–7.82 (m, 4H, Ph), 4.74 (d, 1H, *J*=8.6 Hz, H-1), 4.41 (dd, 1H, *J*=8.3, 10.3 Hz, H-2), 4.14 (t, 1H, *J*=10.6 Hz, H-3), 3.92 (dd, 1H, *J*=1.3, 12.1 Hz, H-6a), 3.74 (dd, 1H, *J*=4.7, 12.0 Hz, H-6b), 3.45–3.43 (m, 2H, H-4, 5); $^{13}$C NMR (72.5 Hz, $CD_3OD$): δ 170.4 (*C*O$_2$CH$_3$), 169.43, 169.37 (2×Ph*C*ON), 135.7, 132.8, 124.3 (Ph), 82.0, 74.8, 73.0, 72.1, 62.5, 55.7, 53.0 (C-1,2,3,4,5,6, CO$_2$*C*H$_3$); Anal. Calcd for $C_{16}H_{17}O_8N\cdot 1/2H_2O$: C, 53.33; H, 5.04; N, 3.89. Found: C, 53.51; H, 4.99; N, 3.66.

**4.1.3. (2*R*,3*R*,4*R*,5*S*,6*R*)-3-Amino-tetrahydro-4,5-dihydroxy-6-(hydroxymethyl)-2*H*-pyran-2-carboxylic acid hydrochloride (8).** Compound **7** (11.3 g, 35.2 mmol) was dissolved in 100 mL of MeOH/$H_2O$ 3:1, cooled in an ice bath for 10 min, and then added to a suspension of 8.85 g of LiOH·$H_2O$ (211 mmol) in 20 mL of MeOH/$H_2O$ 3:1 at 0 °C, then the mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the pH of the solution was adjusted to neutral by the addition of 1 N hydrochloric acid, and then the solvent was evaporated. Furthermore, 300 mL of 3 N hydrochloric acid was added to the residue and the acidic mixture was brought to reflux for 3 h. After the solution was concentrated to remove HCl, the resin was dissolved in 2 L of water and the pH adjusted to 7.0–7.5 using 1 N aqueous $NH_4OH$. The crude reaction mixture was then eluted onto a Dowex 50W-X8 [H$^+$] column, and washed with water, MeOH, water (each 500 mL), and then

eluted with 1 L of 1 N aqueous $NH_4OH$. Ninhydrin-active fractions were collected and concentrated, then the resin was suspended in 50 mL of 1 N hydrochloric acid and evaporated. Lyophilization with a small amount of water gave **8** (8.10 g, 33.2 mmol; 95%) as a colorless amorphous powder: $^1$H NMR (300 MHz, $D_2O$): $\delta$ 4.10 (d, 1H, $J$=10.5 Hz, H-1), 3.63 (1H, H-6a), 3.51–3.42 (m, 2H, H-4, 6b), 3.31–3.16 (m, 2H, H-2, 5), 3.10 (t, 1H, $J$=10.4 Hz, H-3); $^{13}$C NMR (72.5 Hz, $D_2O$): $\delta$ 171.8 ($CO_2H$), 80.5, 74.02, 73.93, 70.2, 61.4, 53.7 (C-1,2,3,4,5,6).

**4.1.4. (2*R*,3*R*,4*R*,5*S*,6*R*)-2-Oxo-2-phenylethyl 4,5-diacetoxy-6-(acetoxymethyl)-3-(*tert*-butoxycarbonylamino)-tetrahydro-2*H*-pyran-2-carboxylate (9).** To a stirred solution of **8** (4.2 g, 12.0 mmol) and $Et_3N$ (7.21 mL, 51.7 mmol) in water (30 mL) was added a solution of BOC-ON (6.43 g, 25.9 mmol) in 1,4-dioxane (30 mL). After 3 h at room temperature, the solution was concentrated, and the residue was dissolved in 50 mL of water. The water solution was then adjusted to neutral using Dowex 50W-X8 [$H^+$] and washed with 50 mL of $CH_2Cl_2$, followed by evaporation of the aqueous layer. To a DMF solution (50 mL) of the residue was added 2-bromoacetophenone (phenacylbromide) (5.25 g, 25.8 mmol) and $Et_3N$ (3.6 mL, 25.8 mmol). The mixture was stirred at room temperature for 3 h, then pyridine (60 mL) and acetic anhydride (30 mL) were added to the solution and stirred at room temperature for 12 h. The mixture was poured into ice water and extracted three times with EtOAc (200 mL each), and organic layers were washed with 0.5 N hydrochloric acid, water, saturated aqueous $NaHCO_3$, and brine. After drying ($MgSO_4$), the solution was filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc 5:1) to afford **9** (4.81 g, 8.70 mmol; 73% overall) as a white powder, mp 194–197 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.90 (2H, Ph), 7.62 (1H, Ph), 7.49 (2H, Ph), 5.47 (t, 1H, $J$=9.5 Hz, H-3), 5.40 (t, 2H, $J$=16.3 Hz, C$H_2$COPh), 5.10 (t, 1H, $J$=9.6 Hz, H-4), 4.45 (d, 1H, $J$=10.4 Hz, H-1), 4.27 (dd, 1H, $J$=5.2, 12.5 Hz, H-6a), 4.15 (dd, 1H, $J$=2.2, 12.4 Hz, H-6b), 3.88 (1H, H-2), 3.80–3.75 (m, 1H, H-5), 2.08, 2.06, 2.03 (3s, 3H each, 3×C$H_3$CO), 1.40 (s, 9H, NHC$O_2t$*Bu*); $^{13}$C NMR (72.5 Hz, $CDCl_3$): $\delta$ 170.5, 170.4, 169.4, 167.1 (CO), 133.9, 128.8, 127.7 (Ph), 76.8, 75.9, 72.7, 68.7, 66.7, 62.3 (C-1,2,3,4,5,6), 28.1 (*t*-Bu), 20.6, 20.51, 20.45 (3×$C$H$_3$CO); mass spectrum (EI) *m/e* 569.2349 ($M^+$, calcd 569.2347).

**4.1.5. (2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-Diacetoxy-6-(acetoxymethyl)-3-(*tert*-butoxycarbonylamino)-tetrahydro-2*H*-pyran-2-carboxylic acid (β(1→3)-linked monomer) (10).** Compound **9** (2.70 g, 4.90 mmol) was dissolved in EtOAc/EtOH 2:1 (60 mL), and 10% Pd/C (400 mg) was added to the solution. The resulting mixture was stirred at room temperature for 16 h under $H_2$. Analysis of the reaction mixture by TLC ($CHCl_3$/MeOH, 2:1) indicated the disappearance of the starting material. The catalyst was filtered off and washed with MeOH. The combined solution was concentrated in vacuo to provide a crude product. Column chromatography ($CHCl_3$/MeOH, 20:1) of the residue gave compound **10** (1.91 g, 4.38 mmol; 90%) as a white powder, mp 193–195 °C; $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 5.17 (t, 1H, $J$=9.4 Hz, H-3), 4.99 (t, 1H, $J$=9.6 Hz, H-4), 4.29 (dd, 1H, $J$=5.0, 12.4 Hz, H-6a), 4.10 (dd, 1H, $J$=2.0, 12.3 Hz, H-6b), 3.97–3.86 (m, 2H, H-1, 2), 3.79–3.75 (m, 1H, H-5), 2.04, 2.00, 1.99 (3s, 3H each, 3×C$H_3$CO), 1.40 (s, 9H, NHC$O_2t$*Bu*); $^{13}$C NMR (72.5 Hz, $CD_3OD$): $\delta$ 172.5 ($CO_2H$), 171.9, 171.4 (3×$CH_3CO$), 157.6 (NH$CO_2t$Bu), 80.9, 76.9, 75.9, 70.3, 63.8, 54.4 (C-1,2,3,4,5,6), 28.7 (*t*-Bu), 20.7, 20.68, 20.61 (3×$C$H$_3$CO); mass spectrum (EI) *m/e* 451.1928 ($(M+NH_4)^+$, calcd 451.1928).

**4.1.6. (2*R*,3*S*,4*R*,5*R*,6*R*)-2-(Acetoxymethyl)-5-(*tert*-butoxycarbonylamino)-6-(1-methoxy-1-oxo-3-phenylpropan-2-ylcarbamoyl)-tetrahydro-2*H*-pyran-3,4-diyl diacetate (11).** DEPC (524 μL, 3.21 mmol) was added to a stirred solution of compound **10** (1.16 g, 2.68 mmol), L-phenylalanine methyl ester (692 mg, 3.21 mmol), and $Et_3N$ (821 μL, 5.89 mmol) in DMF (30 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h, and then at room temperature for 12 h. The reaction mixture was diluted with EtOAc (200 mL), and then washed successively with water (200 mL), and saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, and concentrated to dryness in vacuo. The residue was chromatographed on silica gel using toluene/EtOAc 5:1 to give **11** (1.23 g, 2.30 mmol; 86%) as a white powder, mp 231–234 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.27–7.12 (m, 5H, Ph), 6.87 (d, 1H, $J$=8.1 Hz, NH), 5.27 (m, 2H, H-1, 3), 5.03 (t, 1H, $J$=9.7 Hz, H-4), 4.80 (m, 1H, C$H$C$O_2$CH$_3$), 4.21 (dd, 1H, $J$=5.0, 12.4 Hz, H-6a), 4.14 (dd, 1H, $J$=1.2, 11.9 Hz, H-6′), 4.03 (d, 1H, $J$=9.9 Hz, H-6b), 4.03 (d, 1H, $J$=9.9 Hz, NH), 3.81–3.70 (m, 5H, H-2, 5, $CO_2CH_3$), 3.18–3.02 (m, 2H, C$H_2$Ph of L-Phe), 2.07, 2.06, 2.02 (3s, 3H each, 3×C$H_3$CO), 1.39 (s, 9H, NHC$O_2t$*Bu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): $\delta$ 171.1, 170.4, 169.2 (3×$CH_3CO$), 170.2 ($CO_2CH_3$), 166.8 (NH$CO$), 154.9 (NHO$CO$*t*Bu), 135.6, 129.0, 128.2, 126.9 (Ph), 79.5, 76.8, 75.2, 73.1, 68.4, 62.0 (C-1,2,3,4,5,6), 52.6 ($CHCO_2CH_3$), 52.0 ($CO_2CH_3$), 37.6 ($CH_2$Ph of L-Phe), 27.9 (*t*-Bu), 20.44, 20.38, 20.33 (3×$CH_3CO$); mass spectrum (EI) *m/e* 595.2513 ($(M+H)^+$, calcd 595.2503).

**4.1.7. β(1→2)-Linked dimer (13).** A solution of 4 N HCl in EtOAc (10 mL) was added to a stirred solution of compound **11** (887 mg, 1.49 mmol) in EtOAc (10 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was washed with ether to give **12** as a white powder. This compound was reacted without further purification. Compound **12**, BOP reagent (792 mg, 1.79 mmol), and DIEA (572 μL, 3.94 mmol) were added to a solution of compound **10** (776 mg, 1.79 mmol) in DMF (20 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 16 h, then diluted with EtOAc (200 mL), and successively washed with water, saturated aqueous $NaHCO_3$, and brine (150 mL each). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel using toluene/EtOAc 5:1–1:1 to afford **13** (800 mg, 879 μmol; 59%) as a white powder, mp 198–203 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.29–7.11 (m, 5H, Ph), 7.01 (d, 1H, $J$=7.9 Hz, NH), 6.70 (d, 1H, $J$=7.1 Hz, NH), 5.38 (t, 1H, $J$=9.7 Hz, 1H-3), 5.21 (t, 1H, $J$=9.5 Hz, 2H-3), 5.07–4.98 (m, 3H, 1H-4, 2H-1, 4), 4.72 (dd, 1H, $J$=6.3, 14.0 Hz, C$H$C$O_2$CH$_3$), 4.29–4.08 (m, 5H, 1H-6a, 6b, 2H-1, 6a, 6b), 3.97–3.87 (m, 2H, 1H-2, 5), 3.77–3.55 (m, 5H, 2H-2, 5, $CO_2CH_3$), 3.18–3.06 (m, 2H, C$H_2$Ph of L-Phe), 2.08, 2.06, 2.05, 2.02

(s, 3H each, 6×C$H_3$CO), 1.39 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): $\delta$ 171.1, 170.9, 170.6, 170.5, 169.30, 169.25 (6×$CH_3$*C*O), 170.1 (*C*O$_2$CH$_3$), 167.7, 166.8 (NH*C*O), 155.2 (NHO*C*O*t*Bu), 135.8, 129.0, 128.4, 126.9 (Ph), 79.8, 76.3, 76.2, 75.5, 73.3, 72.3, 68.4, 68.3, 62.1, 61.9, 52.9 (*C*HCO$_2$CH$_3$), 52.2 (CO$_2$*C*H$_3$), 37.4 (*C*H$_2$Ph of L-Phe), 28.0 (*t*-Bu), 20.6, 20.5, 20.4 (6×*C*H$_3$CO); mass spectrum (FAB) *m/e* 932.2 ((M+Na)$^+$, calcd 932.3), 810.1 ((M−Boc+2H)$^+$ calcd 810.3).

**4.1.8. β(1→2)-Linked trimer (15).** As described for **13**, 4 N HCl in EtOAc (10 mL) was added to a stirred solution of compound **13** (712 mg, 783 μmol) in EtOAc (10 mL), followed by treatment with BOP reagent (415 mg, 938 μmol), DIEA (300 μL, 1.72 mmol), and compound **10** (407 mg, 938 μmol) in DMF (20 mL) at room temperature under argon to give **15** (478 mg, 390 μmol; 50%) as a white powder, mp 118–121 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.28–7.11 (m, 5H, Ph), 6.94 (d, 1H, *J*=6.9 Hz, NH), 5.25 (t, *J*=8.7 Hz, 2H), 5.14–4.98 (m, 4H), 4.77 (dd, 1H, *J*=5.5, 12.1 Hz, C*H*CO$_2$CH$_3$), 4.35–4.00 (m, 10H), 3.78–3.72 (m, 6H), 3.55 (dd, 1H, *J*=8.8, 15.5 Hz), 3.22–3.08 (2H, C*H*$_2$Ph of L-Phe), 2.07–1.99 (s, 3H each, 9×C$H_3$CO), 1.45 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): $\delta$ 170.9, 170.4, 170.3, 170.2, 170.1, 169.9, 169.3, 169.2, 169.1 (9×$CH_3$*C*O, *C*O$_2$CH$_3$), 168.2, 167.9, 166.8 (NH*C*O), 156.2 (NHO*C*O*t*Bu), 135.5, 129.0, 128.7, 126.9 (Ph), 80.4, 77.2, 77.1, 75.3, 75.2, 74.9, 73.4, 73.3, 72.7, 68.9, 68.4, 62.4, 62.1, 62.0, 52.7 (*C*HCO$_2$CH$_3$), 52.0 (CO$_2$*C*H$_3$), 37.3 (*C*H$_2$Ph of L-Phe), 27.9 (*t*-Bu), 20.3, 20.26, 20.18 (9×*C*H$_3$CO); mass spectrum (FAB) *m/e* 1247.5 ((M+Na)$^+$, calcd 1247.4), 1125.3 ((M−Boc+2H)$^+$ calcd 1125.4).

**4.1.9. β(1→2)-Linked tetramer (17).** As described for **13**, 4 N HCl in EtOAc (10 mL) was added to a stirred solution of compound **15** (478 mg, 390 μmol) in EtOAc (10 mL), followed by treatment with BOP reagent (207 mg, 468 μmol), DIEA (150 μL, 859 μmol), and compound **10** (203 mg, 468 μmol) in DMF (10 mL) at room temperature under argon to give **17** (269 mg, 175 μmol; 45%) as a white powder, mp 134–138 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.29–7.14 (m, 5H, Ph), 7.09 (d, 1H, *J*=7.5 Hz, NH), 7.00 (d, 1H, *J*=7.7 Hz, NH), 5.46 (m, 1H), 5.37–5.28 (m, 3H), 5.10–4.99 (m, 4H), 4.73 (dd, 1H, *J*=6.0, 13.6 Hz, C*H*CO$_2$CH$_3$), 4.30–4.10 (m, 13H), 3.94–3.83 (m, 2H), 3.73–3.61 (m, 8H), 3.21–3.07 (m, 2H, C*H*$_2$Ph of L-Phe), 2.11–2.00 (s, 3H each, 12×C$H_3$CO), 1.41 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): $\delta$ 171.0, 170.7, 170.6, 170.5, 170.4, 170.2, 169.5, 169.4, 169.3, 169.1 (12×$CH_3$*C*O, *C*O$_2$CH$_3$), 168.7, 168.0, 167.7, 167.1 (NH*C*O), 156.1 (NHO*C*O*t*Bu), 135.6, 129.2, 128.9, 127.1 (Ph), 79.8, 76.7, 75.4, 75.2, 75.0, 74.7, 72.3, 68.6, 68.4, 68.2, 62.2, 62.1, 62.0, 53.0 (*C*HCO$_2$CH$_3$), 52.3 (CO$_2$*C*H$_3$), 37.5 (*C*H$_2$Ph of L-Phe), 28.3 (*t*-Bu), 20.8, 20.6, 20.5, 20.4, 20.3 (12×*C*H$_3$CO); mass spectrum (FAB) *m/e* 1562.7 ((M+Na)$^+$, calcd 1562.5), 1540.6 ((M+Na)$^+$, calcd 1540.5), 1440.5 ((M−Boc+2H)$^+$, 1440.5).

**4.1.10. β(1→2)-Linked tetramer (1).** 30% MeONa in MeOH was added to a solution of compound **17** (269 mg, 175 μmol) in MeOH (10 mL) at room temperature and the pH was adjusted to 10–11. The mixture was stirred at room temperature for 3 h. Dowex 50W [H$^+$] was added and the pH was adjusted to neutral. After the removal of Dowex 50W [H$^+$], the filtrate was concentrated. The residue was purified by Sephadex G-10 to afford **1** (123 mg, 120 μmol; 68%) as a white powder, mp 125–128 °C; $^1$H NMR (300 MHz, $D_2O$): $\delta$ 7.32–7.17 (m, 5H, Ph), 4.57 (dd, 1H, *J*=6.5, 8.2 Hz, C*H*CO$_2$CH$_3$), 3.87–3.58 (m, 21H), 3.50–3.32 (m, 10H), 3.10 (dd, 1H, *J*=8.2, 14.0 Hz, C*H*$_2$Ph of L-Phe), 2.95 (dd, 1H, *J*=6.5, 14.0 Hz, C*H*$_2$Ph of L-Phe), 1.35 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $D_2O$): $\delta$ 173.5 (*C*O$_2$CH$_3$), 171.8, 171.5, 171.1, 170.5 (NH*C*O), 158.3 (NHO*C*O*t*Bu), 136.7, 129.6, 129.2, 127.7 (Ph), 81.8, 79.6, 79.5, 79.4, 78.1, 77.1, 77.0, 75.1, 74.9, 74.7, 74.4, 70.0, 69.7, 69.6, 61.0, 60.9, 60.7, 55.8, 54.3, 54.2, 54.1, 53.5, 53.3 (CO$_2$*C*H$_3$), 37.0 (*C*H$_2$Ph of L-Phe), 28.1 (*t*-Bu); mass spectrum (FAB) *m/e* 1036.3 ((M+H)$^+$, calcd 1036.4).

**4.1.11. (2*R*,3*R*,4*S*,5*S*,6*R*)-Methyl tetrahydro-3,4,5-trihydroxy-6-(hydroxymethyl)-2*H*-pyran-2-carboxylate (19).** Compound **19** was prepared from D-glucose pentaacetate by a known sequence in large quantities as a colorless oil: $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 4.31–3.74 (br, 3H, OH), 3.66–3.61 (m, 5H, H-1, 6, 6′), 3.37 (dd, 1H, *J*=6.0, 11.9 Hz, H-5), 3.29 (t, 1H, *J*=9.2 Hz, H-3), 3.19–3.11 (m, 4H, H-4 and CO$_2$C*H*$_3$), 3.04 (dd, 1H, *J*=9.1, 17.8 Hz, H-2); $^{13}$C NMR (72.5 MHz, $CD_3OD$): $\delta$ 171.5 (*C*O$_2$CH$_3$), 81.3, 79.4, 78.3, 72.5, 70.4, 62.1, 52.9 (C-1,2,3,4,5,6, CO$_2$*C*H$_3$); mass spectrum (FAB) *m/e* 223.1 ((M+H)$^+$, calcd 223.1).

**4.1.12. (2*R*,3*R*,4*S*,5*S*,6*R*)-Methyl tetrahydro-3,4,5-trihydroxy-6-((*tert*-butyldimethylsilyloxy)methyl)-2*H*-pyran-2-carboxylate (20).** To a solution of **19** (9.60 g, 43.2 mmol) in DMF (50 mL) was added *tert*-butyldimethylsilyl chloride (7.81 g, 51.8 mmol) and imidazole (7.35 g, 10.8 mmol) at 0 °C, and the suspension was stirred for 2 h at room temperature. The reaction mixture was diluted with EtOAc (300 mL), and successively washed with water (2×200 mL) and brine (200 mL). The organic layer was dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel column chromatography (1:1 toluene/EtOAc to EtOAC only) to afford **20** (12.1 g, 40.0 mmol; 83%) as a white heteromorphic crystals: $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.64–3.58 (m, 2H, H-6, 6′), 3.34 (s, 3H, CO$_2$C*H*$_3$), 3.32–3.24 (m, 2H, H-1, 5), 3.21–3.13 (m, 2H, H-3, 4), 3.09–3.05 (m, 1H, H-2), 0.83 (s, 9H, (C$H_3$)$_3$CSi(CH$_3$)$_2$), 0.006, −0.013 (s, 6H, (CH$_3$)$_3$CSi(C$H_3$)$_2$); $^{13}$C NMR (72.5 MHz, $CD_3OD$): $\delta$ 171.3 (*C*O$_2$CH$_3$), 82.3, 80.2, 79.0, 72.9, 71.0, 64.2, 52.6 (C-1,2,3,4,5,6, CO$_2$*C*H$_3$), 26.4 ((*C*H$_3$)CSi(CH$_3$)$_2$), 19.2 ((CH$_3$)*C*Si(CH$_3$)$_2$), −4.99, −5.04 ((CH$_3$)CSi(*C*H$_3$)$_2$); mass spectrum (FAB) *m/e* 337.2 ((M+H)$^+$, calcd 337.2).

**4.1.13. (2*R*,3*R*,4*S*,5*R*,6*R*)-Methyl 3,4,5-tris(benzyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2*H*-pyran-2-carboxylate (21a) and (2*R*,3*R*,4*S*,5*R*,6*R*)-benzyl 3,4,5-tris(benzyloxy)-6-((*tert*-butyldimethylsilyloxy)-methyl)-tetrahydro-2*H*-pyran-2-carboxylate (21b).** To a solution of **20** (10.0 g, 29.7 mmol) in DMF (100 mL), were added BnBr (31.8 mL, 267 mmol) and $Ag_2O$ (41.4 g, 178 mmol) at room temperature, and the suspension stirred for 20 h in a reaction vessel covered to exclude light. The reaction mixture was diluted with EtOAc (1 L), and then the precipitate was filtered off. The filtrate was washed with saturated aqueous $NaHCO_3$ (2×1 L), brine (1 L), dried

($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (heptane only to 5:1 heptane/EtOAc) to give mixture of **21a** and **21b** (1:1) (12.2 g, 75%) as a white solid: $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.17–7.00 (m, 30H, Ph), 5.03–4.34 (m, 12H, C$H_2$Ph), 3.89–3.28 (m, 14H), 3.39 (3H, $CO_2CH_3$), 0.83 (s, 18H, $(CH_3)_3CSi(CH_3)_2$), 0.006, −0.013 (s, 12H, $(CH_3)_3CSi(CH_3)_2$).

**4.1.14. (2*R*,3*R*,4*S*,5*R*,6*R*)-Methyl 3,4,5-tris(benzyloxy)-tetrahydro-6-(hydroxymethyl)-2*H*-pyran-2-carboxylate (22).** Compounds **21a** and **21b** (10.0 g) were dissolved in AcOH/THF/$H_2O$ (3:1:1) (500 mL) at room temperature, and the solution was stirred for 15 h at room temperature. The mixture was concentrated in vacuo and the residue was azeotropied with toluene twice. The resin was then dissolved in MeOH (200 mL), and 30% NaOMe in MeOH (2.0 mL) was added to the solution. The reaction mixture was stirred at room temperature for 15 min, and then concentrated. Purification by silica gel chromatography (20:1 toluene/EtOAc to 5:1) afforded **22** (7.60 g, 15.4 mmol, 78% overall) as a white powder, mp 76–78 °C; $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 7.31–7.21 (m, 15H, Ph), 4.88–4.52 (m, 6H, C$H_2$Ph), 3.97–3.66 (m, 7H), 3.62 (s, 3H, $CO_2CH_3$); $^{13}$C NMR (72.5 MHz, $CD_3OD$): $\delta$ 169.8 ($CO_2CH_3$), 138.3, 137.8, 137.7 (*C*Ph), 128.52, 128.47, 128.44, 128.04, 127.96, 127.90, 127.7 (Ph), 86.1, 80.0, 79.9, 78.0, 77.4 (C-1,2,3,4,5), 75.6, 75.2, 75.1 ($CH_2$Ph), 61.8 (C-6), 52.5 ($CO_2CH_3$); mass spectrum (FAB) *m/e* 493.2 ((M+H)$^+$, calcd 493.2).

**4.1.15. (2*R*,3*R*,4*S*,5*R*,6*R*)-Methyl 6-(azidomethyl)-3,4,5-tris(benzyloxy)-tetrahydro-2*H*-pyran-2-carboxylate (23).** To a solution of **22** (7.60 g, 15.4 mmol) in $CH_2Cl_2$ (100 mL) was added TsCl (5.94 g, 31.7 mmol) and pyridine (3.74 mL, 46.2 mmol) at 0 °C under argon, and the reaction mixture was stirred for 12 h at room temperature. The solution was poured into stirred ice and water (200 mL), and immediately extracted with chloroform (2×200 mL). The combined extracts were successively washed with 0.5 N hydrochloric acid (100 mL), water (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was used for the next coupling reaction without further purification. Sodium azido (2.03 g, 31.7 mmol) was added to the residue (prepared from 15.4 mmol of **22**) in DMF (50 mL) at room temperature under Ar, and the reaction mixture was stirred for 12 h at 60 °C. The reaction mixture was diluted with EtOAc (300 mL) and washed successively with water (300 mL), saturated aqueous $NaHCO_3$ (300 mL), and brine (300 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (5:1 to 3:1 hexane/EtOAc) to give **23** (6.50 g, 12.6 mmol; 81% overall) as white needles, mp 76–77 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36–7.19 (m, 15H, Ph), 4.95–4.77 (m, 4H, C$H_2$Ph), 4.62 (d, 1H, *J*=9.3 Hz, C$H_2$Ph), 3.95 (d, 1H, *J*=9.5 Hz, H-1), 3.84 (t, 1H, *J*=8.6 Hz, H-3), 3.77–3.71 (t, 1H, *J*=8.1 Hz, H-4), 3.61–3.48 (m, 2H, H-6a, 6b), 3.33 (dd, 1H, *J*=5.5, 13.6 Hz, H-2); $^{13}$C NMR (72.5 MHz, $CDCl_3$): $\delta$ 169.2 ($CO_2CH_3$), 138.3, 137.80, 137.75 (*C*Ph), 128.54, 128.50, 128.44, 128.04, 128.00, 127.9, 127.8, 127.5 (Ph), 86.1, 79.9, 78.7, 78.1 (C-1,2,3,4,5), 75.6, 75.2, 75.1 ($CH_2$Ph), 52.4 ($CO_2CH_3$), 51.1 (C-6); mass spectrum (FAB) *m/e* 490.2 ((M−$N_2$+H)$^+$, calcd 490.2).

**4.1.16. (2*R*,3*R*,4*S*,5*R*,6*R*)-6-(Azidomethyl)-3,4,5-tris(benzyloxy)-tetrahydro-2*H*-pyran-2-carboxylic acid (24).** To the solution of **23** (4.40 g, 8.50 mmol) in MeOH/THF/$H_2O$ (3:3:1) was added LiOH·$H_2O$ (713 mg, 17.0 mmol), and the reaction mixture was stirred at room temperature for 12 h. The solution was evaporated and the residue was chromatographed on silica gel (10:1 EtOAc/MeOH) to afford **24** (3.51 g, 6.97 mmol; 82%) as a white powder, mp 68–70 °C; $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 7.35–7.07 (m, 15H, Ph), 4.8–4.53 (m, 12H, C$H_2$Ph), 3.85–3.64 (m, 3H), 3.58–3.31 (m, 4H); $^{13}$C NMR (72.5 MHz, $CD_3OD$): $\delta$ 138.9, 137.8, 138.4 (*C*Ph), 129.0, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2 (Ph), 86.6, 82.2, 81.1, 78.4, 76.0, 75.5, 75.3; mass spectrum (FAB) *m/e* 526.2 ((M+Na)$^+$, calcd 526.2).

**4.1.17. (2*R*,3*R*,4*S*,5*R*,6*R*)-6-(*tert*-Butoxycarbonylaminomethyl)-3,4,5-tris(benzyloxy)-tetrahydro-2*H*-pyran-2-carboxylic acid (25).** A mixture of **24** (3.51 g, 6.97 mmol) and Lindlar catalyst (2.0 g) in MeOH (100 mL) was stirred in an $H_2$ atmosphere at room temperature for 3 h, and then filtered through Celite. The filtrate was evaporated, then the resin was dissolved in MeOH/$H_2O$ (3:1). To the solution were added LiOH·$H_2O$ (585 mg, 13.9 mmol) and $BOC_2O$ (2.35 g, 10.5 mmol), and the reaction mixture was stirred at room temperature for 12 h. The solution was evaporated and the residue was chromatographed on silica gel (10:1 EtOAc/MeOH) to give **25** (2.17 g, 3.76 mmol; 54% overall) as white needles, mp 110–112 °C; $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 7.34–7.22 (m, 15H, Ph), 4.87 (d, 1H, *J*=11.3 Hz, C$H_2$Ph), 4.83 (d, 1H, *J*=13.2 Hz, C$H_2$Ph), 4.78 (d, 1H, *J*=3.9 Hz, C$H_2$Ph), 4.75 (d, 1H, *J*=2.5 Hz, C$H_2$Ph), 4.66 (d, 1H, *J*=9.9 Hz, C$H_2$Ph), 4.62 (d, 1H, *J*=10.1 Hz, C$H_2$Ph), 3.78 (t, 1H, *J*=4.8 Hz, H-3), 3.71–3.62 (m, 2H, H-1, 4), 3.54 (dd, 1H, *J*=3.8, 13.9 Hz, H-6a), 3.47–3.29 (m, 3H, H-2, 5, 6b), 1.45 (s, 9H, $NHCO_2tBu$); $^{13}$C NMR (72.5 MHz, $CD_3OD$): $\delta$ 172.5 (C-1), 166.5 (NH*C*O), 154.7 (NHO*C*O*t*Bu), 138.3, 137.78, 137.66, 135.6 (*C*Ph), 129.2, 128.7, 128.5, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4 (Ph); mass spectrum (FAB) *m/e* 600.3 ((M+Na)$^+$, calcd 600.3), 478.2 ((M−Boc+2H)$^+$, calcd 478.2).

**4.1.18. (*S*)-Methyl 2-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(*tert*-butoxycarbonylaminomethyl)-tetrahydro-2*H*-pyran-2-carboxamido)-3-phenylpropanoate (26).** DEPC (339 μL, 1.93 mmol) was added to a cooled solution of **25** (800 mg, 1.38 mmol), L-phenylalanine methyl ester (358 mg, 1.67 mmol), and $Et_3N$ (579 μL, 4.15 mmol) in DMF (10 mL) at 0 °C under Ar, and the mixture was stirred for 1 h at 0 °C, and then for an additional 12 h at room temperature. The reaction mixture was diluted with EtOAc (200 mL), and successively washed with water (200 mL), saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (toluene/EtOAc 5:1) to give **26** (941 mg, 1.27 mmol; 92% yield) as a white powder, mp 111–115 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.31–7.23 (m, 18H, Ph), 7.10 (2H, Ph), 6.57 (d, 1H, *J*=7.5 Hz, NH), 4.92–4.77 (m, 4H, C$H_2$Ph), 4.67–4.56 (m, 3H, C$H_2$Ph, C*H*$CO_2CH_3$), 3.80 (d, 1H, *J*=9.0 Hz, H-1), 3.73–3.53 (m, 7H, H-3, 4, 6a, 6b, $CO_2CH_3$), 3.41–3.31 (m, 2H, H-2, 5), 3.25 (1H, NH), 3.15 (dd, 1H, *J*=5.8, 14.0 Hz, C$H_2$Ph of L-Phe), 3.10 (dd, 1H, *J*=6.2, 14.0 Hz, C$H_2$Ph of L-Phe), 1.47 (s, 9H, $NHCO_2tBu$); $^{13}$C NMR (72.5 MHz, $CDCl_3$): $\delta$ 171.6, 168.3, 155.7 (C-1,

CO), 138.3, 137.78, 137.66, 135.6 (*C*Ph), 129.2, 128.7, 128.5, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4 (Ph), 85.7, 80.4, 79.5, 78.5, 77.9, 75.5 (C-2,3,4,5,6,7), 75.0 ($CH_2$Ph), 52.6 ($CHCO_2CH_3$ of L-Phe), 52.3 ($CO_2CH_3$ of L-Phe), 37.4 ($CH_2$Ph of L-Phe), 28.4 (*t*-Bu); mass spectrum (FAB) *m/e* 761.3 ($(M+Na)^+$, calcd 761.4), 739.3 ($(M+H)^+$, calcd 739.4), 639.2 ($(M-Boc+2H)^+$, calcd 639.3).

**4.1.19. β(1→6)-Linked dimer (28).** A solution of 4 N HCl in EtOAc (30 mL) was added to a stirred solution of compound **26** (864 mg, 1.17 mmol) in EtOAc (30 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was washed with ether to give **27** as a white powder. This compound was used without further purification. Compound **27**, DEPC (292 μL, 1.75 mmol), and $Et_3N$ (498 μL, 3.51 mmol) were added to a solution of compound **25** (826 mg, 1.43 mmol) in DMF (20 mL) at room temperature under argon. The reaction mixture was stirred at room temperature for 16 h, then diluted with EtOAc (200 mL), and successively washed with water, saturated aqueous $NaHCO_3$, and brine (150 mL each). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated and the residue was chromatographed on silica gel using toluene/EtOAc 5:1–1:1 to afford **28** (1.24 g, 1.05 mmol; 90%) as a white powder, mp 128–131 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.32–7.16 (m, 33H, Ph), 7.08 (m, 2H, Ph), 6.88 (d, 1H, *J*=6.9 Hz, NH), 6.44 (1H, NH), 4.93–4.61 (m, 13H, C$H_2$Ph, C$H$CO$_2$CH$_3$), 3.74–3.63 (m, 10H), 3.48–3.33 (m, 7H), 3.07 (2H, C$H_2$Ph of L-Phe), 1.43 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): δ 171.8 (C-1), 168.8, 168.2 (NH*C*O), 156.0 (NH*C*O*t*Bu), 138.3, 138.2, 137.91, 137.86, 137.79, 137.6, 135.8 (*C*Ph), 129.2, 128.6, 128.5, 128.4, 128.33, 128.27, 128.13, 128.08, 128.0, 127.9, 127.8, 127.7, 127.2 (Ph), 85.7, 85.5, 80.3, 79.7, 79.4, 78.7, 78.2, 77.2, 75.4, 75.0, 74.8, 53.0 (*C*HCO$_2$CH$_3$ of L-Phe), 52.3 (CO$_2$*C*H$_3$ of L-Phe), 37.6 (*C*H$_2$Ph of L-Phe), 28.2 (*t*-Bu); mass spectrum (FAB) *m/e* 1198.7 ($(M+Na)^+$, calcd 1198.6), 1098.6 ($(M-Boc+2H)^+$, calcd 1098.6).

**4.1.20. β(1→6)-Linked trimer (30).** As described for **28**, deprotection of the Boc group of compound **28** (1.2 g, 1.00 mmol) with 4 N HCl in EtOAc (30 mL) followed by treatment with DEPC (248 μL, 1.50 mmol), $Et_3N$ (424 μL, 3.00 mmol) and compound **25** (702 mg, 1.22 mmol) in DMF (20 mL) at room temperature under argon gave **30** (1.40 g, 8.52 mmol; 85%) as a white powder, mp 156–158 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.32–7.17 (m, 48H, Ph), 7.04 (m, 2H, Ph), 6.95 (d, 1H, *J*=6.9 Hz, NH), 6.75 (2H, NH), 4.96–4.60 (m, 19H, C$H_2$Ph, C$H$CO$_2$CH$_3$), 3.74–3.54 (m, 15H), 3.45–3.30 (m, 9H), 3.02 (2H, C$H_2$Ph of L-Phe), 1.41 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): δ 171.6 (C-1), 169.0, 168.8, 168.2 (NH*C*O), 156.0 (NH*C*O*t*Bu), 138.3, 138.2, 137.9, 137.8, 137.7, 135.8 (*C*Ph), 129.2, 129.0, 128.6, 128.5, 128.4, 128.33, 128.29, 128.2, 128.0, 127.79, 127.75, 127.69, 127.2 (Ph), 85.7, 85.6, 85.5, 80.1, 79.7, 79.3, 78.6, 78.4, 78.2, 78.1, 77.8, 77.3, 75.5, 75.3, 74.9, 74.8, 53.1 (*C*HCO$_2$CH$_3$ of L-Phe), 52.3 (CO$_2$*C*H$_3$ of L-Phe), 37.6 (*C*H$_2$Ph of L-Phe), 28.4 (*t*-Bu); mass spectrum (FAB) *m/e* 1681.0 ($(M+H+Na)^+$, calcd 1681), 1558.8 ($(M-Boc+3H)^+$, calcd 1558.7).

**4.1.21. β(1→6)-Linked tetramer (32).** As described for **28**, 4 N HCl in EtOAc (30 mL) was added to a stirred solution of compound **30** (581 mg, 350 μmol) in EtOAc (10 mL), followed by treatment with DEPC (86.5 μL, 526 μmol), $Et_3N$ (148 μL, 1.05 mmol), and compound **25** (245 mg, 424 μmol) in DMF (10 mL) at room temperature under argon to give **32** (600 mg, 283 μmol; 81%) as a white powder, mp 165–167 °C; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.29–7.17 (m, 60H, Ph), 7.08–7.00 (m, 5H, Ph), 6.77, 6.71, 6.42 (br s, 3H, NH), 5.02–4.57 (m, 25H, C$H_2$Ph, C$H$CO$_2$CH$_3$), 3.86–3.52 (m, 19H), 3.47–3.27 (m, 12H), 3.07 (2H, C$H_2$Ph of L-Phe), 1.39 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): δ 171.8 (C-1), 169.22, 169.16, 168.9, 168.2 (NH*C*O), 156.1 (NH*C*O*t*Bu), 138.4, 138.2, 138.1, 138.0, 137.9, 137.83, 137.78, 137.5, 135.8 (*C*Ph), 129.2, 128.51, 128.46, 128.4, 128.3, 128.2, 128.11, 128.08, 128.00, 127.9, 127.8, 127.74, 127.69, 127.62, 127.1 (Ph), 86.1, 85.8, 85.7, 85.4, 80.6, 80.1, 79.8, 79.4, 79.2, 78.9, 78.6, 78.3, 78.1, 78.0, 77.5, 77.2, 77.0, 76.8, 76.6, 75.6, 75.4, 75.21, 75.16, 75.0, 74.8, 74.7, 53.3 (*C*HCO$_2$CH$_3$ of L-Phe), 52.2 (CO$_2$*C*H$_3$ of L-Phe), 37.8 (*C*H$_2$Ph of L-Phe), 28.4 (*t*-Bu); mass spectrum (FAB) *m/e* 2117.8 ($(M+2H)^+$, calcd 2118.0), 2017.7 ($(M-Boc+3H)^+$, calcd 2017.9).

**4.1.22. β(1→6)-Linked tetramer (4).** A mixture of **32** (300 mg, 142 μL) and 20% $Pd(OH)_2$/C (400 mg) in MeOH (20 mL), THF (20 mL), and $H_2O$ (4 mL) was stirred in an atmosphere of $H_2$ at 20 °C for 12 h, and then filtered through Celite, and concentrated in vacuo. The residue was chromatographed on Sephadex G-25 ($H_2O$) followed by lyophilization to give **4** (126 mg, 122 μmol; 86%) as a white powder: $^1$H NMR (300 MHz, $D_2O$): δ 7.23–7.11 (m, 5H), 4.60 (m, 1H, C$H$CO$_2$CH$_3$), 3.74–3.07 (m, 31H), 2.95 (C$H_2$Ph of L-Phe), 1.29 (s, 9H, NHCO$_2$*tBu*); $^{13}$C NMR (72.5 MHz, $CDCl_3$): δ 172.5 (CO), 129.7, 129.0, 127.5 (Ph), 28.6 (*t*-Bu); mass spectrum (FAB) *m/e* 1036.4 ($(M-H)^+$ calcd 1036.4), 936.4 ($(M-Boc+H)^+$, calcd 936.4).

**4.1.23. Sulfated compounds 18 and 33.** O-Sulfation of the oligomers was performed based on the published procedure.[21] A mixture of the tetramer **1** or **4** and a large excess of $SO_3 \cdot NMe_3$ (10 equiv per free OH groups) in DMF was stirred at 50 °C for 5 days, and cooled. Saturated aqueous $Ba(OH)_2$ solution was added to the reaction mixture until it became slightly basic (pH 8.0 judged by a pH paper). The formed white precipitate was removed by centrifugation with microcentrifuge (Eppendorf Centrifuge 5415C) at 13×1000 cpm for 10 min. The clear supernatant was collected and was passed through a column of Dowex 50W-X8 $[Na]^+$(1×5 cm), and then eluted with water. The eluate was collected and concentrated in vacuo. The residue was chromatographed, for desalting, on a column of Sephadex G-15 (1×65 cm), and then eluted with water. Each fraction was examined with an Azure assay and the positive fractions were pooled and concentrated in vacuo. The residue was lyophilized from water (10 mL) and NMR was taken. If the reaction was completed, only single peak corresponding to the methyl ester was observed. (If not, several peaks for the methyl ester were observed.)

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## References and notes


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