ELSEVIER

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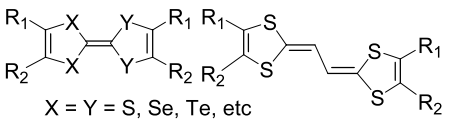
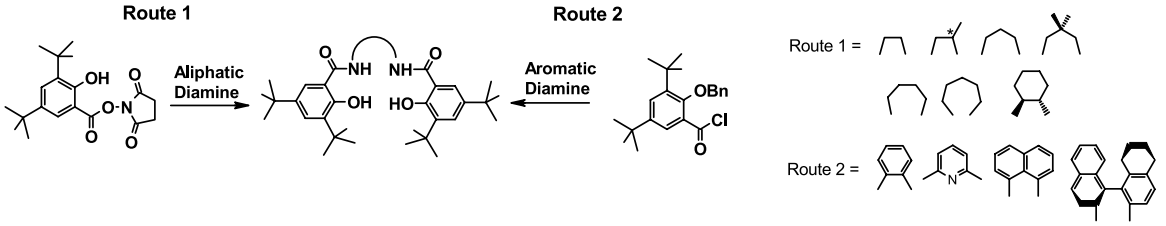
Contents

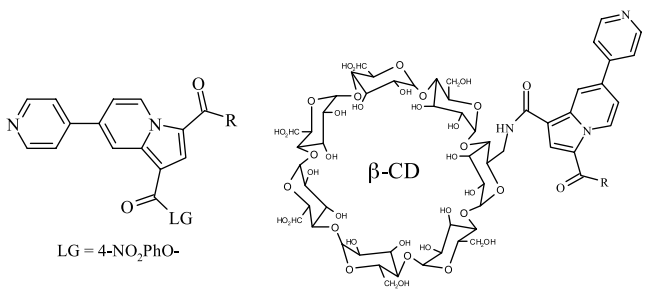
REPORT

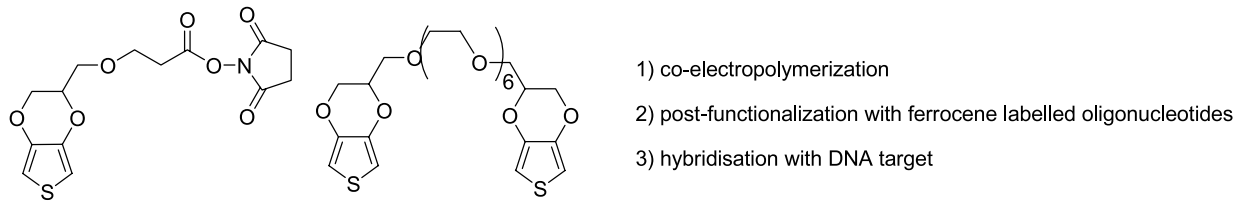


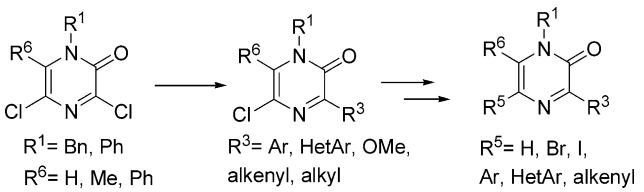
The synthesis and applications of tetrathiafulvalenes and related analogues as electroactive organic materials are reviewed.

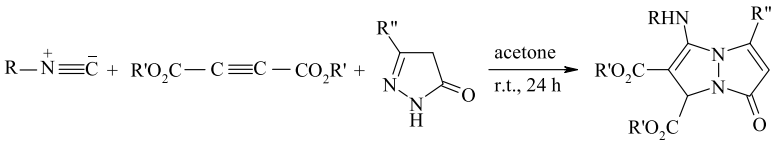
ARTICLES

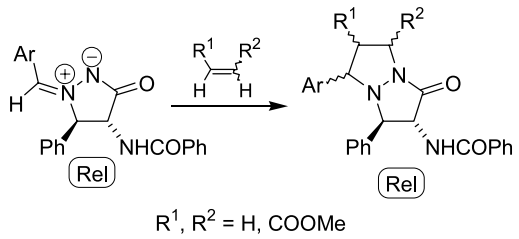


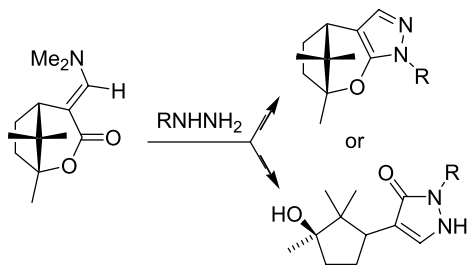


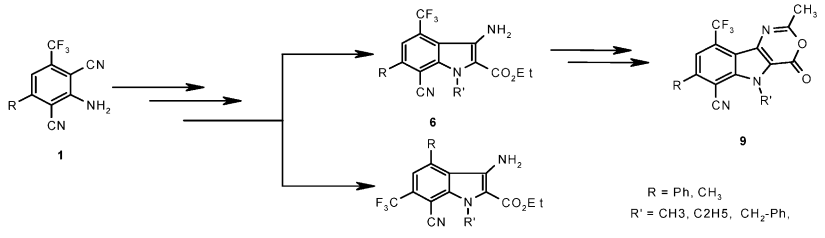


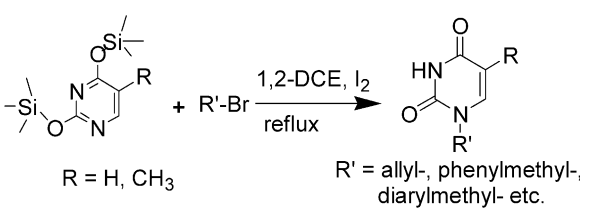




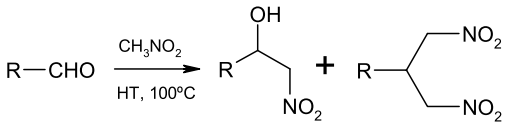




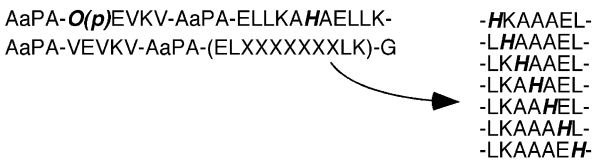


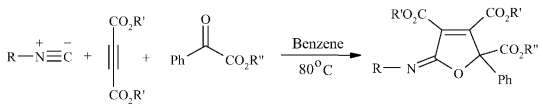


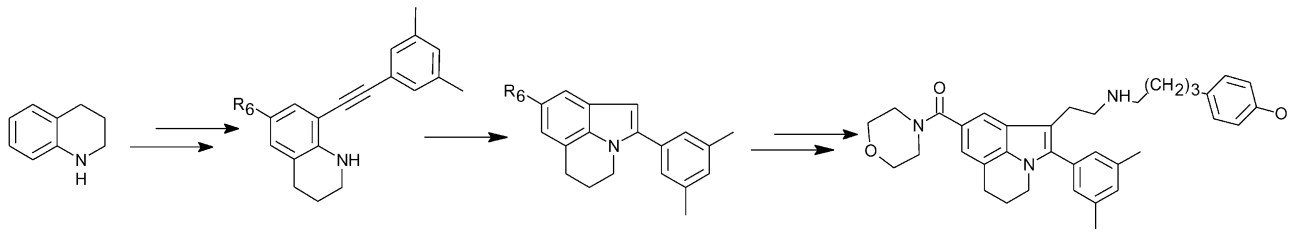
2,4-Bis(trimethylsiloxy)pyrimidines with allyl bromides, primary and secondary aryl alkyl and diaryl methyl halides undergo regioselective substitution at N-1 to provide respective 1-substituted-uracil/thymine derivatives.

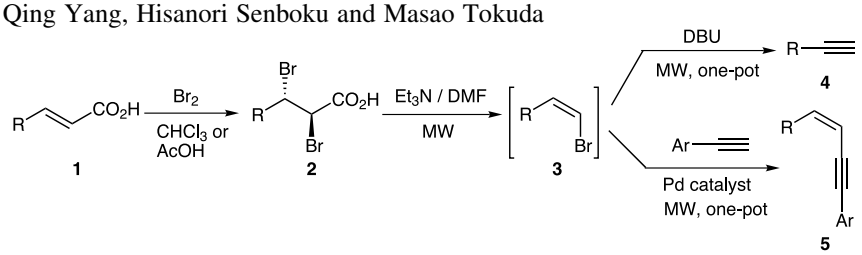


The reaction of aldehydes with nitromethane in the presence of Mg:Al 2:1 hydrotalcite at higher temperature yielded the formation of the nitroaldol product and 1,3-dinitropropane. A novel mechanism is proposed.

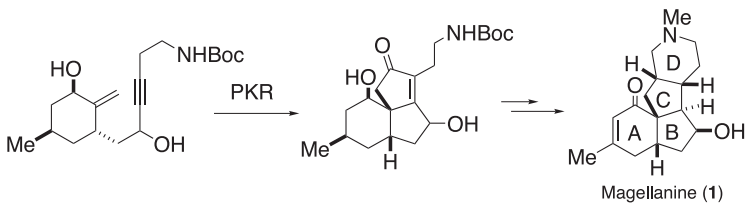


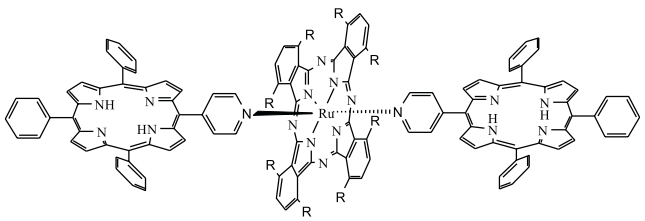


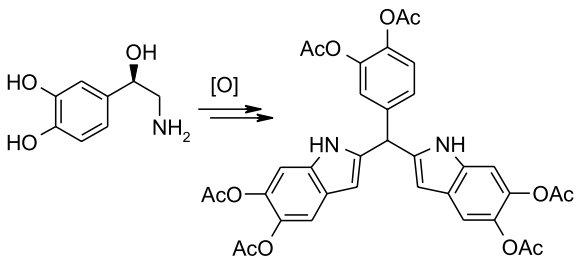


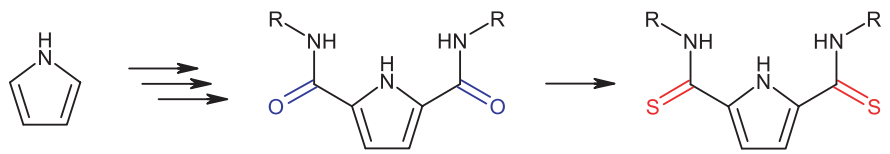


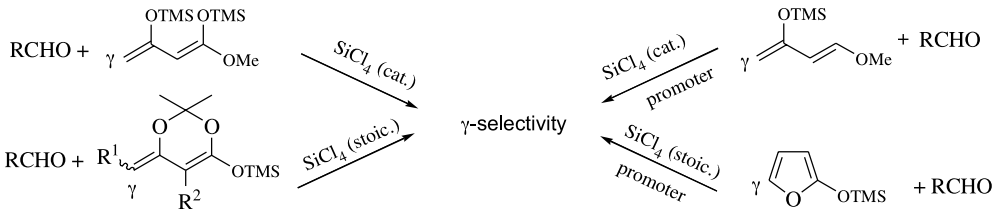
(*Z*)-1-Bromo-1-alkenes were stereoselectively prepared in high yields in a short reaction time by microwave irradiation of the corresponding *anti*-2,3-dibromoalkanoic acids in a Et_3N/DMF system. A one-pot synthesis of terminal alkynes and enynes from *anti*-2,3-dibromoalkanoic acids were also developed by microwave-induced reaction.

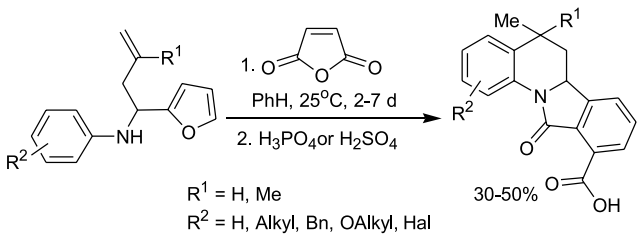


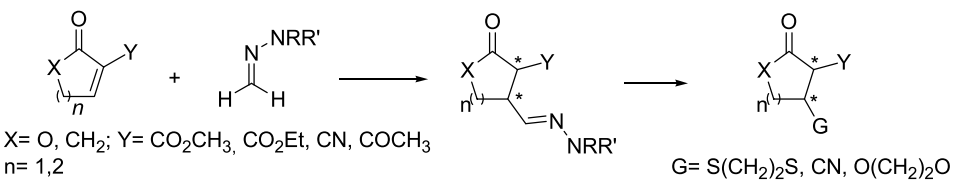


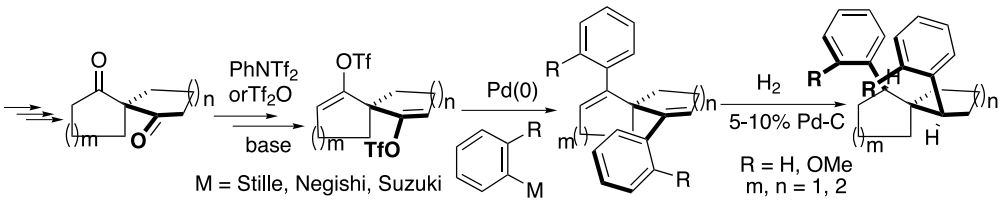


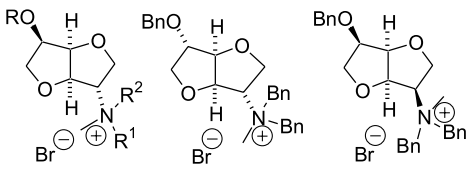


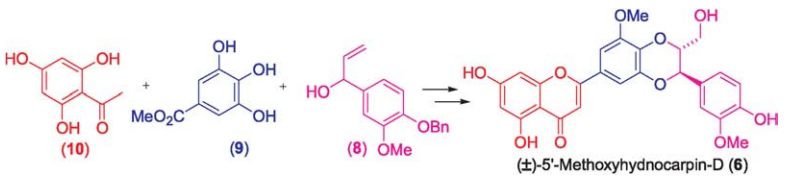


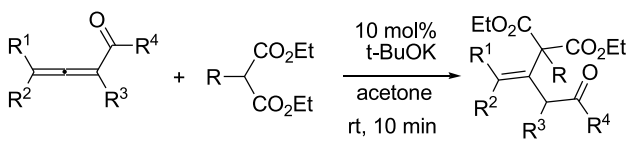


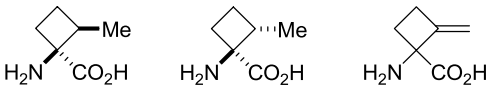












OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Complementary syntheses of 1,4,8,11,15,18,22,25-octakis(alkyl) substituted ruthenium phthalocyanines, in which either one or two axial ligands can be added, have been developed. The chemistry is sufficiently robust and efficient to permit elaborate, supramolecular complexes to be prepared, as demonstrated by the synthesis of porphyrin-phthalocyanine multichromophore arrays. *Tetrahedron* **2005**, *61*, 4067–4074.

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Synthesis and applications of tetrathiafulvalenes and ferrocene-tetrathiafulvalenes and related compounds

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Contents

Keywords: 1,3-Dithiole ring; Ferrocene; Coulombic repulsion; Electron donors; Tetrathiafulvalenes; CT-complexes; Superconductors.
Abbreviations: BEDT-TTF, bisethylendithia-tetrathiafulvalene; BMT-TTF, bismethylthio-tetrathiafulvalene; CT, charge-transfer; CV, cyclic voltammetry; DT, 1,3-dithiole ring; ODCB, *o*-dichlorobenzene; DT-DAF, dithiadiazafulvalenes; DEAD, diethyl azadicarboxylate; DF-TTF, difurotetrathiafulvalene; DDQ, dichlorodicyanoquinone; F-TTF, furotetrathiafulvalene; DAF-DT-TTF, diazafluorene-dithia-tetrathiafulvalene; DS-DTF, diselenadithiafulvalenes; DS-DAF, diselenadiazafulvalene; DB-TAF, dibenzo-tetraazafulvalenes; DBTOF, dibenzotetraoxafulvalenes; DNTOF, dinaphthotetraoxafulvalenes; DBOTF, dibenzodioxa-dithiafulvalenes; DB-TTeF, dibenzo-tetratellurafulvalenes; DB-TSF, dibenzo-tetraselenafulvalenes; ICT, intramolecular charge transfer; LDA, lithium diisopropylamide; NLO, nonlinear optical materials; PROXYL, 3,4-diiodmethyl-2,2,5,5-tetramethylpyrrolidin-1-yloxyl radical; SAM, self assembled monolayer; SCE, saturated calomel electrode; TMEDA, tetramethylethylidenediamine; TMTTF, tetramethyltetrathiafulvalene; TTF, tetrathiafulvalene; TTP, tetrathiapentalene; TBAF, tetrabutylammonium fluoride; TSF, tetraselenafulvalene; TAF, tetraazafulvalenes; THF, tetrahydrofuran; TCNQ, 7,7,8,8-tetracyano-*p*-quinodimethane; TCNAQ, 9,10-tetracyanoanthraquinodimethane.
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1. Introduction

In the last two decades, new materials based on the versatile 1,3-dithiole ring (DT) have been developed. The fundamental DT building block possesses several intrinsic molecular properties that make it attractive to the synthetic chemist as well as to the physical chemist. The 1,3-dithiole ring is considered to be the main part of dithiafulvalene (DTF) or tetrathiafulvalene (TTF) which could be named as five-membered rings similar to 1,3-selenathiole or 1,3-diselenole (Chart 1).

Although in recent years several chemical modifications have been carried out on the TTF unit to prepare building blocks for macro- and supramolecular chemistry at the molecular level, the chemical modifications carried out on the TTF skeleton are aimed at increasing the electrical conductivity.[1a] There are several ways in which the basic TTF framework can be modified to give new functionalized π-donor systems useful for specific applications. Following the first report of the synthesis of TTF in 1970,[1] the main

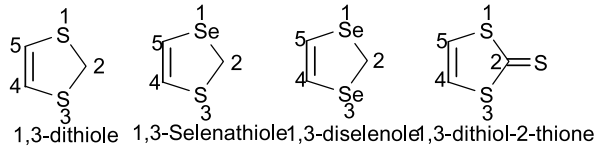
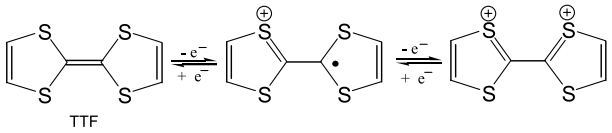


Chart 1.

direction of efforts in the area of DT-based donors was towards centrosymmetric TTF derivatives substituted in the 2,3 and 6,7 positions, and subsequently towards selenium and tellurium analogues of TTF.

The oxidation potentials of TTF are established from cyclic voltammetry (CV) and are relatively low. For TTF, the reported half-wave potentials are $E^1_{1/2} = 0.37$ V and $E^2_{1/2} = 0.67$ V in dichloromethane CH_2Cl_2 vs a saturated calomel electrode (SCE)[1e] (Scheme 1).



Scheme 1.

Organic superconductors are considered as part of the organic conductor family, which includes; molecular salts, polymers and pure carbon systems such as carbon nanotubes and C_{60} compounds. The molecular salts within this family are large organic molecules that exhibit superconductivity properties at very low temperatures. For this reason, they are often referred to as 'molecular' superconductors.

About 50 organic superconductors have since been found with T_cs extending from 0.4 to near 12 K at ambient pressure. Since these T_cs are in the range of Type 1 superconductors, engineers have yet to find a practical application for them. Their rather unusual properties, however, have made them the focus of intense research. Organic superconductors are composed of an electron donor such as a tetrathiafulvalene and an electron acceptor.

Ferrocene is one of the simplest organometallic molecules. It has a sandwich structure with the iron sandwiched between two five-membered carbon rings (C_5H_5). It is named as dicyclopentadienyliron $(C_5H_5)_2Fe$ and is orange in color with a distinct smell. The discovery of ferrocene revolutionized the area of organometallic chemistry.

This review describes the classification, synthesis and applications of dithiafulvalene (DTF), tetrathiafulvalene (TTF), ferrocene-dithiafulvalene (Fc-DTF), and ferrocene-tetrathiafulvalene (Fc-TTF) derivatives and their related analogues with different substituents at the 4,5- and 4′,5′-positions in the TTF system. Precursor materials for tetrathiafulvalenes and tetraselenafulvalenes (TSFs) and their related compounds, namely 1,3-dithiole, and 1,3-diselenole derivatives and their phosphonates or phosphoranes are also described.

1.1. Dithiafulvalenes (DTFs)

The chemistry of dithiafulvalenes **1**–**3**, ferrocene **4**, thiafulvalenes incorporated into the ferrocene moiety **5** (Chart 2) and tetrathiaselenafulvalenes **6**–**9** (Chart 3) and related homologues has been intensively studied since the discovery of the first metallic charge-transfer TTF complex.[1] The high electrical conductivity of the chloride salt of TTF **6**[1] and metallic behavior in the charge-transfer

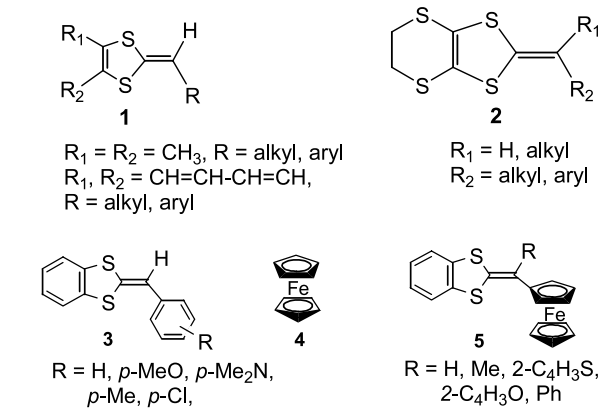


Chart 2.

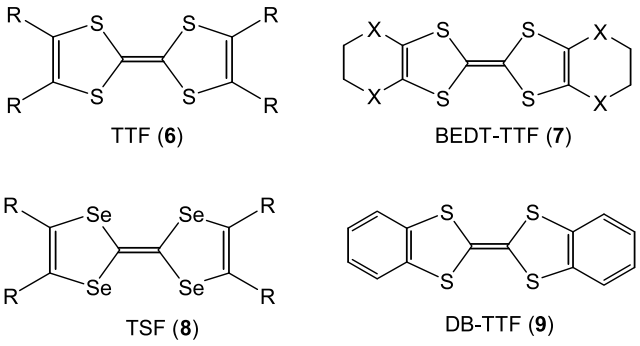


Chart 3.

complex with 7,7,8,8-tetracyano-*p*-quinodimethane (TCNQ), along with the synthesis of a huge number of TTF derivatives, have been studied.[2–4]

1.2. Tetrathiafulvalene (TTF) and its derivatives

Recently, the tetrathiafulvalenes (TTFs), (Chart 3) have become an interesting theme of organic synthesis. This is due to the high electrical conductivity and super conductor properties of these highly sophisticated compounds.[5] It was also reported that the tetrathiafulvalenes have a good π-donor ability.[6]

1.3. π-Extended tetrathiafulvalenes (ex-TTFs)

The syntheses of two dithiole rings separated by a conjugated spacer have received great attention as a consequence of their potential interest in the preparation of compounds with nonlinear optical properties or useful as semiconductors. The synthesis of derivatives and analogues of dithiafulvalene and tetrathiafulvalene is of considerable interest.[7]

It is known that the extended TTF derivatives having a *p*-quinodimethane structure (**10**–**13**, Chart 4) have been used as strong electron donors due to the extended conjugation which results in a decrease of the intramolecular on-site Coulombic repulsion[8] and for the formation of monostoichiometric complexes with acceptor molecules, on the basis of their different sizes.[9]

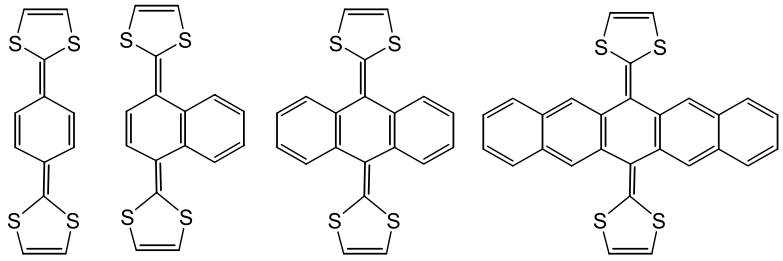


Chart 4.

In contrast to TTF **6** and its derivatives, the *p*-quinodimethane analogues of TTF form stable dication species, which form CT complexes with electrical and magnetic properties.[9,10] In spite of the interest in these π-extended *p*-quinodimethane analogues of TTF in the search for new opto-electronic properties, the synthesis of π-extended *p*-quinodimethane connected directly to a ferrocene moiety in addition to highly conjugated TTF units seems to be worthy of study.

1.4. Ferrocene-tetrathiafulvalenes (Fc-TTFs) as electron donors

Due to the structural and electrochemical properties of ferrocene-containing tetrathiafulvalene derivatives, several ferrocene-tetrathiafulvalenes **14**, **15**, (Chart 5) were constructed as donors for conducting CT complexes. The first compound belonging to this class of donor conducting materials has been reported by Ueno et al.[11] A very similar type of donor molecule has also, recently been reported by Bryce and co-workers.[12] Several CT complexes of metal bis(arene) compounds containing, among others, the familiar organic acceptor TCNQ have been prepared. Recently, Togni et al.[13] have synthesized 1,1′-disubstituted ferrocene derivatives **15** as novel donors for the preparation of CT complexes, which are structurally and electronically related to the TTFs conjugated with a ferrocene moiety. Togni[14] observed that, none of these materials has been shown to display physical properties superior to those of the metallocene systems. We described very recently the synthesis and properties of novel TTFs derivatives **15**.[14]

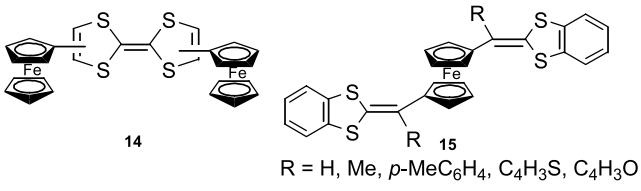


Chart 5.

Tetrathiafulvalenes have received considerable attention due to their ability to serve as electron donors in charge-transfer salts that behave as organic metals. The synthesis of tetrathiafulvalenes and tetramethyltetrathiafulvalene (TMTTF) from 1,3-dithiol-2-thione or 4,5-dimethyl-1,3-dithiol-2-thione in order to use these materials as organic conductors is of interest and the synthetic details are discussed in Section 6.[15]

2. Synthesis of phosphonate, phosphorane and thione derivatives as precursor materials

Heteroaromatic cations such as pyrilium, thiopyrilium, pyridinium, thiazolium, and dithiolium have been synthesized from the corresponding compounds **16**–**19** (Chart 6) as attractive targets of research for synthetic chemists. The preparation and use of dithiolium salts have acquired renewed interest in connection with the synthesis of tetrathiafulvalene derivatives. The synthesis of fulvalenes starting from 1,3-dithiolium salts has been reported in the literature.[16]

2.1. Synthesis of 2-dialkoxyphosphinyl-1,3-benzodithioles

2-Dimethoxyphosphinyl-1,3-benzodithiole (**19**; R=Me) was prepared from anthranilic acid in several steps by following well-established procedures.[16] 2-Methylbutoxy-1,3-benzodithiole (**20**) was obtained through four reaction steps from anthranilic acid. This method was modified by Sarhan and Izumi[16d] and 2-methylbutoxy-1,3-benzodithiole (**20**) was obtained in 77% yield. Reaction of the 2-methylbutoxy-1,3-benzodithiole (**20**) with HBF_4 in acetic anhydride gave the corresponding 1,3-benzodithiolium

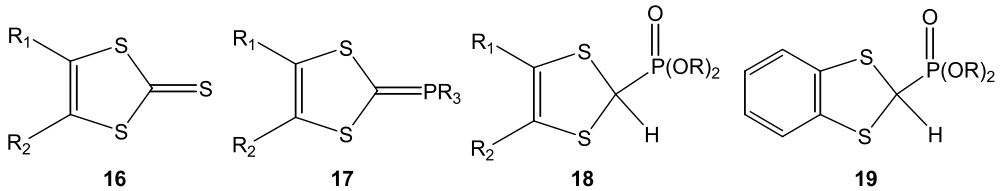
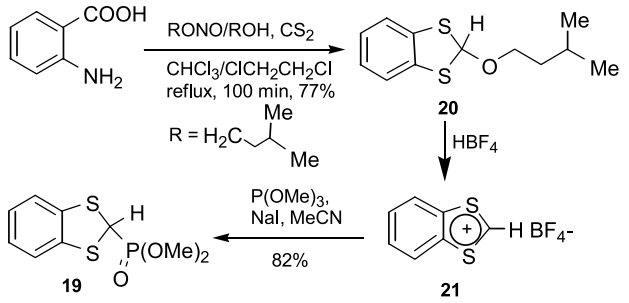


Chart 6.

fluoroborate (**21**) in good yield. Refluxing of the fluoroborate **21** with trimethyl phosphite $P(OMe)_3$ in acetonitrile in the presence of NaI afforded **19** in 82% yield, (Scheme 2).[16]



Scheme 2.

2.2. Synthesis of 4,5-dialkylthio-1,3-dithiole-2-phosphonate esters

The known thiones **22** were methylated using neat dimethyl sulphate (DMS) to yield the dithiolium cation **23**. Reduction of the cationic salt **23** with sodium borohydride gave the thioether derivative **24**, which, on treatment with acetic anhydride, followed by the addition of tetrafluoroboric acid, gave the dithiolium cation salt **25** as a white solid. Salt **25** reacted with trimethyl phosphite to afford the phosphonate ester **26** in high yield (Scheme 3).[17]

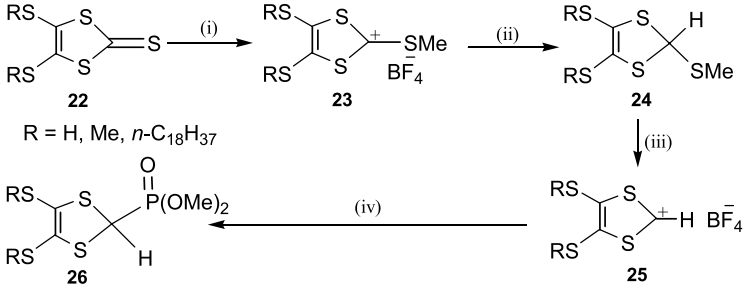
2.3. Synthesis of phosphoranes

Methylation of 1,3-dithiole-2-thione **27** using dimethyl sulphate (DMS) gave the tetrafluoroborate salt **28**. The cation **28** was reduced by sodium borohydride to give the thioether derivative **29**. Conversion of compound **29** into the cationic salt **30** occurred readily upon treatment with acetic anhydride followed by the addition of tetrafluoroboric acid. The corresponding phosphonium salt **31** was obtained from the cation **30** on treatment with triphenylphosphine (PPh_3). The generation of the phosphorane derivative **32** from **31** proceeded smoothly under basic conditions (Et_3N) in tetrahydrofuran as the solvent (Scheme 4).[18]

Phosphoranes were obtained via modification of the method reported in the literature by Cava et al.[19] Treatment of the carbon disulfide-tributylphosphine adduct with dimethyl acetylene-dicarboxylate **33** and fluoroboric acid at −65 °C gave the phosphorane **17**, which was trapped by protonation and the resulting cation **34** was isolated in 72% yield (Scheme 5).

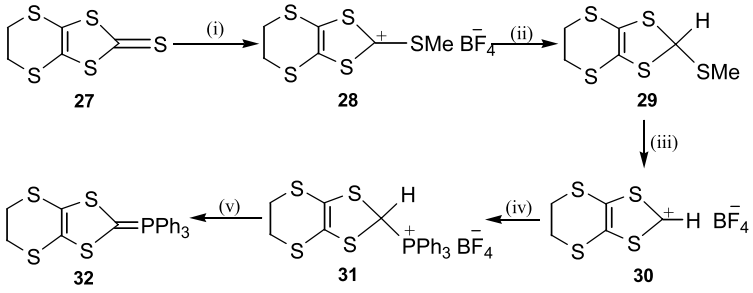
2.4. Synthesis of 1,3-dithiol-2-thione derivatives

The synthetic strategy described by Benitez and Grunwell[20a] for the preparation of 1,3-dithiol-2-thione derivatives was adapted for compound **16a** (R=H) and **16b** (R=COOMe) as shown in Scheme 6. Treatment of phenylacetylene or its related ester with carbon disulfide at 140 °C using an autoclave in the presence of bis-morpholine disulfide gave the corresponding 1,3-dithiole-2-thione derivatives **16a**,**b**, in low yield, respectively.[20b]



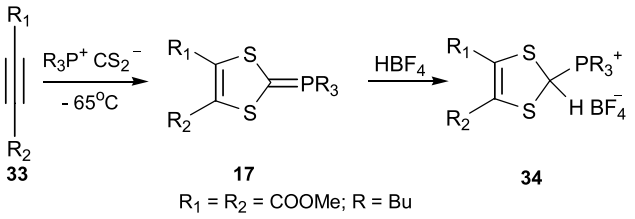
(i) DMS, 100°C, 1 h, then HBF_4-Et_2O, 0°C, 1 h. (ii) $NaBH_4$/EtOH, 20°C, 3 h.
(iii) Ac_2O, HBF_4-Et_2O, Et_2O, - 5°C, 1 h. (iv) $P(OMe)_3$, NaI, MeCN, 20°C, 2 h.

Scheme 3.

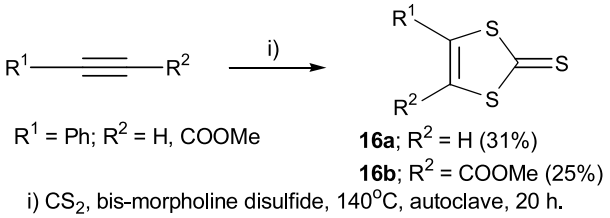


(i) DMS, 95-100°C, 30 min, 2. AcOH, 0°C, 10 min, 3. HBF_4, 0°C, 10 min, 90%.
(ii) $NaBH_4$/EtOH, 0°C - 20°C, 2 h, 95%. (iii) Ac_2O, 0°C, HBF_4, 0°C, 15 min, 90%.
(iv) PPh_3/MeCN, 20°C, 2 h, 95%. (v) Et_3N /THF, - 78°C, 30 min, 2 h.

Scheme 4.



Scheme 5.



Scheme 6.

2.5. Synthesis of 1,3-dithiol/diselenol-2-thione/selenone derivatives

Otsubo et al.[21] have reported that the synthesis of a number of 1,3-dithiol/diselenol-2-thione/selenone derivatives **37** proceeded upon treatment of 2-(3-butynyl-oxy)tetrahydro-2*H*-pyran **35** with *n*-butyllithium (*n*-BuLi) at −70 °C in THF to generate the intermediate **36**, which was successively reacted with elemental selenium at −70 °C and carbon diselenide at −90 °C. The resulting vinyl anion was quenched by the addition of ethyl (or methyl)thiocyanate to give the corresponding 1,3-diselenol-2-selenone derivative **37a** (X=Y=Se, R=SEt) in 80% yield. Successive one-pot treatment of the lithium acetylide with selenium, then CS_2, and finally ethyl thiocyanate gave the hybrid 1,3-thiaselenol-2-thione **37b** (X=Se, Y=S, R=Se) in 95% yield. Similarly, a successive treatment with sulfur, carbon diselenide, and methyl thiocyanate afforded the 1,3-thiaselenol-2-selenone **37c**. Quenching of the intermediate **36** with selenium and methyl iodide instead of alkylthiocyanate afforded the corresponding methylseleno derivatives of 1,3-thiaselenole **37d** and **37e** respectively, (Scheme 7).

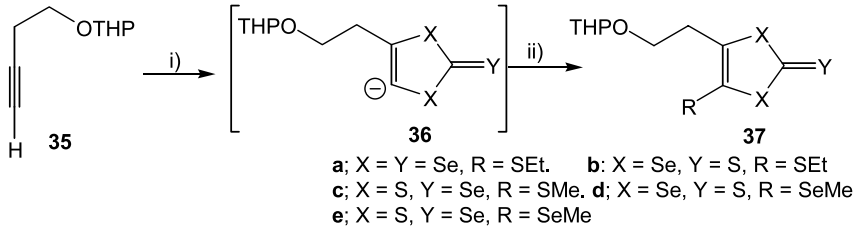
2.6. Synthesis of 4,5-ethylenedioxy-1,3-dithiol-2-thione

Reaction of 2,3-dichloro-1,4-diox-2-ene **38** with sodium dimethyldithiocarbamate afforded the bis(dithiocarbamate) **39** in good yield and refluxing **39** in toluene gave **40** in 95% yield. Bromination of **40** in CH_2Cl_2 produced the bromide derivative **41**, which on dehydrobromination under reduced pressure at 110 °C afforded **42** in quantitative yield. The reaction of **42** with sodium hydrogen sulfide in an ethanol/acetic acid mixture gave the thione **43** in 73% yield (Scheme 8).[22,23]

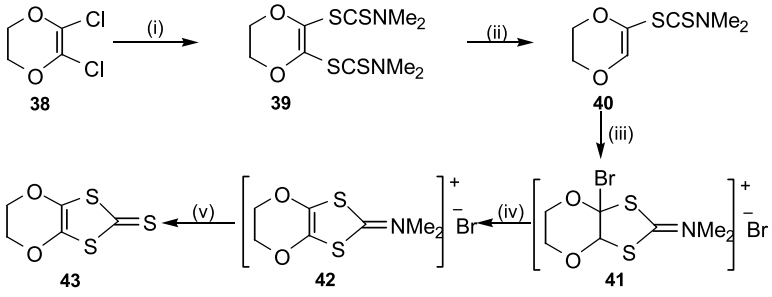
2.7. Synthesis of tetrathiapentalene and related derivatives

Several derivatives of 1,3,4,6-tetrathiapentalene **44**, 1,3-diselenol-2-selenones **45**,[24] and 1,3-dithiol-2-diethoxyphosphonate esters **46**[25] (Chart 7) were synthesized using different methods. The synthesis and reactions of these compounds were reviewed by Narita and Pittman,[26] Krief,[27] and Fanghanel et al.[28,29]

Treatment of 1,3-dithiole-2-one **47** with sodium methoxide, and then with α,α-dichloromethyl methyl ether afforded **48**.



Scheme 7.



Scheme 8.

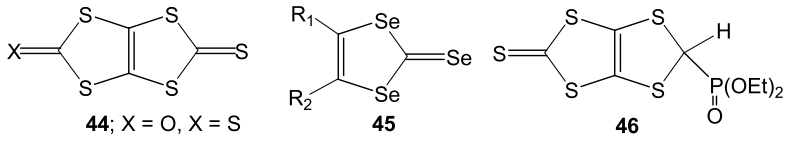
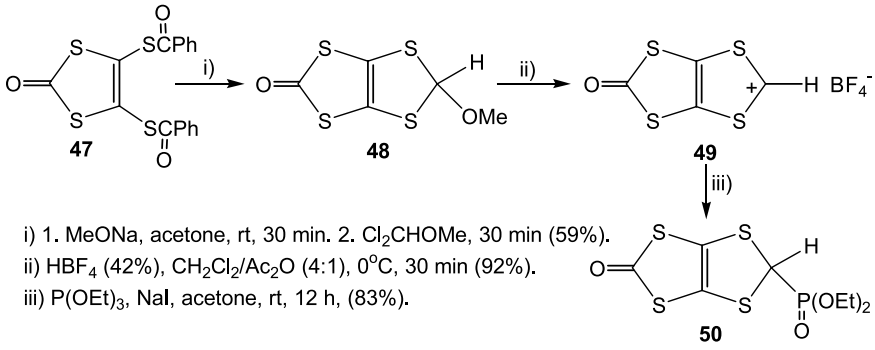


Chart 7.



Scheme 9.

This one-pot reaction was carried out in acetone to avoid the reaction of α,α-dichloromethyl methyl ether with solvents like methanol. The reaction of **48** with aqueous hydrofluoroboric acid gave the corresponding 1,3-dithiolium salt **49**, which was converted into a phosphonate **50** by treatment with triethyl phosphite in the presence of sodium iodide (Scheme 9).[25]

3. Synthesis of dithiafulvalenes and related analogues

A number of dithiafulvalenes **1** and **2** (Chart 8) were prepared from the reaction of phosphonate esters **18**, **19** phosphoranes **17**, **32** and or 1,3-dithiol-2-thione derivatives **16** with different mono carbonyl compounds in moderate to high yields by adopting the well-established Wittig–Horner procedures.[16]

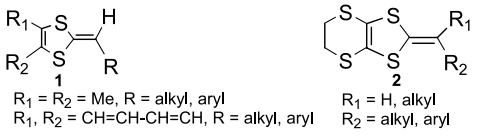
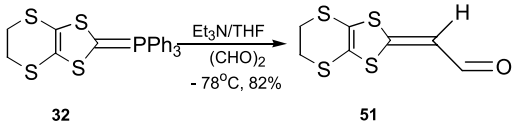


Chart 8.

3.1. From reaction of glyoxal with phosphonate or phosphorane derivatives

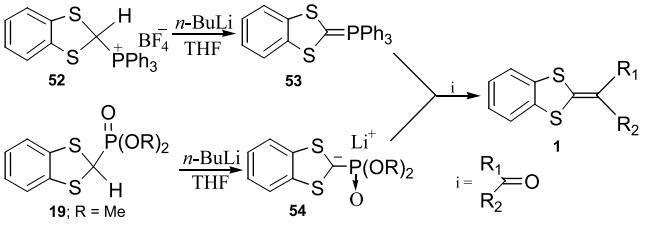
Aqueous glyoxal with phosphorane **32** underwent a Wittig reaction to give the corresponding dithiafulvalene **51**, in 82% yield, which is considered as potential precursor to vinylogous BEDT-TTF systems (Scheme 10).[18]



Scheme 10.

3.2. From carbonyl compounds

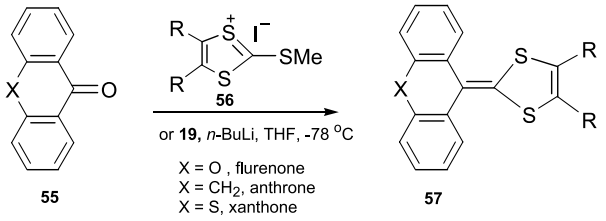
The reaction of 2-triphenylphosphino-1,3-benzodithiole tetrafluoroborate **52** or benzo-1,3-dithiole-2-phosphonate **19** (R=Me) with *n*-butyllithium in THF at −78 °C gave phosphorane **53** or phosphonate carbanion **54**. The reaction of **53** or **54** with a wide variety of carbonyl compounds afforded the corresponding dithiafulvalenes **1** in very good yields (Scheme 11).[16,30]



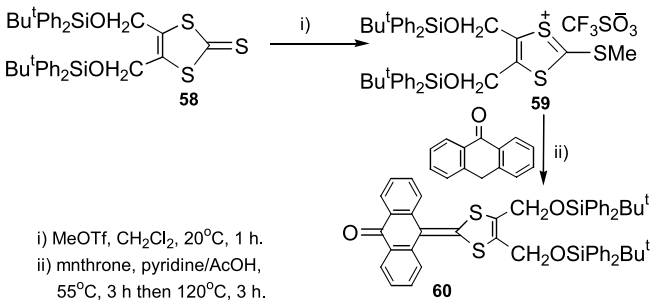
Scheme 11.

3.3. From anthrone or flurenone and or xanthone

The reaction of anthrone, flurenone or xanthone **55** with 2-methylthio-1,3-dithiolium iodides **56** in a refluxing pyridine/acetic acid mixture afforded the corresponding dithiafulvalenes **57** in good yields. The dithiafulvalenes **57** were also obtained by using the Wittig–Horner cross-coupling reaction between **55** and phosphonate ester **19** in THF at −78 °C in the presence of *n*-BuLi (Scheme 12).[20,31]



Scheme 12.



Scheme 13.

3.4. Horner–Wadsworth–Emmons olefination reaction

The 1,3-dithiol-2-thione derivative **58** was methylated with MeOTF in dichloromethane at 20 °C to give the unstable salt **59**, which was sufficiently pure for immediate reaction with the anion of anthrone according to Horner–Wadsworth–Emmons olefination, which gave the dithiafulvalene derivative **60** in 70% overall yield (Scheme 13).[32]

3.5. From 2-thiophenecarboxaldehyde or 2-acetylthiophene

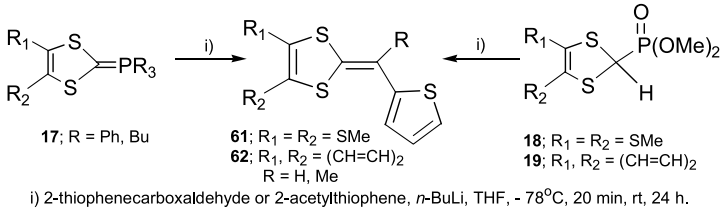
Wittig–Horner olefination of 2-thiophene-carboxaldehyde or 2-acetylthiophene with phosphoranes **17** and/or phosphonates **18**, **19** gave the 4,5-disubstituted-1,3-dithiol-2-ylidenes **61** and **62**, respectively, in good yields (Scheme 14).[33]

4. Synthesis of diazafulvalenes

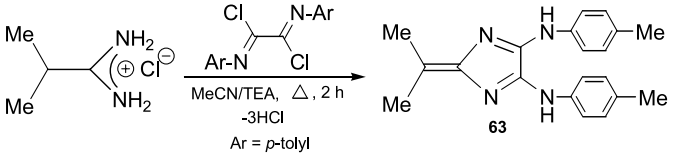
Reaction of the amidine derived from isobutyric acid with a bisimidoyl chloride in acetonitrile as the solvent in the presence of triethylamine (TEA) as a basic catalyst under reflux for 3 h afforded the diazafulvalene derivative 4,5-bis(*p*-tolylamino)-2-propan-2-ylidene-1*H*,2*H*-imidazole (**63**) in 57% isolated yield (Scheme 15).[34]

5. Synthesis of ferrocene-dithiafulvalenes (Fc-DTFs)

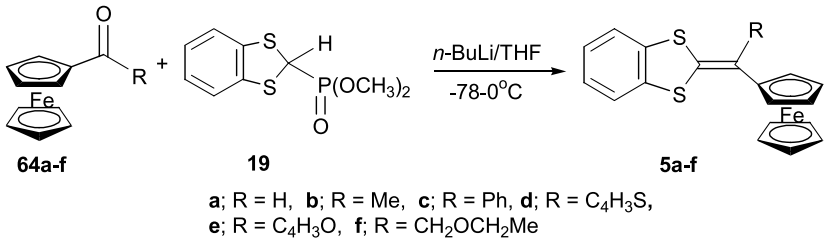
Ferrocene has attracted the interest of many scientists and research groups worldwide because of its applications in materials science and asymmetric synthesis.[35] Ferrocene chemistry was revived during the recent years because ferrocenyl derivatives have found numerous uses in various fields of science from biology to materials chemistry.[36] Due to the inherent importance of ferrocene as a starting material in synthetic organometallic systems and its industrial applications, ferrocene and its derivatives have become an important area of interest for many researchers and industrial chemists. It was reported that ferrocenyl alkenes and dienes are important substrates for the synthesis of copolymers and homopolymers, which are used as coating materials for aerospace applications to increase resistance towards photodegradation.[37] Ferrocene-1,3-butadiene has been used as a fuel in solid propellants.[37] Polymers containing directly linked ferrocene centers have been prepared and many studies on linked ferrocene dimers and oligomers have also been reviewed.[38] Several compounds bearing ferrocenyl moieties have been synthesized and used for the chemotherapy of drug-resistant cancer and tropical diseases.[39] It is also known that ferrocene behaves in many aspects like an aromatic electron-rich phenol compound, and this has led to its use as a precursor for the synthesis of several crown ethers, azacrown ethers and thiacrown ethers.[40] It has been reported that a wide variety of macrocycles, cryptands, and cavitands containing the ferrocene unit have been synthesized and characterized[36] and that ferrocenes have been incorporated into a number of anion sensors.[41] It is now more than 50 years after the discovery of ferrocene and this compound has shown a continuously growing rich chemistry. Effectively, ferrocene is currently employed as a crucial component for redox-active chemical sensors for the voltammetric detection of cations as well as anions and metal-containing signaling probes for the detection of estrogen receptors, and DNA hybridization, thus opening the way to DNA and gene sensors. Classical areas of ferrocene materials chemistry such as liquid crystals, and conductive, magnetic and optical devices nowadays co-exist with emergent areas such as electron-transfer devices and ferrocene dendrimers.[42] The



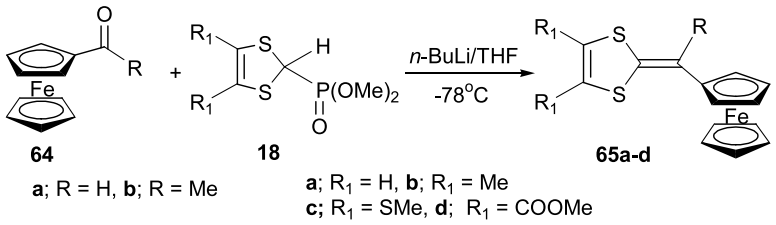
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

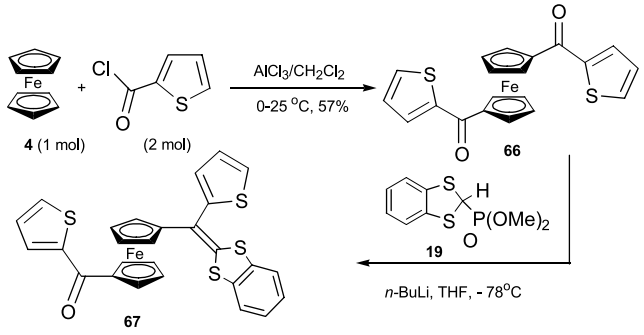
magnetic properties of charge-transfer CT complexes of peralkylated ferrocenes and other metallocenes have led to the discovery of the first organometallic bulk ferromagnet dicyclopentadienyliron–tetracyanoethylene complex [$FeCp_2$][TCNE], which has been intensively studied by Miller and co-workers.[43] The synthesis of ferrocene compounds bearing heterocyclic rings and the study of the biological and electrochemical behavior of these new ferrocenyl heterocycles seem to be of interest, since a marked biological activity has appeared recently for the ferrocene derivatives.[44]

5.1. From formylferrocene or acetyl/aroylferrocenes

Treatment of phosphonate ester **19** with ferrocenyl ketones **64a–f** using the Wittig–Horner method in the presence of *n*-BuLi at −78 to ∼0 °C in dry THF afforded the donor compounds **5a–f** in variant yields. Upon using the same method with 1-benzoylferrocene **64c**, the target compound **5c** could not be obtained and an unknown product was isolated in good yield.[45] A slight modification was made to this method by the addition of the ferrocenyl ketone **64c** to the dithiolium solution at 0 °C with continuous stirring which led to the formation of **5c** (R=Ph) in low yield (Scheme 16).

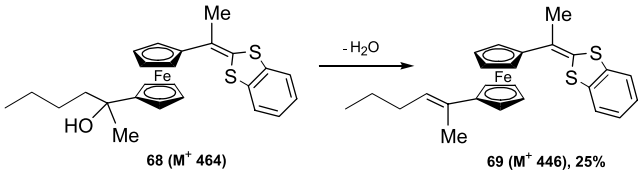
Furthermore, the syntheses of 1,4-dithiafulvalene-substituted ferrocene derivatives **65a–d** have also been achieved by Bryce et al.[46] upon reaction of formylferrocene **64a** or acetylferrocene **64b** with phosphonate esters **18** (R_1=H, Me, Sme or COOMe) in THF in the presence of *n*-BuLi to afford the corresponding ferrocene-dithiafulvalene derivatives **65a–d** in high yields (Scheme 17).

The reaction of 1,1′-dithienoylferrocene (**66**) with the phosphonate ester **19** according to the Wittig–Horner procedure gave the ferrocene-dithiafulvalene **67** as the major product rather than the ferrocene-tetrathiafulvalene. The yield of this reaction was low and the starting ketone **66** was recovered in 73.5% yield (Scheme 18).[3]



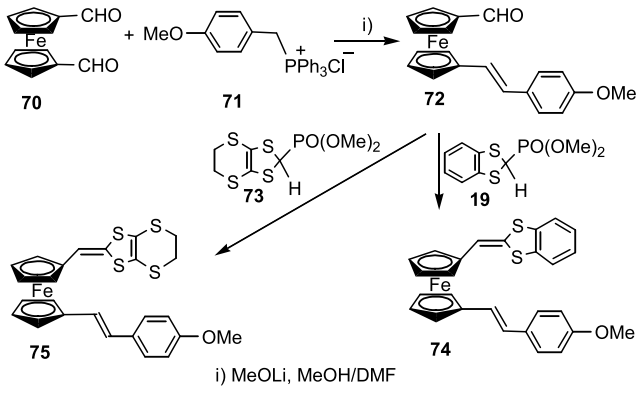
Scheme 18.

On reaction of 1,1′-diacetylferrocene with phosphonate ester **19** (R=Me) the expected 1,1′-bis[(benzo-1,3-dithiol-2-ylidene)ethyl]ferrocene DTF-Fc-DTF (**15**, R=Me) was obtained in 28% yield. In addition the unexpected ferrocene-dithiafulvalene (Fc-DTF) **69** was also isolated in 25% yield. The formation of Fc-DTF **69** was explained by dehydration of **68**, Scheme 19.[3]



Scheme 19.

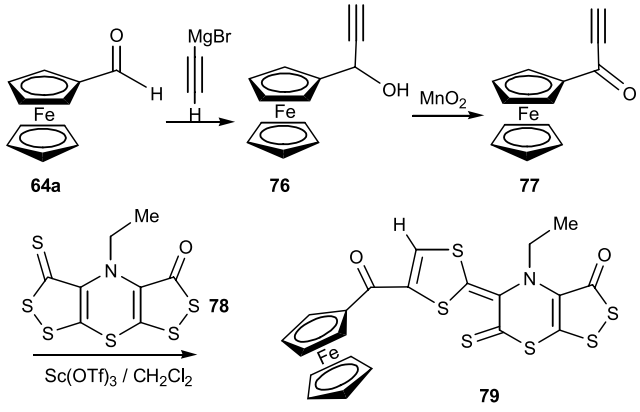
Compounds **74** and **75** were obtained in 35 and 39% yields, respectively, from 1,1′-diformyl-ferrocene **70** by stepwise addition of the Wittig reagent generated from *p*-$MeOC_6H_4$-$CH_2P^+Ph_3Cl^-$ **71** by deprotonation with MeOLi in MeOH/DMF mixed solvents to form **72**, followed by the addition of either **19** or **73** (Scheme 20).[13]



Scheme 20.

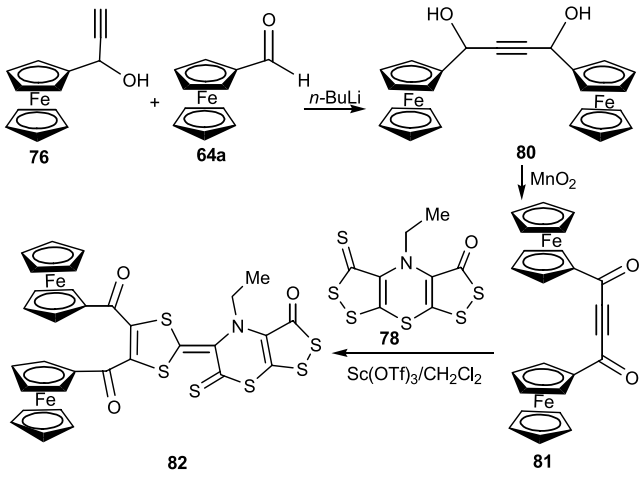
5.2. From reaction of ferrocenecarbonyl-2-butyne with bisdithiolothiazine ketothiones

4(5)-Ferrocenecarbonyl-1,3-dithiol-2-ylidene derivative **79** was obtained in high yield from the starting ferrocenecarboxaldehyde **64a** according to literature procedures.[42] Treatment of **64a** with ethynylmagnesium bromide gave the propargylic alcohol **76**, which was successively oxidized with manganese oxide (MnO_2) to 1-ferrocenyl-prop-2-yn-1-one **77**. Reaction of **77** with the bisdithiolothiazine ketothione **78**[47] in the presence of scandium triflate in dichloromethane gave a *Z*/*E* mixture of 91% of the corresponding dithiafulvalene derivatives **79** (Scheme 21).[42]



Scheme 21.

Reaction of the propargylic alcohol **76** with *n*-butyllithium followed by the ferrocene carboxaldehyde **64a** gave the expected diol **80** in moderate yield. This diol was successively oxidized with manganese oxide to give the 1,4-bisferrocenylbut-2-yn-1,4-dione **81** in good yield. Cycloaddition of the dione **81** with the bisdithiolothiazine ketothione **78** in the presence of scandium triflate $Sc(OTf)_3$ in dichloromethane gave the corresponding dithiafulvalene derivative **82** with two ferrocenyl units (Scheme 22).[42]



Scheme 22.

6. Tetrathiafulvalenes (TTFs)

Tetrathiafulvalene (TTF) **6** is one of the simplest symmetrical tetrachalcogenafulvalenes. It was synthesized for the first time in 1970,[1] although some substituted derivatives, such as DB-TTF **9**,[48] had been synthesized some years before. The tetraselenafulvalenes TSF **8**,[49] tetratelluraful-valenes TTeF **83**[50] and diazadithiafulvalenes DADTF **84** are three other simple symmetrical tetrachalcogenafulvalenes that have also been reported (Chart 9).

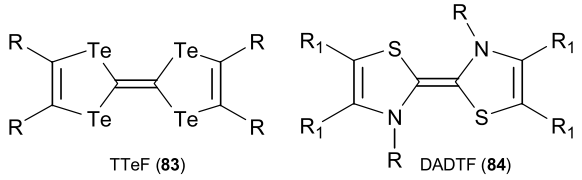
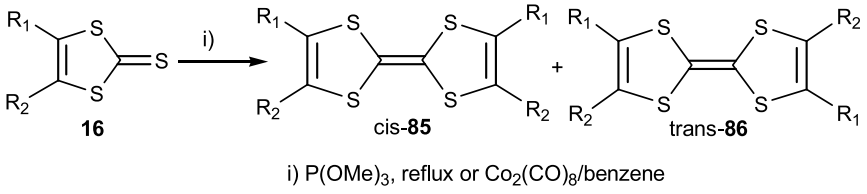


Chart 9.

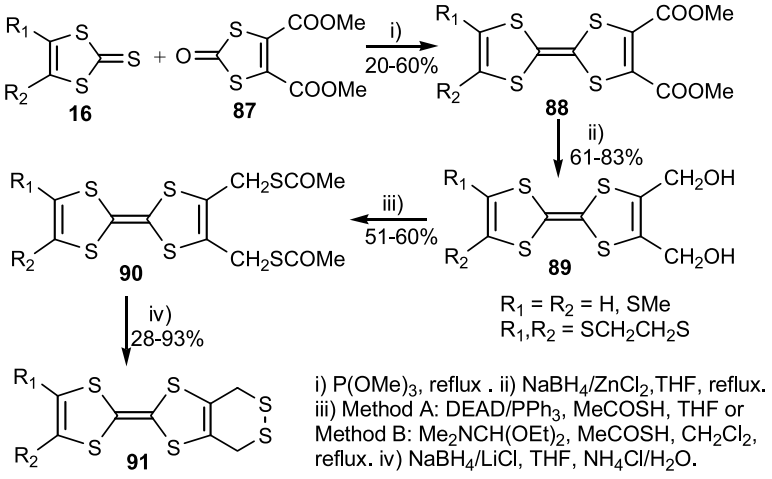
Several reviews have been reported[26–28] describing the synthetic approaches to the tetrathiafulvalenes and their selenium analogues, the tetraselenafulvalenes **8**. The synthetic methods are conveniently classified according to the general mechanistic path way found in the literature. The preparations of the precursors of the tetrathiafulvalenes **6** and tetraselenafulvalenes **8**, namely 1,3-dithiole and 1,3-diselenole derivatives, are also surveyed.[26–29] The relationship between the structures of the donors and the properties of conducting charge-transfer complexes has also been reviewed.[2]

Tetrathiafulvalene (TTF) is a planar nonaromatic 14π-electron system in which oxidation to the cation radical $TTF^{+\cdot}$ and the dication TTF^{2+} occurs sequentially at low potentials. The sulfur atoms in the TTF core are primarily responsible for the close packing and overlap between the TTF-molecules. The electrochemical behavior of the tetrathiafulvalenes enhanced the synthesis of several TTFs, which could be used as superconductor materials.[51]

Tetrathiafulvalene is a reversible and stable two-electron donor. The contribution from 6π-electron heteroaromaticity of both the 1,3-dithiolium cation and the dication leads to a thermodynamically very stable donor system.[52]



Scheme 23.



Scheme 24.

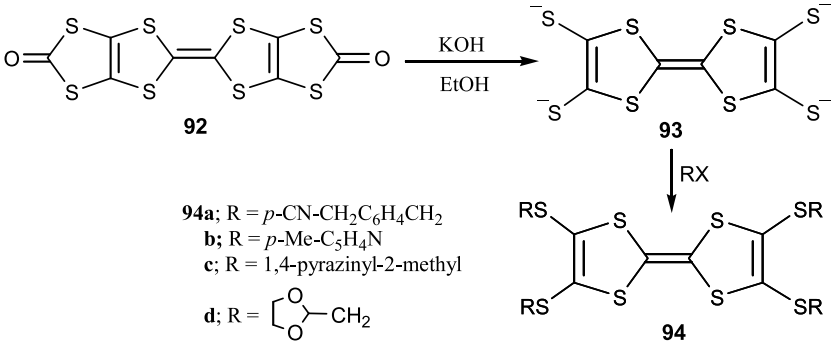
6.1. Synthesis of tetrathiafulvalenes via cross-coupling reactions

Coupling of asymmetrically substituted 1,3-dithiole-2-thione derivatives **16** in the presence of trimethyl phosphite $P(OMe)_3$ afforded a mixture of *cis*-TTF **85** and *trans*-TTF **86** isomers in variable yields.[2,20] A one-step synthesis afforded TTFs **85** and **86** directly from the thione **16** in 20–45% yield when **16** was heated with dicobalt octacarbonyl in boiling benzene or toluene solution (Scheme 23).[53]

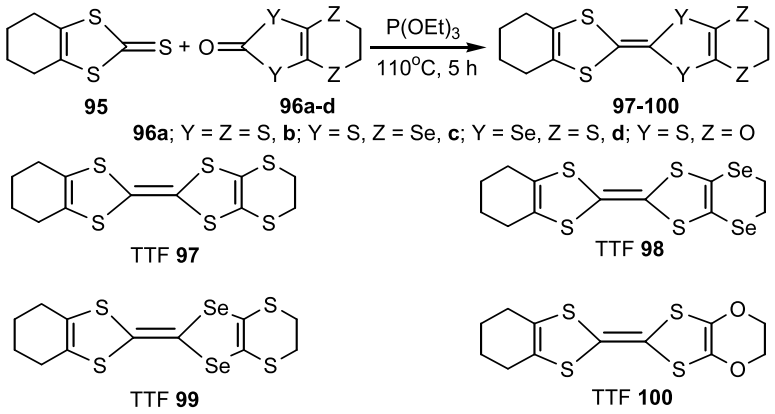
Cross-coupling reactions of 1,3-dithiole-2-thiones **16** with 1,3-dithiole-2-one **87** in an equimolecular ratio in the presence of trimethyl phosphite afforded the corresponding TTF products **88** in variable yields. Reduction of **88** with $NaBH_4/ZnCl_2$ afforded TTFs **89**, which were able to undergo a Mitsumobu procedure to prepare the thioesters **90**. Reduction of the thioesters **90** with $NaBH_4$ in the presence of LiCl in THF under reflux and subsequent treatment with an aqueous solution of ammonium chloride efficiently afforded **91** in variable yields (Scheme 24).[54]

6.2. From bis-(tetrathiapentalene-5-ones)

Decurtins et al.[55] have reported that the classical synthetic method for the preparation of functionalized TTF derivatives is sometimes unsuccessful. Some TTF derivatives are not easy to obtain via the coupling of two 1,3-dithiol-2-thiones or -2-ones in refluxing $P(OMe)_3$ or $P(OEt)_3$ or PPh_3. Furthermore, this classical multistep procedure starting from CS_2 results in very poor yields of the target molecules. In this method, the key step relies on the generation of the tetra-anion **93**. The tetra-anion can be readily prepared from 2,2′-bis(1,3,4,6-tetrathiapentalene-5-one) (**92**) under carefully controlled conditions. The nucleophilic displacement reaction of **93** with primary alkyl halides gave in one step the corresponding TTF derivatives **94** in good yields (Scheme 25).



Scheme 25.



Scheme 26.

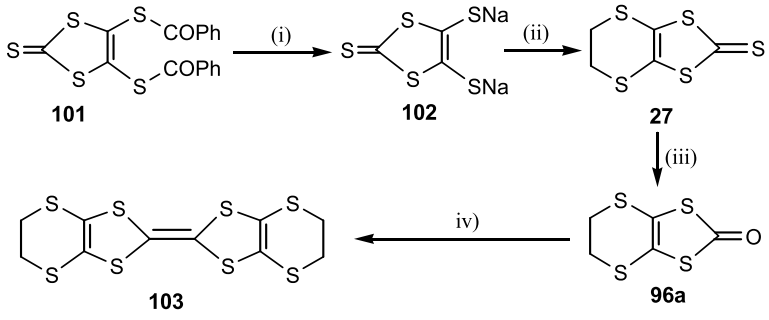
6.3. Synthesis of BEDT-TTF and related derivatives

It has been reported that cyclohexene-fused donors have the same framework as bisethylenedithia-tetrathiafulvalene (BEDT-TTF), which provides many stable metallic conductors and superconductors.[56] The syntheses of these donors were achieved by the cross coupling of the asymmetric dithiol-2-thione **95** with dithiol-2-ones **96** in the presence of triethyl phosphite $P(OEt)_3$ to give the corresponding asymmetric TTF derivatives **97–100** in 8, 2, 8 and 8% yields, respectively. The donors **97** and **99** were synthesized in better yields upon application of the Wittig procedure [**97** (69%) and **98** (59%)] (Scheme 26).[57]

Treatment of the disodium salt **102**, obtained from the diester **101**, with 1,2-dibromoethane in the presence of ammonium acetate gave **27** in good yield. Oxidation of the thione **27** with mercuric acetate using a chloroform/glacial acetic acid mixture gave the oxo-compound **96a** in quantitative yield. Treatment of **96a** with freshly distilled triethyl phosphite at 100–110 °C gave the corresponding bisethylenedithia-tetrathiafulvalene BEDT-TTF **103** in 61% yields (Scheme 27).[58]

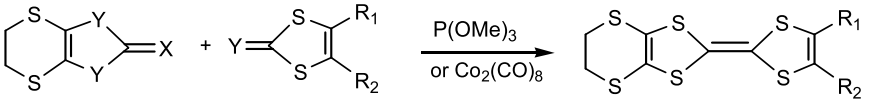
The cross-coupling reaction between 1,3-dithiole-2-thiones **27** or **96a** with **87** was achieved using dicobaltoctacarbonyl $Co_2(CO)_8$ to give the BEDT-TTF derivatives **105a–d** in relatively low yields. Contrary to phosphine PPh_3 or phosphite $P(OR)_3$, dicobalt octacarbonyl $Co_2(CO)_8$ also induced the predicted desulfurizing cross coupling reaction (Scheme 28).[59]

The syntheses of BEDT-TTF **103** and the parent TTF were also achieved by the reaction of 4,5-bis(benzoylthio)-1,3-dithiole-2-thione (**101**) with tetrathianaphthalene (TTN) **106**, which was synthesized from compound **101** by



(i) 1. NaOEt/EtOH, rt, 20 min, 2. Et_2O, - PhCOOEt, quant. (ii) NH_4OAc/MeOH, $BrCH_2CH_2Br$, rt, 18 h, -2NaBr, 55% (iii) $Hg(OAc)_2$, $CHCl_3$ / AcOH, rt, 20 min, quant. (iv) $P(OEt)_3$, 100-110°C, 40 min, 61%.

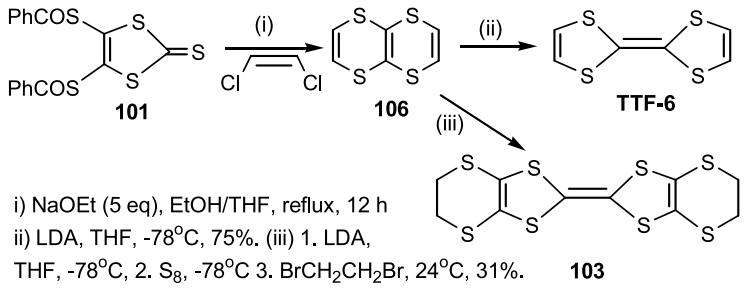
Scheme 27.



87a; $R_1 = R_2$ = COOMe; Y = O
87b; R_1 = COOMe, R_2 = H; Y = O
104a; R_1 = COOMe, = R_2 = CH_2OH; Y = S
104b; $R_1 = R_2 = SCH_2CH_2CN$; Y = O

a; $R_1 = R_2$ = COOMe
b; R_1 = COOMe, R_2 = H
c; R_1 = COOMe, R_2 = CH_2OH
d; $R_1 = R_2 = SCH_2CH_2CN$

Scheme 28.



Scheme 29.

refluxing with *cis*-dichloroethylene in good yield.[60] TTN **106** is a very useful starting material for the synthesis of many organic metals and is electrochemically oxidized to TTF. It was stated that TTN could be converted into tetrathiafulvalene in 70% yield via reaction with LDA (Scheme 29).[61]

6.4. Synthesis of furo- and difurotetrathiafulvalenes (F-TTFs and DF-TTFs)

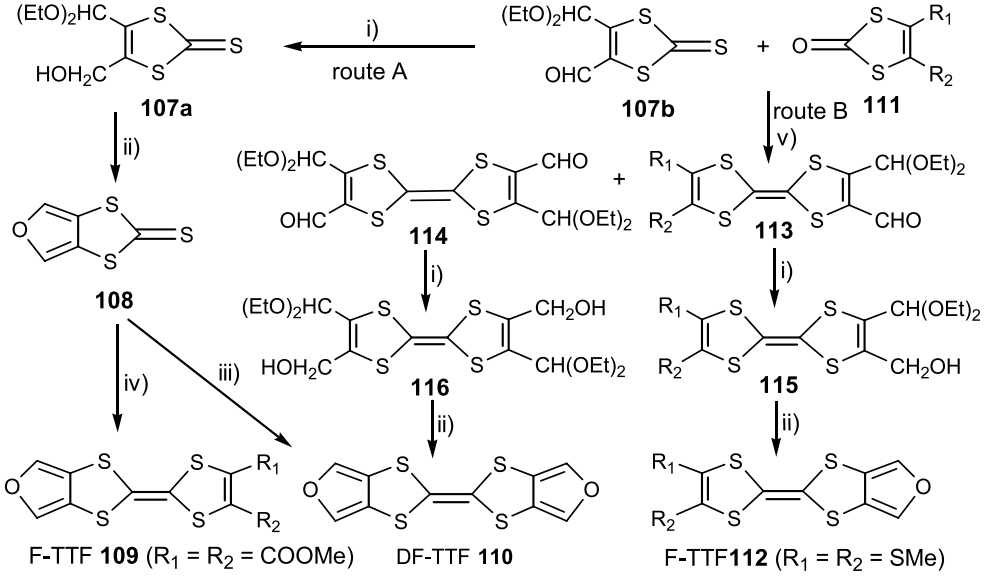
Starting from 4-formyl-5-diethoxymethyl-2-thioxo-1,3-dithiole **107a**, the synthesis of F-TTF **109**, DF-TTF **110** and F-TTF **112** was explained by Gorgues et al.[62] In route A, the furan cycle is first formed with the synthesis of a fused[3,4] [*d*]furo-2-thioxo-1,3-dithiole **108**, followed by a self coupling in the presence of $P(OMe)_3$ to give DF-TTF **110** in 5% yield. Cross-coupling of **108** with **87** ($R_1=R_2=$ COOMe) gave the F-TTF **109** in 13% yield. On the contrary, route B proceeds via the coupling of thione **107b** with **111** ($R_1=R_2=$SMe) in the first step to form **113** and **114**, which on reduction by $NaBH_4$ produced **115** and **116**. Due to the instability of **115** and **116**, the subsequent cyclization in formic acid leads to the formation of F-TTF **112** and DF-TTF **110** in 17 and 13% yields, respectively, as shown in Scheme 30.[62]

6.5. Synthesis of crown annelated tetrathiafulvalenes

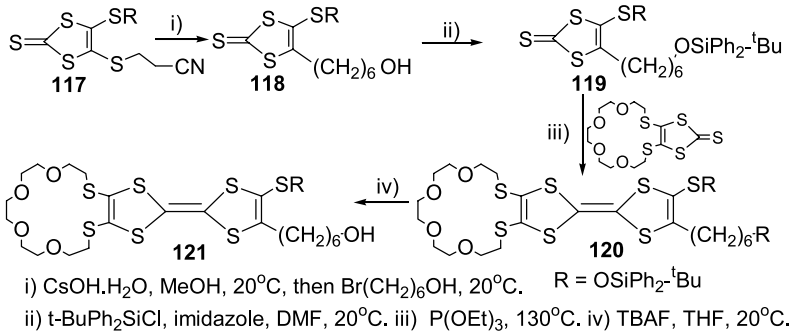
The crown annelated tetrathiafulvalenes could be synthesized via deprotection of the thiolate group in compounds **117** with cesium hydroxide followed by trapping with 6-bromohexane-1-ol to afford compounds **118** in high yields. Reaction of **118** with *tert*-butyldiphenylsilyl chloride in the presence of imidazole afforded compounds **119** in very high yields. Reaction of compounds **119** with thione derivative in the presence of triethyl phosphite gave the tetrathiafulvalene derivatives **120** in low yields. Deprotection of **120** with tetrabutylammonium fluoride (TBAF) produced the alcohols **121** in high yields (Scheme 31).[63] The crown ether part is annelated also in the 2,7-positions of the TTF framework and has been synthesized as a self assembled monolayer SAM.[64]

6.6. Synthesis of pyrrolo annelated tetrathiafulvalenes

A variety of donor molecules have been synthesized in which the TTF core is annelated to benzenoid **9**,[65] BEDT-TTF **103**,[58] furan,[62,66] thiophene,[67] and selenophene units **122** and to pyrrole units **123–126** (Chart 10).[68] These compounds have oxidation potentials appreciably higher than that of TTF **6**.[69]



Scheme 30.



Scheme 31.

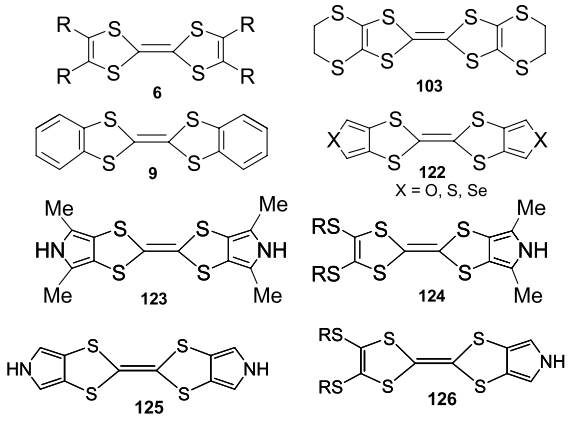
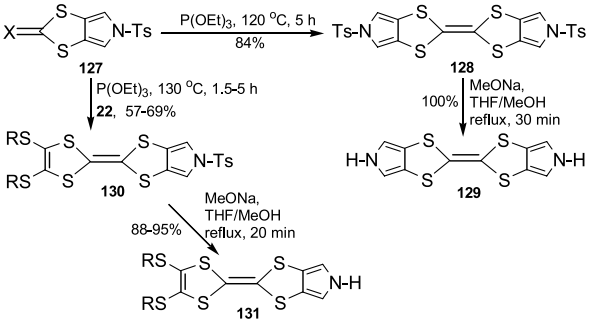


Chart 10.

The pyrrolo-tetrathiafulvalene compounds were prepared according to the method reported in the literature by direct coupling of annelated pyrrolo derivatives with 1,3-dithiol-2-thione derivatives using triethyl phosphite at reflux temperature (Scheme 32).[1d,69]



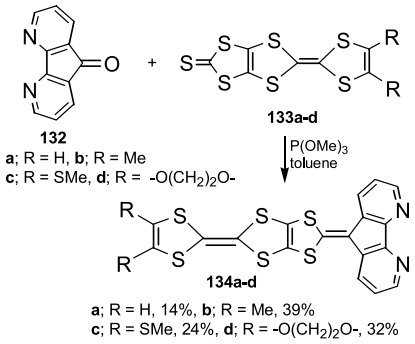
Scheme 32.

6.7. Synthesis of diazafluorene-functionalized tetrathiafulvalene donors

The synthesis of DAF-DT-TTF **134a–d** was carried out using a cross-coupling reaction of 4,5-diazafluoren-9-one (**132**) with the appropriate TTF derivatives **133a–d** in the presence of trimethyl phosphite, as shown in Scheme 33.[70]

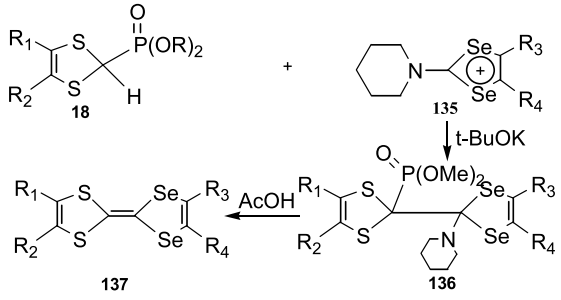
6.8. Synthesis of diselenadithiafulvalenes (DS-DTFs)

Diselenadithiafulvalenes DS-DTFs **137** were synthesized



Scheme 33.

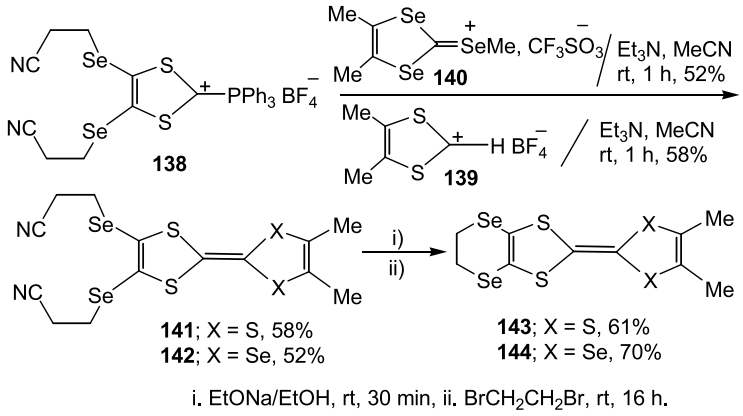
via formation of **136** by coupling of phosphonate esters **18** of various substituted 1,3-dithioles with 2-amino-1,3-diselenolium salts **135** under Wittig-like conditions in 30–50% yields (Scheme 34).[71]



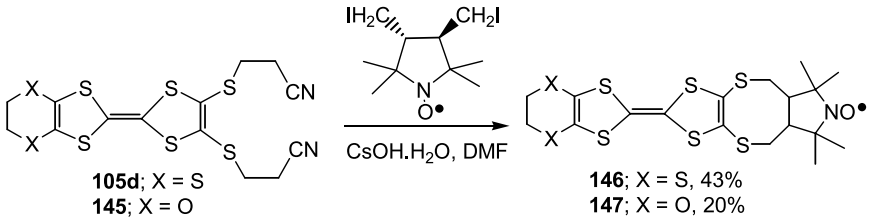
Scheme 34.

Compounds **143** and **144** were obtained in good yields (58 and 52%, respectively) by a pseudo Wittig reaction of **138** with the dithiolium salt **139** or the diselenolium salt **140** in the presence of triethylamine. The triphenylphosphonium fluorborate **138**[72] was used as starting reagent in the presence of TEA in MeCN to give compounds **141** and **142**, in 58 and 52% yields, respectively. The compounds **141** and **142** were converted into **143** and **144** in similar high yields (61 and 71%, respectively), as shown in Scheme 35.[73]

The synthesis and physical properties of TTF containing PROXYL radicals were reported by Fujiwara et al.[74] Treatment of the TTF derivatives **105d** and **145** with $CsOH/H_2O$ in DMF gave the corresponding dithiolate salts. The bis(iodomethyl)-substituted PROXYL radical was



Scheme 35.

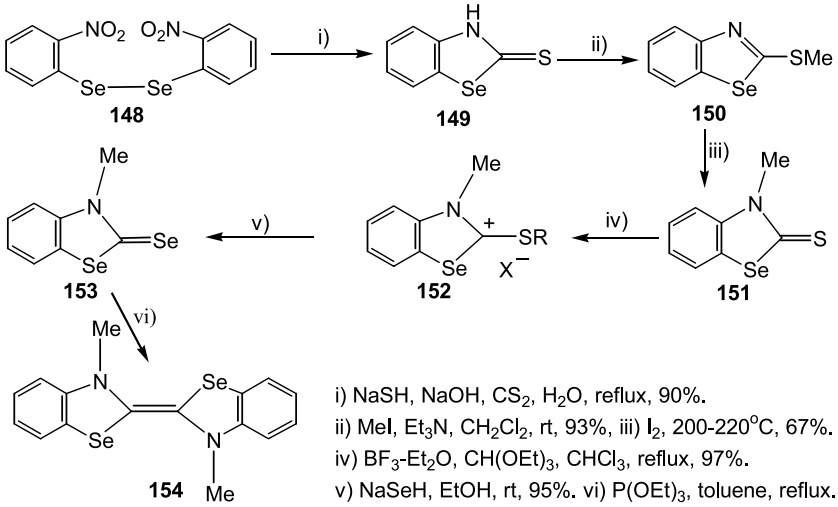


Scheme 36.

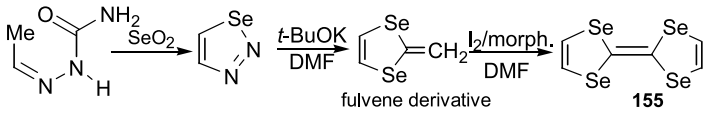
prepared as a racemic mixture according to the method described in the literature.[75] Reaction of the dithiolate derivatives obtained from the TTFs **105d** and **145** with the PROXYL radical gave the corresponding tetrathiafulvalenes **146** and **147** as racemic mixtures in 43 and 20% yields, respectively, (Scheme 36).

6.9. Synthesis of diselenadiazafulvalene (DS-DAFs)

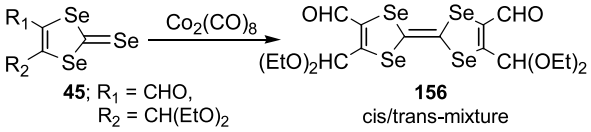
Lorcy et al.[76] have reported that the first diselenadiazafulvalene DS-DAF **154** has been chemically synthesized and electrochemically characterized. It showed a similar sensitivity to atmospheric air as its sulfur analogue and exhibited an extremely good donor character of benzo-DS-DAF. The electrochemical investigations indicated two reversible monoelectronic waves at low potentials on the cyclic voltammogram and these are associated with the redox behavior of the DS-DAF **154** formed in the medium. They correspond, respectively, to the formation of the radical cation and dication of **154** ($E_{pa1}=70$ mV, and $E_{pa2}=90$ mV). The synthetic route to DS-DAF **154** was achieved by the reaction of **148** with CS_2 in the presence of NaH or NaSH to produce **149**, which converted to **150**. Isomerization of **150** to **151** followed by reaction with triethyl-*o*-formate in the presence of BF_3–Et_2O gave the salt **152** which could be converted to **153** in very good yields (Scheme 37).



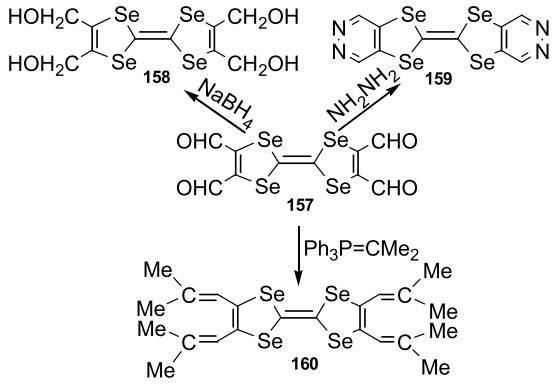
Scheme 37.



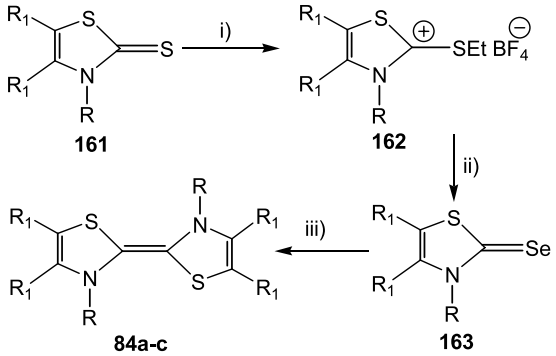
Scheme 38.



Scheme 39.



Scheme 40.



Scheme 41.

6.10. Synthesis of tetraselenafulvalenes (TSFs)

Tetraselenafulvalene TSF **155** was obtained according to the method previously reported in a three-step reaction.[77] Acetaldehyde semicarbazone reacted with selenium dioxide to form 1,2,3-selenadiazole, which reacted with potassium *t*-butoxide in DMF/*t*-BuOH to provide the fulvene derivative. Addition of a mixture of iodine and morpholine in DMF to a solution of fulvene derivative furnished the corresponding tetraselenafulvalene (TSF) **155** as shown in Scheme 38.

By analogy with the synthesis of TTF, the corresponding TSF derivative **156** (*cis*/*trans* mixture) was formed upon reflux of 1,3-diselenol-2-selenone **45** (R_1=CHO, R_2=$CH(OEt)_2$) in toluene with dicobalt octacarbonyl $Co_2(CO)_8$ (Scheme 39).[2]

Tetraformyltetraselenafulvalene **157** is considered as an efficient precursor for heteroannelated and tetra-substituted TSFs. Reduction of **157** using sodium borohydride $NaBH_4$ in a THF/methanol mixture afforded the alcohol **158**. Condensation of TSF **157** with hydrazine hydrate in DMF gave the corresponding dipyridazinotetraselenafulvalene **159**, while the reaction of **157** with Ph_3P=CMe_2 yielded the tetraethylidene product **160** (Scheme 40).[24,78]

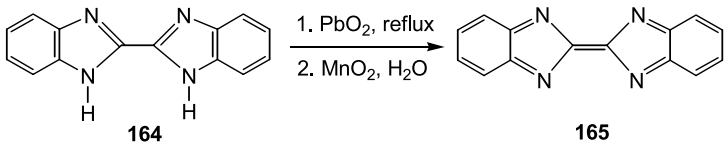
6.11. Synthesis of azafulvalenes (AFs)

Tormos et al.[79] reported that the dithiadiazafulvalenes DT-DAF **84a–c** could be prepared from the thiones **161** through the formation of 2-(ethylthio)-1,3-thiazolium salts **162**, which on treatment with sodium hydrogen selenide afforded the selenones **163**. Compounds **163** were refluxed in triethyl phosphite to yield the DT-DAF derivatives **84a–c** as shown in Scheme 41.

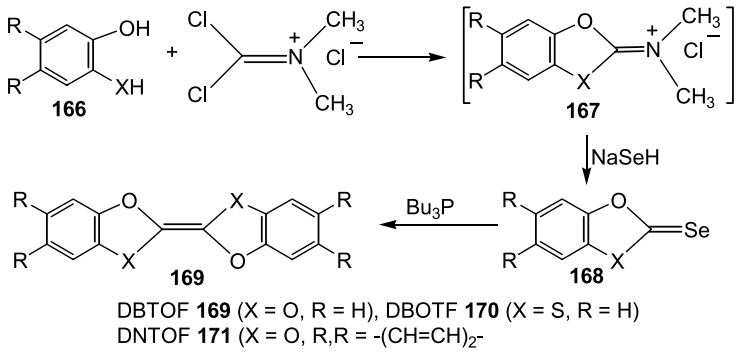
According to the reported methods by Hill[80] and Suschitzky,[81] the tetraazafulvalene (DB-TAF) **165** could be obtained by oxidation of the bisbenzimidazolyl derivative **164** using lead dioxide in benzene or manganese dioxide MnO_2 in chloroform in yields of 65% (method 1) or 30% (method 2), respectively, (Scheme 42).

6.12. Synthesis of oxygen-containing fulvalene derivatives

Nogami et al.[82] have successfully prepared a number of dibenzo-, dinaphtho-tetra-oxafulvalenes DNTOF and dibenzodioxa-dithiafulvalenes DBOTF. Replacement of one sulfur atom of the DBTTF **9** with oxygen has been reported in 1996[83] and replacement of more than one sulfur atom of TTF-skeleton with oxygen has been obtained in 2000.[84] The syntheses of dibenzo-tetraoxafulvalenes DBTOF **169**, dibenzodioxa-dithiafulvalenes DBOTF **170** and dinaphtho-tetraoxafulvalenes DNTOF **171** were



Scheme 42.

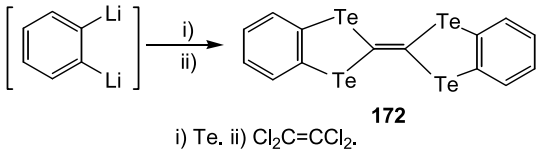


Scheme 43.

achieved by the reaction of **166** with dimethyliminium salt afforded the salt **167**, which treated with NaSeH gave the selenone derivatives **168**. Cross-coupling of **168** using tributyl phosphine gave the targeted compounds **169–171** in variable yields (Scheme 43).[82]

6.13. Synthesis of dibenzotetratellurafulvalenes (DB-TTeFs)

Treatment of 1,2-dilithiobenzene with elemental tellurium followed by tetrachloroethene gave the corresponding dibenzotetratellurafulvalenes (DB-TTeFs) **172** in 10% yield.[85] Electrochemical comparison of DB-TTeF **172** and related compounds such as dibenzotetraselenafulvalene DB-TSF **8** (R,R=–CH=CH–) and dibenzotetrathiafulvalene DB-TTF **9** with TTF **6** (R=H), tetramethyltetrathiafulvalene TMTTF and tetramethyltetraselenafulvalene TMTSF provided valuable oxidation potentials and showed good donor ability (Scheme 44).



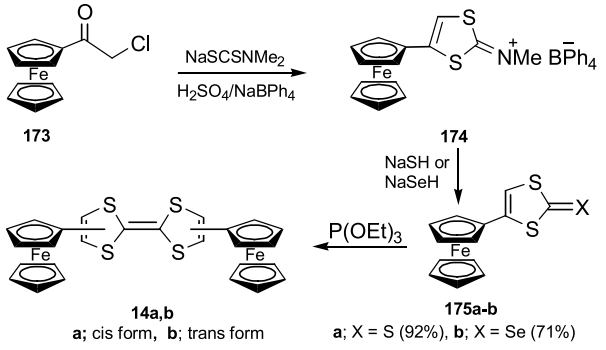
Scheme 44.

7. Synthesis of tetrathiafulvalenes bearing ferrocene, quinone and heterocyclic moieties

Due to their structural and electrochemical properties, it would appear obvious to combine ferrocene-containing fragments and derivatives of tetrathiafulvalene to construct new donors for conducting CT complexes. This approach would lead to multistage redox systems that are likely to display different solid-state properties to those of their congeners. Only a few studies on these types of donor compounds have been reported in the literature over the last 25 years, Ueno et al. synthesizing the first compounds that belong to this class in 1980.[11]

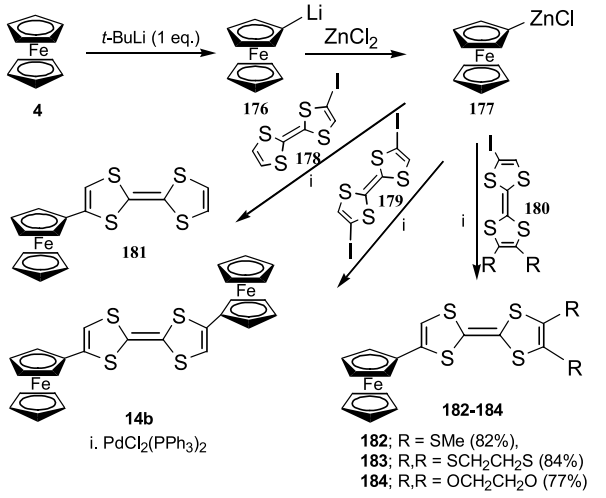
7.1. Tetrathiafulvalene-sandwiched ferrocenes

The synthesis of diferrocenyl-tetrathiafulvalenes **14a**,**b** was accomplished according to the method described in Scheme 45.[12] *N*,*N*-dimethyl-4-ferrocenyl-1,3-dithiol-2-iminium tetraphenyl borate **174** was prepared in 63% yield by the cyclization of 1-chloroacetylferrocene **173**. Reaction of **174** with sodium hydrogen sulphide in dimethylformamide/acetic acid, or sodium hydrogen selenide in ethanol gave the corresponding thiones **175a** (92%) and **175b** (71%), respectively. Coupling of **175a**,**b** in an excess of triethyl phosphite in refluxing benzene resulted in the formation of diferrocenyltetrathiafulvalenes **14a**,**b**.

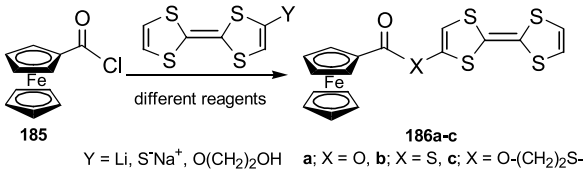


Scheme 45.

The syntheses of ferrocene-tetrathiafulvalenes **14b**, and **181–184** were carried out using the palladium-catalyzed cross-coupling reaction shown in Scheme 46. Ferrocene **4** was treated with *t*-BuLi in THF at −78 °C to form 1-lithioferrocene **176**, which was converted into ferrocenylzinc chloride **177** by treatment with zinc chloride in



Scheme 46.



Scheme 47.

THF.[86] The cross-coupling reaction of **177** with iodo-TTF **178** in the presence of $PdCl_2(PPh_3)_2$ proceeded smoothly to afford **181** in 81% yield.[86] Similarly, the reaction of **177** with the TTF derivatives **180** in the presence of $PdCl_2(PPh_3)_2$ afforded the corresponding **182** (R=SMe), **183** (R,R=SCH_2CH_2S) and **184** (R,R=OCH_2CH_2O). Treatment of **177** with **179** afforded **14b** in 67% yield. Although a mixture of the isomers *cis*-**14a** and *trans*-**14b** was synthesized using another procedure,[11] pure *trans*-**14b** was prepared in a better yield using the method described in Scheme 46.[87]

7.2. Ferrocene substituted tetrathiafulvalenes

The synthesis of prototype systems comprising covalently linked ferrocene and TTF moieties has been reported by Bryce and co-workers.[12] Additionally, the electrochemical properties of these materials and X-ray crystal structure as well as preliminary data on complex formation with tetracyano-*p*-quinodimethane (TCNQ) have been also investigated. Ferrocene has been attached both to the periphery of TTF as in compounds **186a–c**, **187**, and **188** and incorporated as a spacer unit between two 1,3-dithiole-2-ylidene rings as in **15a**,**b** and compound **190**. Compounds **186a–c** comprising one ferrocene and one TTF unit separated by one-, two-, and five-atoms spacer groups, respectively, were synthesized following the well-established method reported in the literature.[12] Ferrocenylcarbonyl chloride **185** reacted with tetrathiafulvalenyl lithium, TTF-thiolate anion and/or TTF-alcohol affording the corresponding **186a–c**, respectively, in variable yields Scheme 47).

Analogous reactions have provided bis-TTF and bis-ferrocene derivatives **187** and **188**, respectively. Reaction of TTF-dialcohol and ferrocenecarbonyl chloride **185** afforded the corresponding compound **188** in 60% yield (Chart 11).[12]

7.3. Ferrocene as a conjugated spacer

On reaction of 1,1′-diformyl or diacetylferrocene (**189a**,**b**) with the phosphonate esters **19** or **73** under Wittig–Horner reaction conditions the expected 1,1′-bis[(benzo-1,3-dithiol-2-ylidene)methyl/ethyl]ferrocene DTF-Fc-DTF (**15a**,**b**) and 1,1′-bis[(diethylenethio-1,3-dithiol-2-ylidene)-methyl]ferrocene BEDTF-Fc-BEDTF (**190**) were obtained in good yields (Scheme 48).[3,13]

7.4. Aryl-ferrocene-aryl conjugated spacers

Following the methods previously described in the literature, the hydroxymethylaryl derivative **191** was prepared from ferrocene by coupling of the aryldiazonium salt of methyl *p*-aminobenzoate followed by reduction with $NaBH_4$.[4] Oxidation of **191** with MnO_2 in chloroform gave the corresponding 1-(*p*-formylphenyl)-1′-(4-formyl-1-naphthyl)ferrocene (**192**) in good yield (Scheme 49).[4]

Similarly, the 1-(*m*-formylphenyl)-1′-(3-formyl-5-methoxyphenyl)ferrocene (**195**) was synthesized from the ester **193** by reduction with $LiAlH_4$ in ethanol to produce the dialcohol **194**, which oxidized in $CHCl_3$ in the presence of activated MnO_2, in good yield (Scheme 50).[4]

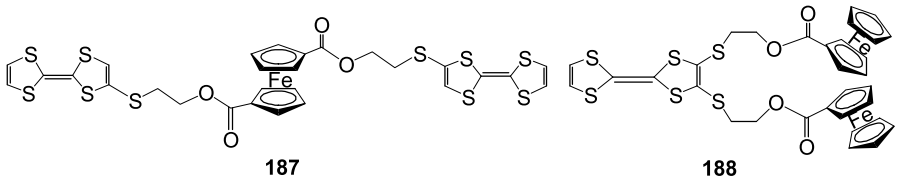
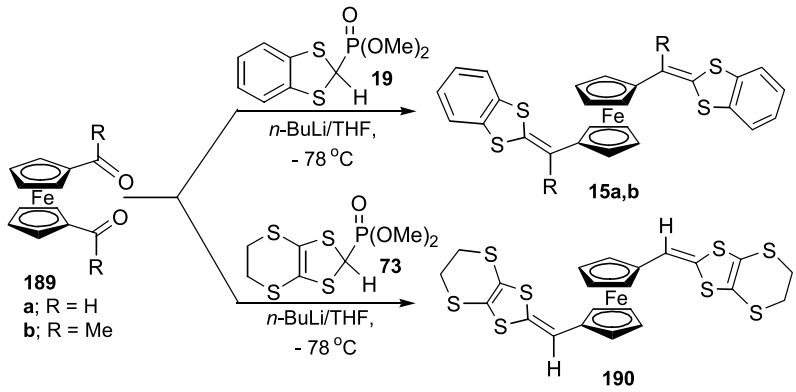
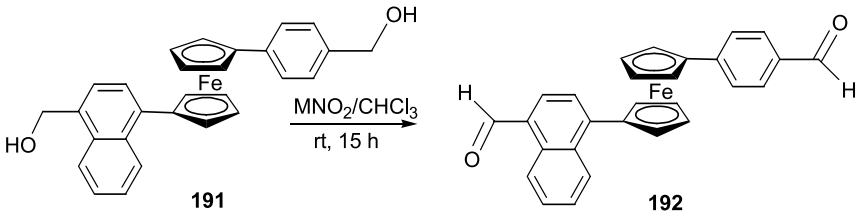


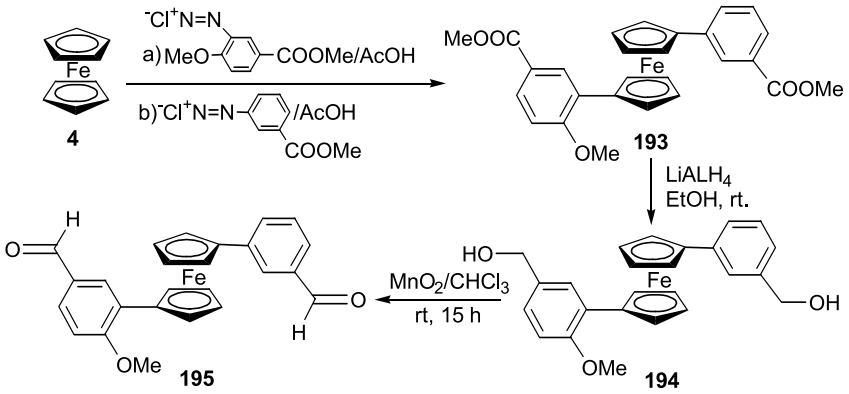
Chart 11.



Scheme 48.



Scheme 49.

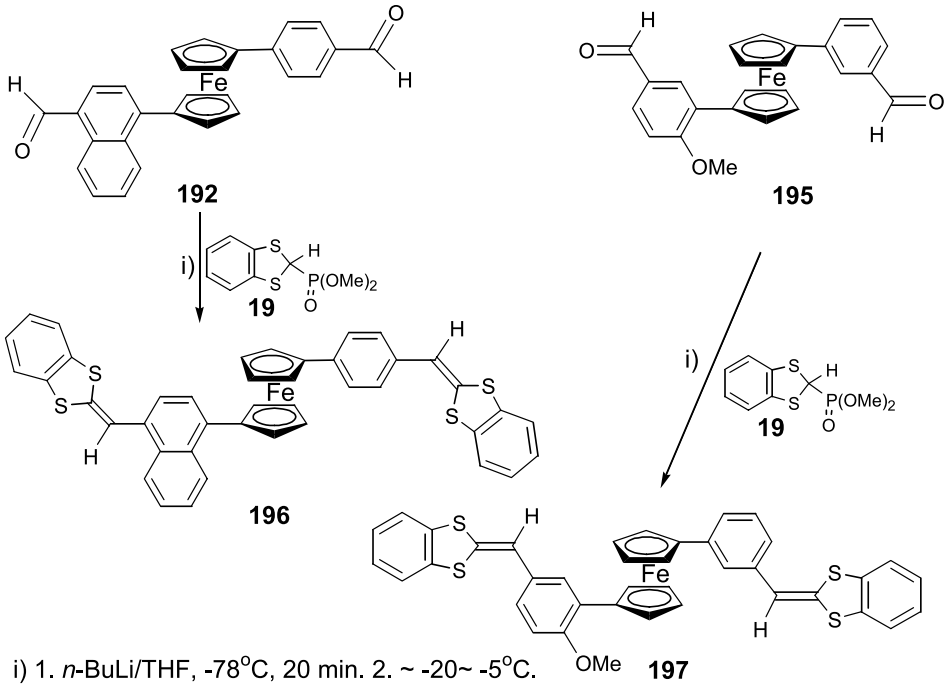


Scheme 50.

Upon reaction of the dialdehyde **192** with the benzo-1,3-dithiole-2-phosphonate (**19**) by using slight modification of the Wittig–Horner procedure, at −20 to −5 °C afforded the expected donor **196** in 80.5% yield. In the same manner, the reaction of **195** with **19** gave the unsymmetrical 1-[3-(benzo-1,3-dithiol-2-ylidene)methylphenyl]-1′-{5-methoxy-3-[(benzo-1,3-dithiol-2-ylidene)-methyl]phenyl}ferrocene (**197**) in 97% yield (Scheme 51).[4]

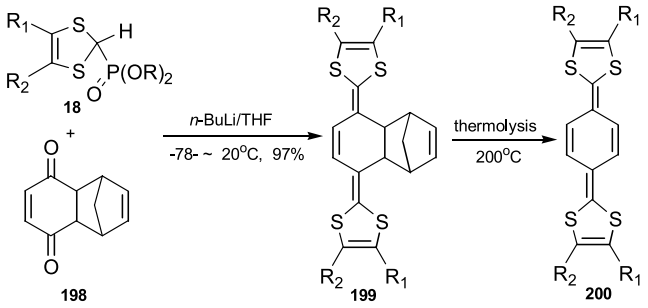
7.5. *p*-Quinodimethane and analogues as conjugated spacers

The tetrathiafulvalene analogues **10**, **201** and **202** could not be prepared directly by using the Wittig–Horner reaction, while using the retro-Diels–Alder reaction facilitates the formation of these donor compounds.[8a,88] Thus, a solution of **18** in dry THF was treated with *n*-BuLi at −78 °C



Scheme 51.

followed by adding the diketone adduct **198** and the reaction was allowed to reach room temperature, whereupon the bis-1,3-dithiole derivative **199** was obtained in 27% yield. Upon thermolysis at 200 °C under reduced pressure, compound **199** furnished, via a retro-Diels–Alder reaction, compound **200** in 54% yield (Scheme 52).



Scheme 52.

The benzo derivatives **201**–**203** were prepared analogously by the reaction of the Diels–Alder adducts of *p*-benzoquinone, 1,4-naphthoquinone, 6,7-dimethylnaphthoquinone and/or the corresponding 1,4-anthraquinone with phosphonate esters **18** and/or **19**. Direct coupling of anthraquinone with the phosphonate ester **19** according to the Wittig–Horner reaction (*n*-BuLi, THF at −78 °C) gave the anthraquinodimethane derivative **204** as yellow crystals in 97% yield (Chart 12).[9,89]

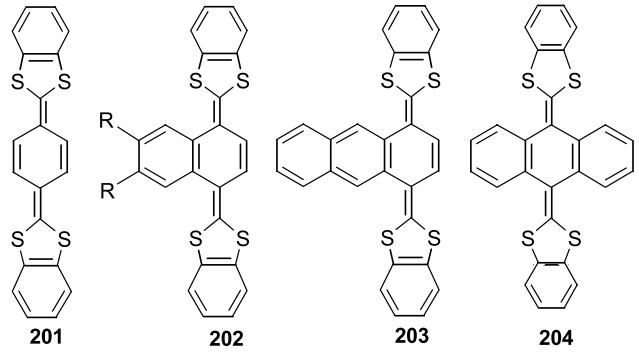


Chart 12.

Bryce et al.[90] have described an efficient route for the synthesis and the multistage redox properties of 9,10-bis(1,3-dithiol-2-ylidene)-9,10-dihydroanthracene—functionalized ferrocenyl and tetra-thiafulvalenyl units. The electrochemical properties of 2,6-bis(ferrocenylcarbonyloxy)-9,10-bis[4,5-bis(methylthio)-1,3-dithiol-2-ylidene]-9,10-dihydroanthracene (**207**) and 2,6-bis(tetrathiafulvalenylcarbonyloxy)-9,10-bis[4,5-bis(methylthio)-1,3-dithiol-2-ylidene]-9,10-dihydro-anthracene (**208**) have been studied by cyclic voltammetry. The synthesis of these highly extended tetrathiafulvalenes was carried out via cross-coupling reaction of **26** with the anthraquinone derivative in the presence of *n*-BuLi to give **205**, which on reaction with TBAF gave the dihydroxy derivative **206**. The reaction of **206** with TTF-COCl or Fc-COCl in the presence of TBAF gave **208** and **209**, respectively, (Scheme 53).

Extended TTF derivatives bearing a *p*-quinodimethane **210** have been used as strong donors due to the extended conjugation, which results in a decrease of the intramolecular on-site Coulombic repulsion and the formation of nonstoichiometric complexes with acceptor molecules, on the basis of the different sizes. In contrast to TTF and its derivatives, the *p*-quinodimethane analogues of TTF form stable dicationic species, which form CT complexes with electrical and magnetic properties. Martin et al.[91] have also synthesized a number of extended TTF-bearing *p*-quinodimethanes **210** using a Wittig–Horner reaction of the bis-anthraquinone derivative **209** with **18**, the electrochemical behavior of these compounds have been also studied. These compounds showed good donor ability to form CT complexes and their electrical conductivity was also investigated indicating that these CT complexes possess considerable conductive properties (Scheme 54).

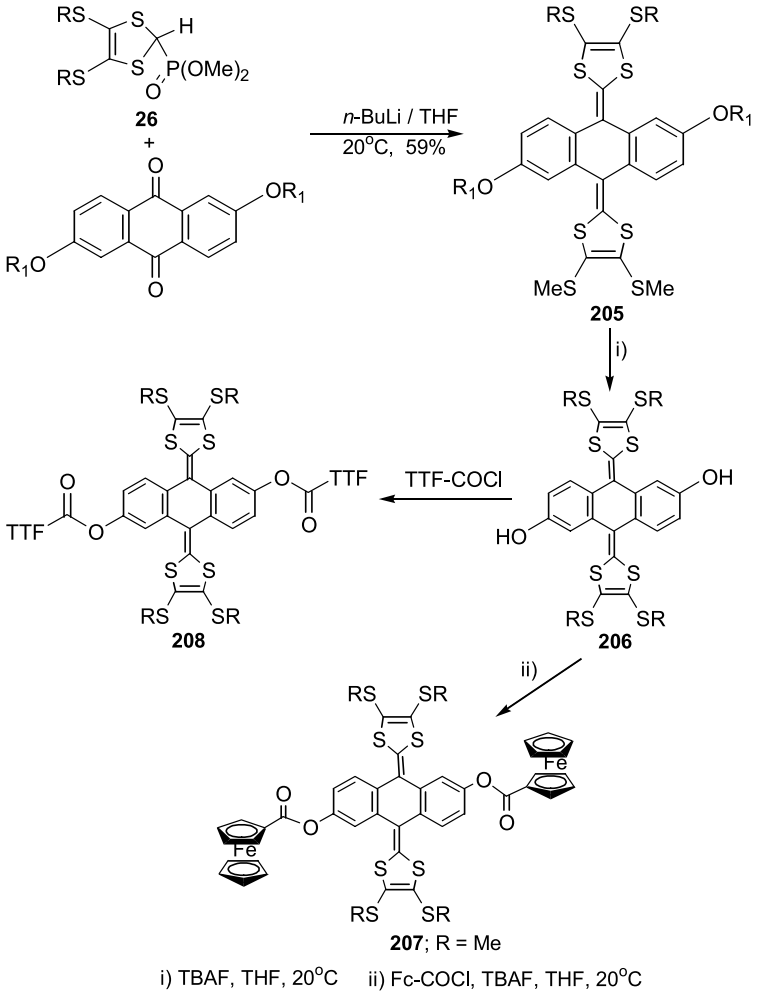
Bryce and Martin[9,92] have determined the redox potentials of the extended tetrathiafulvalenes **212** by using cyclic voltammetric (CV) measurements, carried out in methylene chloride at room temperature with tetrabutylammonium perchlorate (TBAP) as the supporting electrolyte. Two oxidation waves were observed at room temperature.[92] The first oxidation wave corresponded to a quasireversible oxidation process involving two electrons with the formation of the dication. This electrochemical behavior is in agreement with that previously observed for the anthracenylidene derivative **12**, and the coulometric analysis confirmed the two-electron nature of the process. The second irreversible oxidation wave observed at 1.3–1.4 V for compounds **212** has been assigned to the oxidation of the hydrocarbon framework to form the trication radical.

The synthesis of **212** was achieved by reaction of the quinone **211** with phosphonate ester **18** in the presence of *n*-BuLi in THF at −78 °C (Scheme 55).

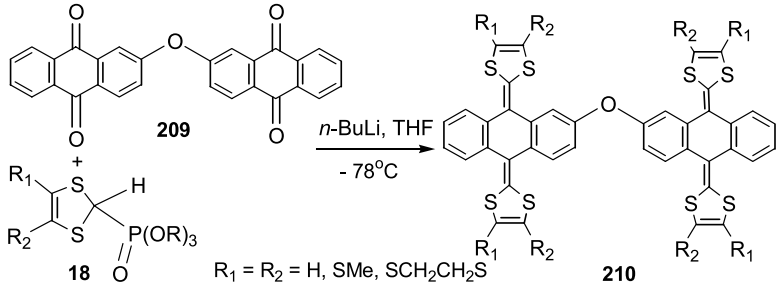
The syntheses of extended tetrathiafulvalenes **215a**,**b** and **216a**,**b** were carried out by a cycloaddition reaction of diazo compounds with C_{60}.[93] In the present case, the diazo compounds are generated from the extended TTF-containing *p*-tosylhydrazones **214a**,**b** by treatment with base. Compounds **214a**,**b** were in turn prepared in good yields from the respective aldehydes **213a**,**b**[93] and toluene-*p*-sulfonylhydrazide. The reaction of *p*-tosylhydrazones **214a**,**b** with C_{60} under basic conditions in toluene at 70–°C afforded **215a**,**b** in 27–31% yield as a mixture of the two possible [5,6]isomers. The [6,6]methanofullerenes **216a**,**b** were prepared either under basic conditions from **214a**,**b** with C_{60} in refluxing toluene or from **215a**,**b** by refluxing in toluene for 30 h in quantitative yield (Scheme 56).[7,94]

7.6. Tetrathiafulvalene-extended-tetrathiafulvalenes (TTF-ex-TTFs)

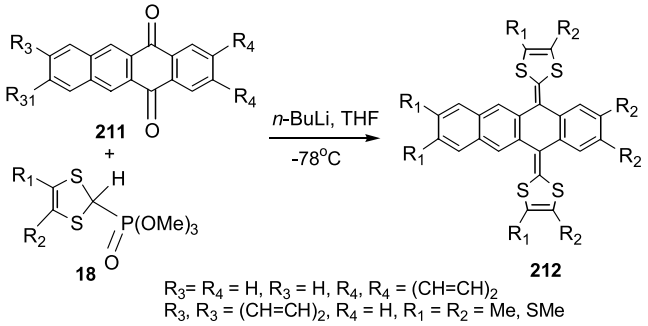
Martin et al.[95] have intensified their research work on finding newly extended tetrathiafulvalene—functionalized *p*-quinodimethanes and their analogues such as



Scheme 53.

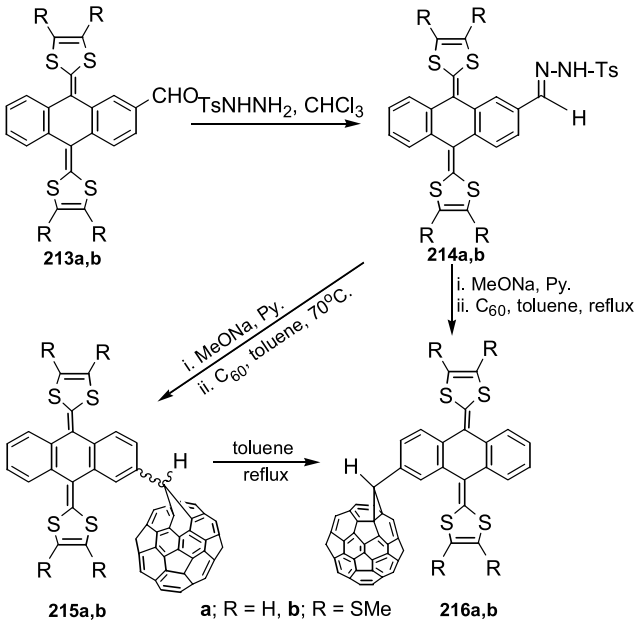


Scheme 54.



Scheme 55.

naphthaquino-dimethane, anthraquinodimethane tetracycline and pentacene as conjugated spacers. Among the modifications reported to date, the extension of the conjugation between the two 1,3-dithiole units of TTF has received much more attention probably due to the predicted importance of these materials as semiconductors,[96] or as having nonlinear-optical properties.[97] Examples of extended TTFs are shown in this text. Yoshida et al.[98] reported the first vinylogue of TTF (**216**), which exhibits a lower oxidation potential than the parent TTF as a result of a decrease in the intramolecular Coulombic repulsion in the dication species. Lorcy et al.[33c] have synthesized the tetrathiafulvalene derivative **217** by using the



Scheme 56.

electrochemical synthesis of 1,4-dithiafulvalenes **218**. Tetrathiafulvalenes bearing a heterocyclic spacer **219** have also been prepared and behaved as strong donors, forming highly conducting CT complexes (Chart 13).[99]

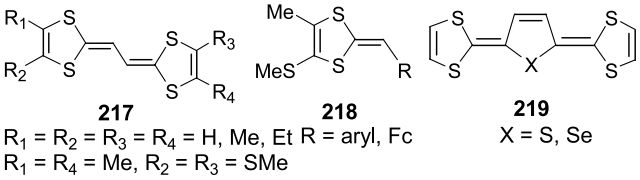


Chart 13.

Recently, Gorgues et al.[100] have reported the first example of a rigid hybrid dimer formed by a TTF unit fused to a quinonoid π-extended TTF **220** (Chart 14). Compound **220** exhibited three reversible oxidation peaks at E^1 0.27 V, E^2 0.71 V and E^3 1.12 V, respectively, vs SCE in dichloromethane CH_2Cl_2. The first peak corresponds to a two-electron process arising from the π-extended TTF moiety.

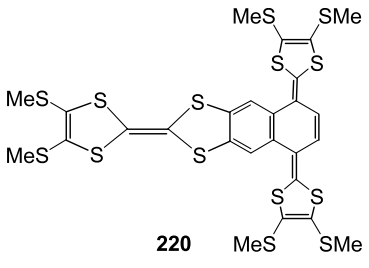


Chart 14.

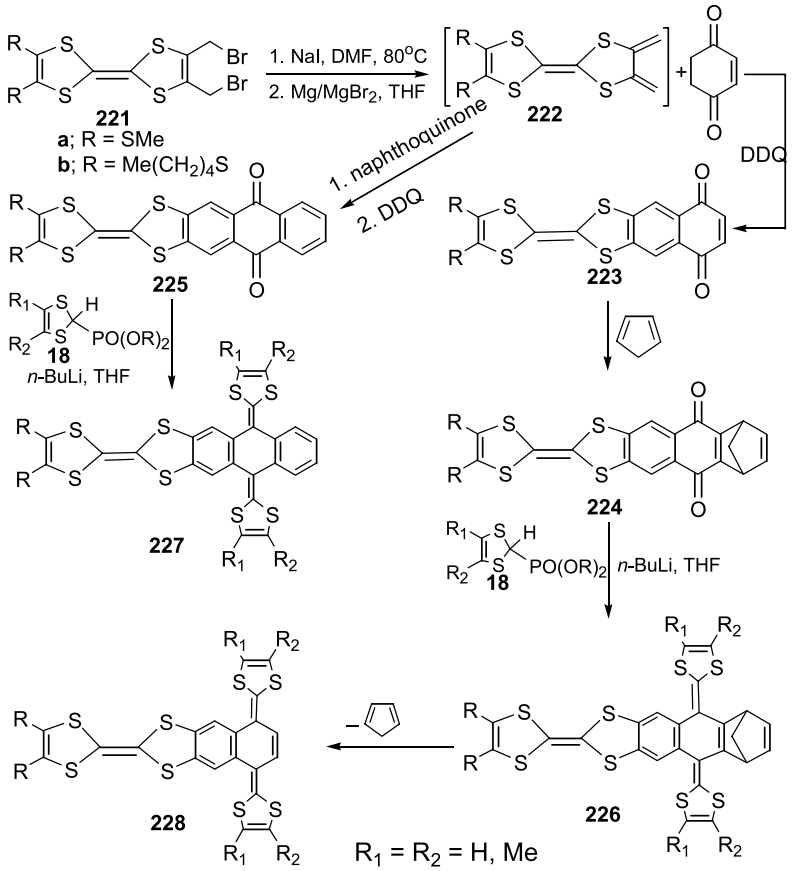
Highly extended and sulfur-rich analogues of tetrathiafulvalene **227** and **228** have been synthesized and characterized by Hudhomme et al.[101] in good yield. The preparation of the π-extended donors **227** was achieved using the tetrathiafulvalene cores in the first step and introducing the quinonoid analogue of TTF in the second step. Vicinal bis(bromomethyl)-TTF derivatives **221**, which are prone to generate 2,3-dimethylene-[2*H*]-TTFs **222** in situ, were used as the starting materials. Cycloaddition of *p*-benzoquinone or 1,4-naphthoquinone to the diene **222** followed by aromatization using the DDQ afforded the corresponding quinones **223** and **225**, which on cycloaddition to cyclopentadiene afforded **224**. Further direct olefination of the diquinones **224** and **225** with phosphonate esters in the presence of *n*-BuLi gave the highly extended donors **227** and **228** in high yield. A retro Diels–Alder reaction could be cleanly performed on **226** upon refluxing in *o*-dichloro-benzene to afford the corresponding extended TTF derivatives **228** (Scheme 57).[101]

7.7. Ferrocene-extended-tetrathiafulvalenes (Fc-ex-TTFs)

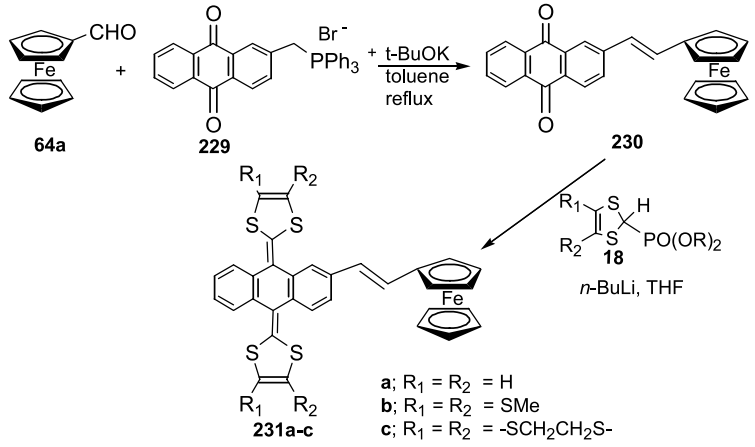
2-Ferrocenylvinyl-9,10-anthraquinone **230** was synthesized according to the method described by Martin et al.[102] and used as a precursor for the synthesis of functionalized tetrathiafulvalene donors **231a–c** by adopting the Wittig–Horner reaction as described in Scheme 58. The reaction of formylferrocene **64a** with 2-anthraquinonyltriphenylphosphinum bromide **229** in refluxing toluene in the presence of *t*-BuOK gave 2-ferrocenylidinyl-9,10-anthraquinone (**230**), which cross-coupled with 1,3-dithiol-2-phosphonate ester **18** afforded the ferrocen-extended-tetrathiafulvalenes **231a–c** in good yields. The electrochemistry of these extended TTF compounds was extensively investigated at different scan rates, temperature, working electrodes and different solvents as well as using cyclic voltammetry. In spite of the fact that that compounds **231a–c** contain two different types of donor moieties (two 1,3-dithioles and a ferrocene), only one oxidation–reduction wave was recognized. From this study and by comparison with derivatives having no ferrocene units such as compound **12**, it was important to recognize that the oxidation process is easier in the case of TTF containing ferrocene.[102] The separation of the three-electron two-oxidation process was clearly resolved upon using the MeCN as the solvent at slow scan rates compared with ferrocene, and similarly TTF without vinylferrocene. All attempts made by Martin to resolve these two-oxidation processes were unsuccessful.[102] In both CH_2Cl_2 and THF, **231b**,**c** exhibited only one oxidation wave due to the coalescence of the two different oxidation processes into one three-electron process leading to the formation of the tricationic state Fc^+-ex-TTF^{2+}.

Recently, Sarhan et al.[103] have prepared the 2-ferrocenylanthraquinone **232** in 21% yield via the diazotization of 2-aminoanthraquinone, followed by coupling with ferrocene in acetic acid at 0 °C. The UV–vis spectrum of the 2-ferrocenylanthraquinone **232** was studied in CH_2Cl_2 and the absorption value was λ_{max} 598 nm (log $\varepsilon = 2.35$), which can be accounted for by an intramolecular charge transfer (ICT) band resulting from the strong electron-donor ferrocene and the electron acceptor anthraquinone moiety (Scheme 59).[103]

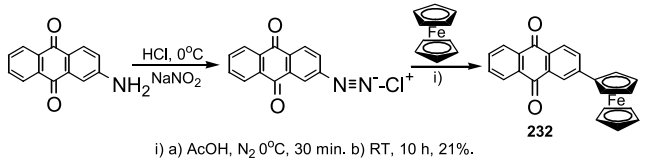
The syntheses of the ferrocene-extended-tetrathiafulvalene **233** and ferrocene-dithiafulvalene **234** were carried out by



Scheme 57.



Scheme 58.

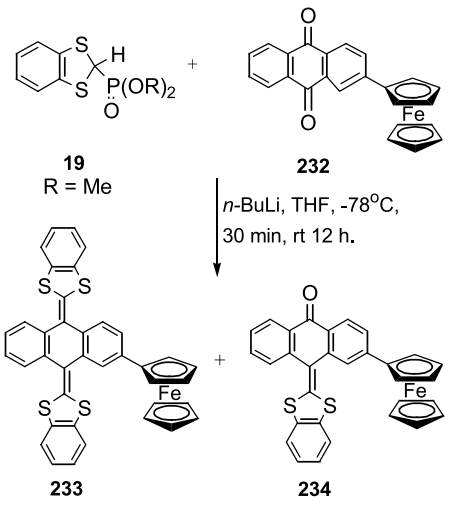


Scheme 59.

application of the Wittig–Horner olefination reaction as described in Scheme 60. Reaction of **232** with **19** in the presence of *n*-BuLi at −78 °C gave a mixture of ferrocene-tetrathiafulvalene **233** and dithiafulvalene **234** in 28 and 24% yields, respectively.[103]

7.8. Crown-annelated derivatives

The first crown-annelated tetrathiafulvalene derivatives were prepared according to the method reported by Bryce



Scheme 60.

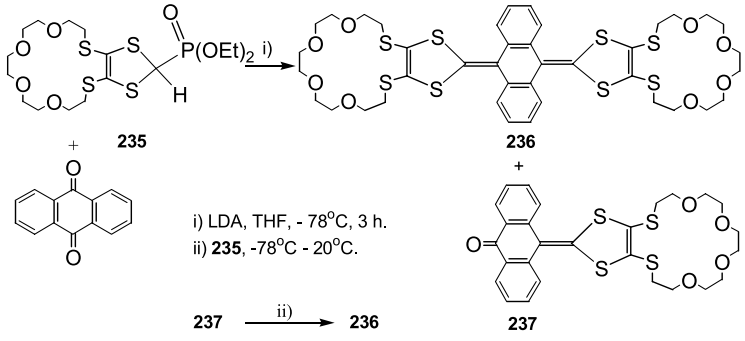
et al.[104] Reaction of anthraquinone with the crown phosphonate ester **235** in THF at −78 °C in the presence of lithium diisopropylamide (LDA) gave a mixture of the crown-annelated derivatives **236** and **237**. The phosphonate ester **235** was prepared according to the standard method previously reported in the literature.[31] The dithiafulvalene derivative **237** was treated under the same conditions with phosphonate ester **235** to afford the crown-annelated 9,10-bis(1,3-dithiol-2-ylidene)-9,10-dihydroanthracene derivative **236**, as shown in Scheme 61.

7.9. Cyclophane-annelated tetrathiafulvalenes

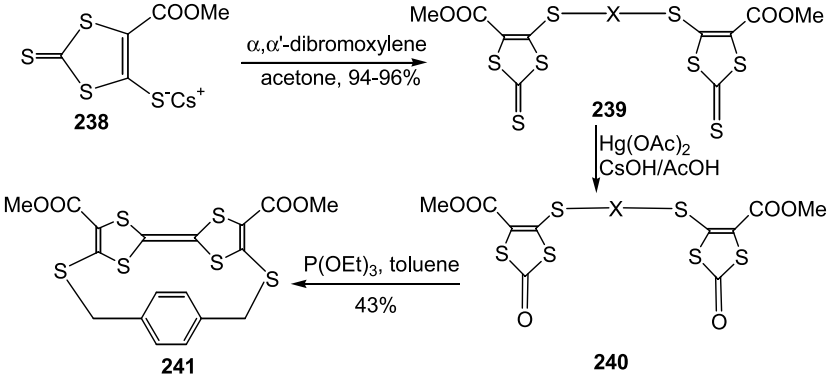
Becher et al.[105] have reported that the synthesis of the tetrathiafulvalenophanes **241** and **242** can be achieved via a Wittig–Horner reaction, as shown in Scheme 62. The cesium 1,3-dithiol-2-thione-5-thiolate **238** was obtained by the reported procedure. Alkylation of **238** with α,α′-dibromoxylenes afforded the bis-1,3-dithiole-2-thiones **239** in quantitative yields. Subsequent transchalcogenation yielded the corresponding bis-1,3-dithiole-2-ones **240**. Treatment of **240** with triethyl phosphite in refluxing toluene gave the corresponding cyclophane **241**.[105]

The macrocycle bis-TTF **242** could be prepared via a stepwise reaction sequence: first a thiolate mono-deprotection of **243** using cesium hydroxide, followed by alkylation with bis[4-(bromomethyl)phenyl]methane gave **245** in 54% yield. Second, subsequent deprotection of the two remaining thiolate functions, followed by a ring-closure reaction under high dilution conditions in the presence of bis[4-(bromomethyl)phenyl]methane, afforded the bis TTF-cyclophane **242** in 55% yield.[105] Similarly, the *cis–trans* mixture of **244** was obtained also as described in Scheme 63.

Bryce et al.[106] have synthesized and investigated a number of cyclophane-annelated tetrathiafulvalenes, which are formed by bridging across the 2,6-positions of the anthracene unit. The 2,6-dihydroxyanthraquinone derivatives **246** were used as the starting materials for the

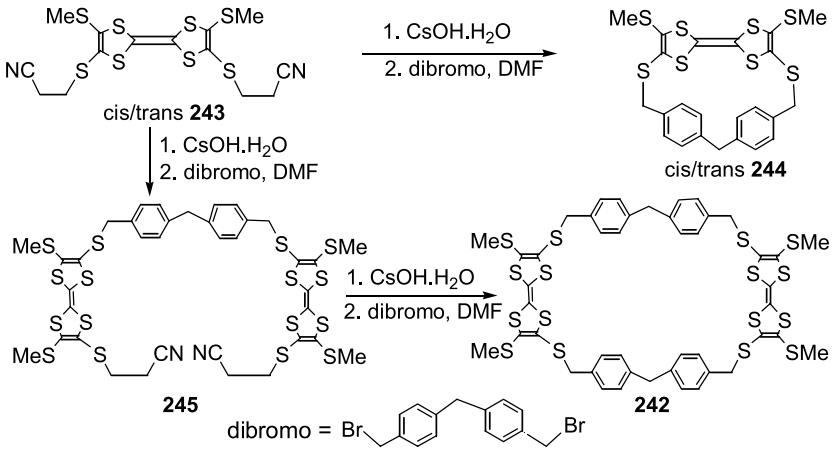


Scheme 61.

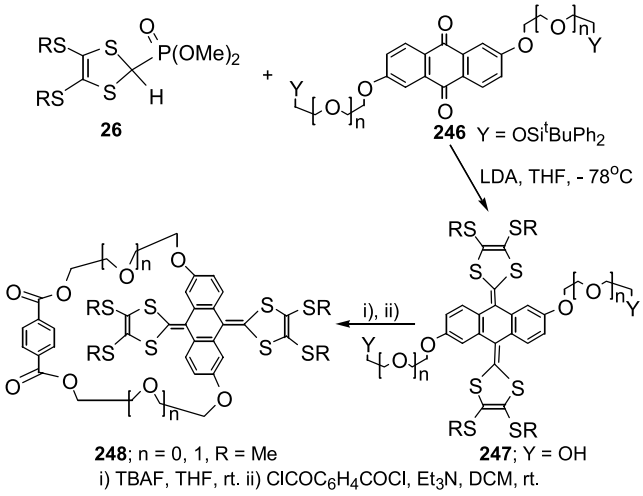


240a; X = α,α′-*o*-xylene, **b**; X = α,α′-*m*-xylene, **c**; X = α,α′-*p*-xylene

Scheme 62.



Scheme 63.



Scheme 64.

syntheses of the cyclophanes **248** using the Horner–Wadsworth–Emmons olefination. Treatment of the phosphonate ester **26** (R=Me) with lithium diisopropylamide (LDA) at −78 °C followed by the addition of **246** yielded the 9,10-bis(1,3-dithiol-2-ylidene(9,10-dihydroanthracene) derivatives **247**, which reacted with phthaloyl chloride to give the cyclophanes **248**, as shown in Scheme 64.

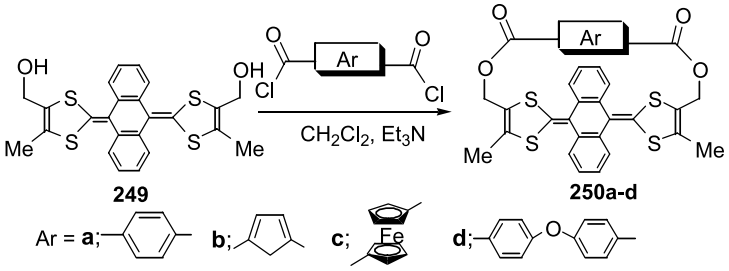
Bridged cyclophanes **250a–d** were also obtained as previously reported by Bryce et al.[107] in low yields (8–15%) from the reaction of the dihydroxy derivative **249** with diacid chlorides in CH_2Cl_2 in the presence of triethylamine. The electrochemical properties and the molecular conformations of the cyclophanes **250a–d** were determined by X-ray crystal analysis, and have been correlated with the steric constraints of the bridging unit (Scheme 65).

Lorcy et al.[108] have described that the synthesis of the cyclophanes **253a**,**b** and **254** could be achieved by Wittig–Horner olefination, as outlined in Scheme 66. The cyclophanes **253** were prepared from **251** by the addition of a stoichiometric amount of terephthalaldehyde or 1,4-diacetyl-benzene in the presence of *n*-BuLi. The bis-aldehyde **252** was obtained by the addition of excess terephthalaldehyde to **251**. Condensation of **252** with the bis(dithiolylphosphonate)-diester **251** ($n=4$) afforded the cyclophane **254** with two extended donor cores.

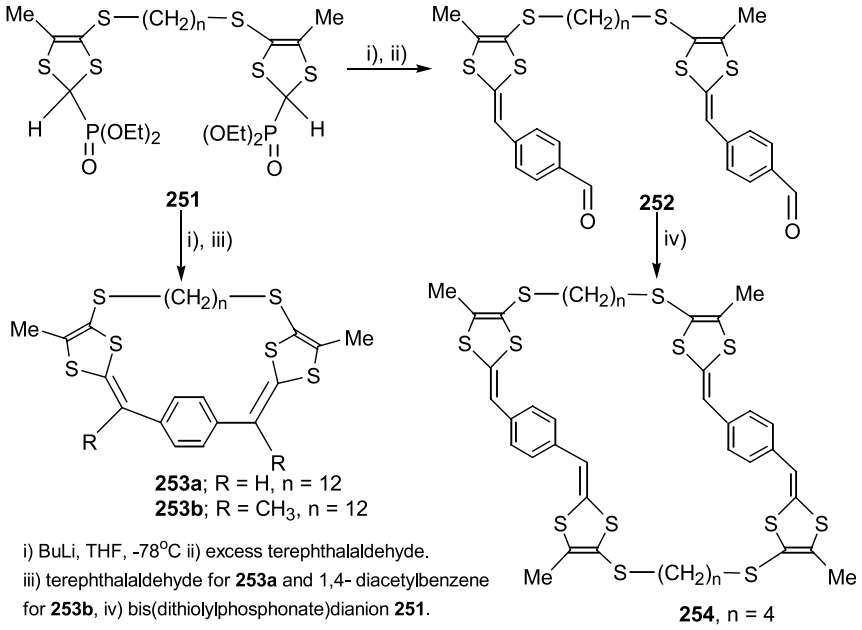
7.10. Heterocyclic ring conjugated spacers

Reaction of phosphonate esters **18** with thiophene-2,5-dicarboxaldehyde **255** (X=S) or the related furan (X=O) or pyrrole (X=NR) derivatives by the application of a Wittig–Horner-type reaction afforded the corresponding conjugated tetrathiafulvalenes **256**, respectively, in variable yields. This reaction was investigated and the TTF donors **256** formed were electrochemically studied using a cyclic voltammetric method by Becher et al. (Scheme 67).[109]

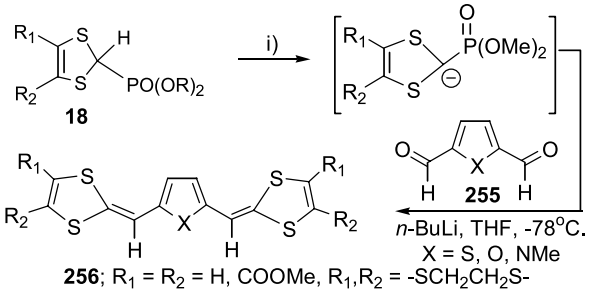
Takahashi and Ise[110] outlined the synthetic routes to the conjugated TTFs **258**, as shown in Scheme 68. The cross-coupling reaction of thiophthalic anhydride with an equimolecular amount of 4,5-bis(methoxycarbonyl)-1,3-dithiol-2-thione (**16**, $R_1=R_2=$COOMe) in the presence of excess trimethyl phosphite in refluxing benzene gave the



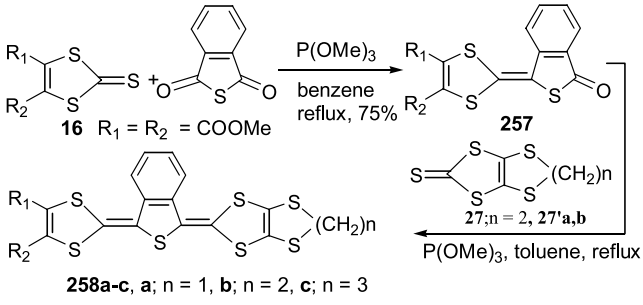
Scheme 65.



Scheme 66.



Scheme 67.



Scheme 68.

mono-capped intermediate **257** in 75% yield. Treatment of **257** with 4,5-alkylenedithio-1,3-dithiol-2-thiones **27** or related derivatives in refluxing toluene containing excess trimethyl phosphite afforded the bis-capped products **258a–c** in 10, 29 and 15% yields, respectively.[110]

Roncali et al.[111] have synthesized the conjugated tetrathiafulvalenes **259–261** (Chart 15) by a double Wittig or Wittig–Horner olefination of the appropriate dicarbaldehyde using the methods described in the literature. The electrochemical behavior of these compounds was also studied and it has been found that the Coulombic repulsion in the dication suggests that the dialkoxy groups induce a major reorganization of the electronic distribution in the molecule.

7.11. 1,3,4,6-Tetrathiapentalene as a conjugated spacer

Yamabe et al.[112] have synthesized and characterized the redox behavior and electrical properties of the unsymmetrical TTFs with 1,3-dithiol-2-ylidene moieties **263a–i** in good yields. Isopropylidene-1,3-dithiolo[4,5-*d*]-1,3-dithiol-2-ones **262** and equimolar amounts of the appropriate 1,3-dithiole-2-thiones **16a–f** were allowed to react in neat triethyl phosphite to give **263a–i** in variable yields. In all cases, the main products were the unsymmetrical TTFs, and the symmetrical molecules were obtained as the minor products. The CT complexes of **263g** and **263i** with tetracyano-*p*-quinodimethane (TCNQ) and tetra-*n*-butylammonium tri-iodide were obtained as the TTF-TCNQ complex and TTF-I_3 salts, respectively. The compressed pellets of these salts using the four-probe technique showed

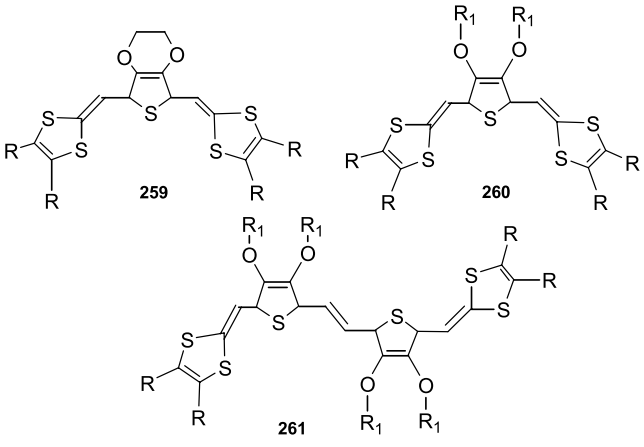
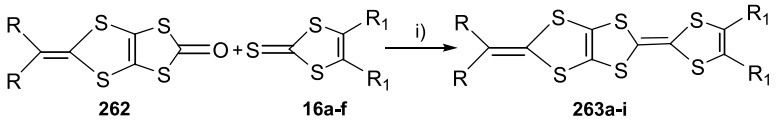
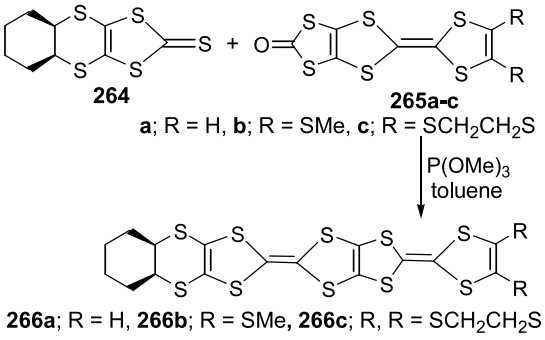


Chart 15.

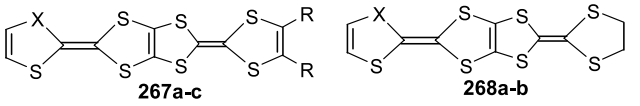


263a: R = Me, R_1 = H
263b; R = Me, R_1 = COOMe
263c; R = Me, R_1 = SMe
263d; R = Me, R_1 = -SCH_2S-
263e; R = Me, R_1 = -$S(CH_2)_2S$-
263f; R = Me, R_1 = -$S(CH_2)_3S$-
263g; R = -$CH_2CH_2SCH_2CH_2$-, R_1 = H
263h; R = -$CH_2CH_2SCH_2CH_2$-, R_1 = COOMe
263i; R = -$CH_2CH_2SCH_2CH_2$-, R_1 = SMe

Scheme 69.



Scheme 70.



267a; X = S, R,R = $S(CH_2)_2S$, **267b**; X = S, R = SMe **268a**; X = S
267c; X = O, R,R = $(S(CH_2)_2S$ **267d**; X = O, R = SMe **268b**; X = O

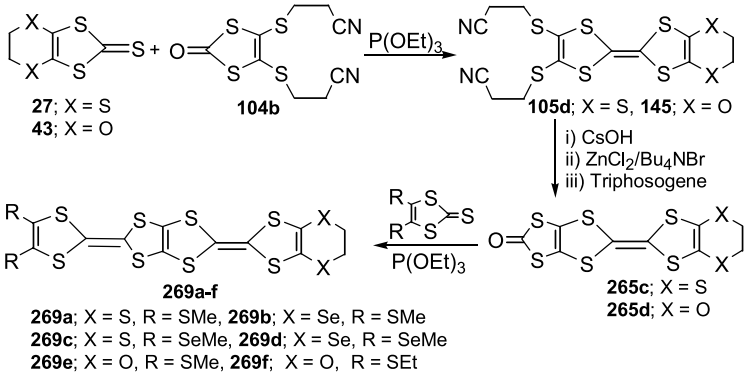
Chart 16.

high electrical conductivities in the range of σ_{rt} 0.4–37 S cm^{-1} at room temperature (Scheme 69).[113]

Mori et al.[114] have shown that the extended tetrathiafulvalene donors **266a–c** could be prepared by the phosphite-mediated cross-coupling of **264** and **265a–c** (Scheme 70). Several radical-cation salts were grown by the electrochemical method. The conductivity of these salts was not very high, but many salts showed metallic behavior at room temperature.

In the same manner, several extended TTF donors such as **267** and **268** (Chart 16) were prepared and used as metallic cation radical salts. The modification of the tetrathiafulvalene TTF skeleton was achieved by replacement of only one outer sulfur atom with an oxygen atom. Although this modification caused a lack of molecular symmetry, the electrochemical studies of these extended tetrathiafulvalenes showed good donor ability to form CT-complexes.[115]

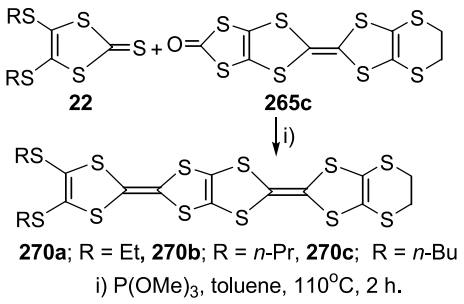
Mori et al.[116] reported that the 2-(4,5-bisthiomethyl-1,3-dithiol-2-ylidene)-5-(4,5-ethylenedithio-1,3-dithiol-2-ylidene)-1,3,4,6-tetrathiapentalene TMET-TTP analogues



Scheme 71.

Table 1. Conductivity of the salts **269a**,**c**,**e**[116]

Comp.	Anion	σ_{rt}/S cm^{-1}	Comp.	Anion	σ_{rt}/S cm^{-1}
269a	I_3	13	**269e**	PF_6	380
	AuI_2	15		ClO_4	560
269c	PF_6	1.6		AsF_6	500
	ClO_4	$>10^{-4}$		$Au(CN)_2$	11
	TCNQ	3.3			



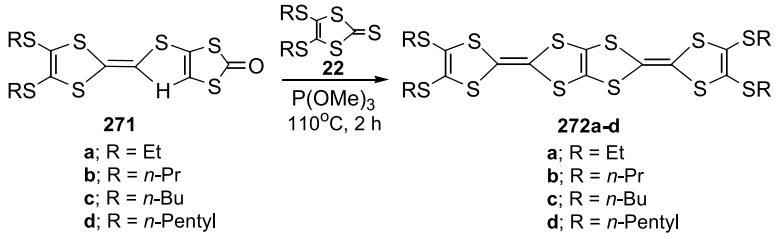
Scheme 72.

269a–f were synthesized using two steps of phosphite-mediated cross-coupling of **27** or **43** with **104b** in the presence of $P(OEt)_3$ to afford the TTFs **105d** (X=S) and **145** (X=O) in good yields. Reaction of **105d** or **145** with CsOH in the presence of $ZnCl_2/Bu_4NBr$ mixture followed by the addition of triphosgene afforded the tetrathiapentalene derivatives **265c** (X=S) and **265d** (X=O) in variable yields. Similarly, cross-coupling of the **265c,d** with the dithione derivatives in $P(OEt)_3$ gave the expected TTFs derivatives **269a–f** as described in Scheme 71.

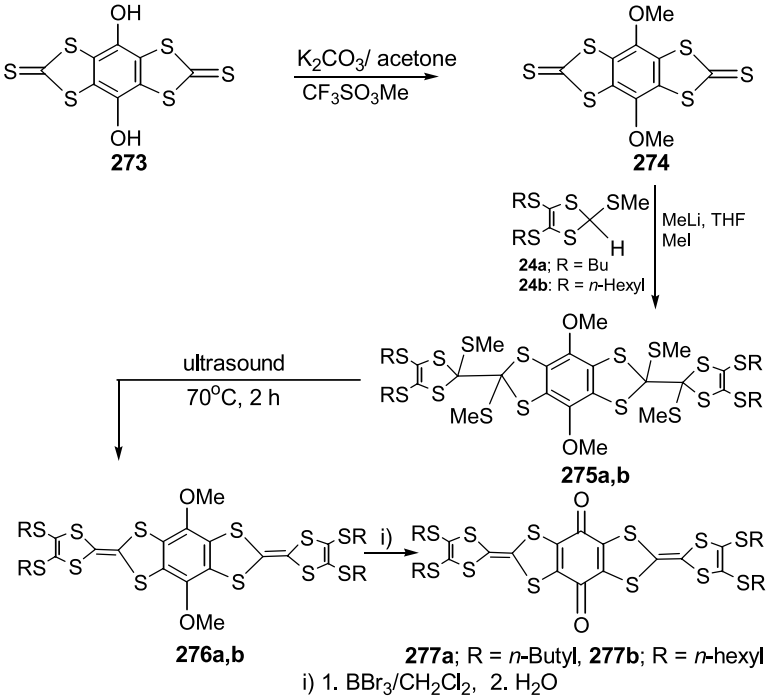
Several radical-cation salts of TTFs **269a–f** were formed and their conductive properties were measured and the results are summarized in Table 1.

Moreover, Mori et al.[117] reported that the donors **270a–c** were synthesized and characterized according to the methods described in Scheme 69. The synthesis of C_nTET-TTP **270a–c** was achieved from 5-(4,5-ethylenedithio-1,3-dithiol-2-ylidene)-1,3,4,6-tetrathiapentalen-2-one **265c**, which was synthesized via 2,3-bis(cyanoethylthio)-6,7-ethylenedithiotetrathiafulvalene according to the reported method.[72,118] The compounds **265c** and **22** were cross-coupled in trimethyl phosphite in toluene at 110 °C to give the corresponding C_nTET-TTP **270a–c** in 10–19% yields (Scheme 72).

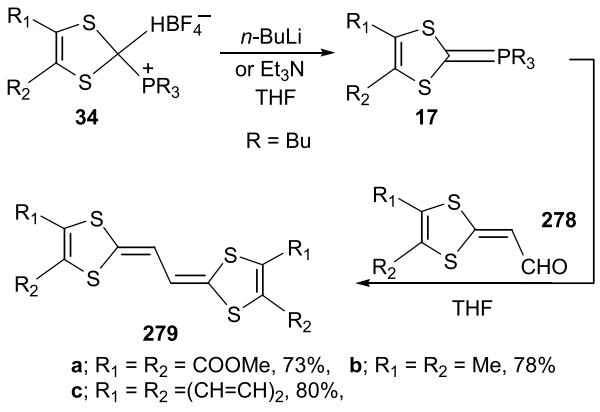
Kimura et al.[119] reported the synthesis of the extended-donor TTC_n-TTP derivatives as shown in Scheme 73. The starting ketones **271** and the thiones **22** were obtained as previously described in literature. The trimethyl phosphite-mediated cross-coupling reaction between **265** and **22** afforded the corresponding TTP derivatives **272a–d** in 10–30% yields (Scheme 73).



Scheme 73.



Scheme 74.



Scheme 75.

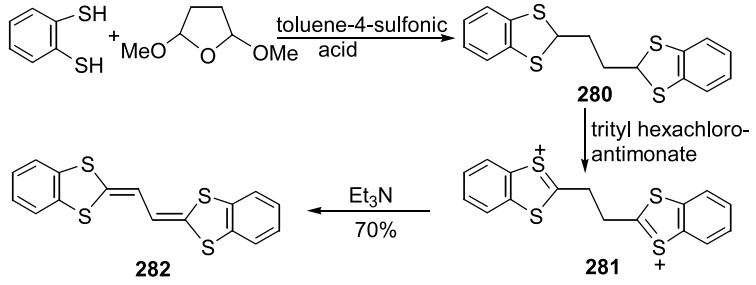
The synthesis of the bis-carbonyl-bridged bis-TTF-systems **277a** and **277b** starts with 4,8-dihydroxy-1,3,5,7-tetrathia-*s*-indacene-2,6-dithione (**273**), which can be etherified with trifluoromethanesulfonic acid methyl ester. Using potassium carbonate as a deprotonating agent led to 4,8-dimethoxy-1,3,5,7-tetrathia-*s*-indacene-2,6-dithione (**274**). Treatment of 4,5-bis(*n*-alkyldisulfanyl)-1,3-dithiol-2-thiones (**24a**,**b**) with **274** produced the bis(hexathioortho-oxalates **275a**,**b** after the addition of an excess of iodomethane. Extrusion of dimethyl disulphide in 1,1,2,2-tetrachloroethane at 70 °C, by ultrasound, afforded the bis(tetrathiafulvalenes) **276a**,**b**. The ether cleavages of **276a**,**b** without affecting the TTF units were carried out by adding the boron tribromide in dry dichloromethane at room temperature, followed by oxidation of the dimethoxy derivatives **276a**,**b** to produce **277a**,**b** (Scheme 74).[120]

8. Conjugated tetrathiafulvalenes

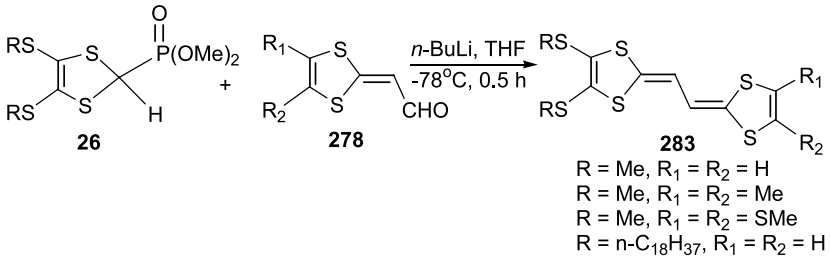
8.1. Synthesis of conjugated tetrathiafulvalenes via cross-coupling reactions

Several TTF analogues have been synthesized with two or more 1,3-dithiol-2-ylidene moieties separated by olefinic bonds such as the conjugated tetrathiafulvalenes **279** in which the two 1,3-dithiole rings are connected with two sp^2 carbons. This class of donor system can be expected to serve as more efficient donor than TTF itself. The synthesis of the conjugated TTFs **279** was achieved by the reaction of 4,5-dithiolyltributylphosphonium tetrafluoroborate **34** with 2-formylmethylene-4,5-disubstituted-1,3-dithiole **277** in THF in the presence of triethylamine or *n*-BuLi in variable yields[121] (Scheme 75).

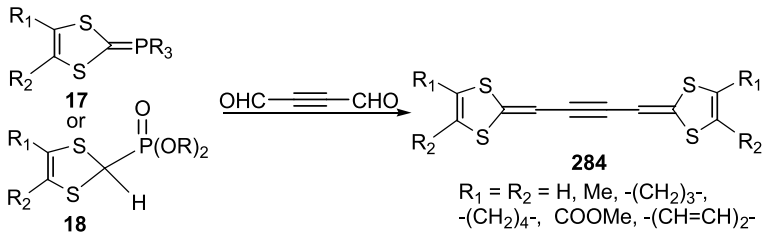
Reaction of two mol equivalents of 1,3-benzenedithiol with 2,5-dimethoxytetrahydrofuran or with succinaldehyde gave compound **280** with a saturated linkage between the



Scheme 76.



Scheme 77.



Scheme 78.

heterocyclic rings. Hydride abstraction from **280** using trityl hexachloroantimonate afforded the salt **281**, which was readily deprotonated by triethylamine to yield the compound **282** in 70% overall yield as a slightly air-sensitive crystalline solid[122] (Scheme 76).

The synthesis of theconjugated donors **283** was accomplished by Bryce and[17] and Becher[123] using the reaction of 4,5-disubstituted-1,3-dithiole-2-phosphonate esters **26** with the appropriate aldehyde derivatives **278** following the established Wittig–Horner procedure in different yields (Scheme 77).

The Wittig or Wittig–Horner reaction of acetylene dicarbaldehyde with phosphoranes or phosphonate esters, respectively, generates the symmetrical acetylenic analogues of TTF **284**.[124] From the mono(diethyl acetal) the unsymmetrical acetylenic analogues of TTF can be obtained. The yields are increased when complexes of the dialdehyde or the mono(diethyl acetal) with dicobalt hexacarbonyl are used as the starting material instead of the corresponding free alkynes. The final decomplexation is achieved by treatment with trimethylamine oxide (Scheme 78).[125]

8.2. Synthesis of conjugated tetrathiafulvalenes by oxidation

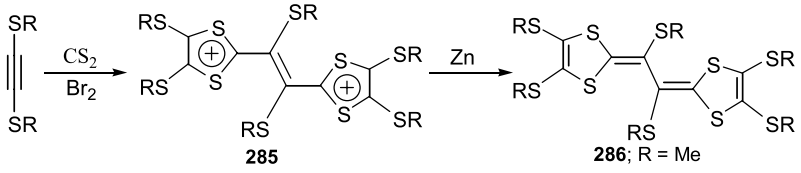
Oxidation of bis(methylthio)acetylene with bromine in carbon disulfide leads to the dication of the corresponding ethandiylidene-2,2′-bis(1,3-dithiole) **283** which can be reduced with zinc to the parent compound **284**.[29,126] An extension of the π-system between the two 1,3-dithiol-2-ylidene moieties can also be achieved with olefinic and acetylenic bonds (Scheme 79).

A cumulene skeleton has been inserted between the 1,3-dithioles in **292** and **293** by the reaction of the dithiolium salts **287** with (trimethylsilyl)acetylene-magnesium bromide, followed by hydrolytic removal of the trimethylsilyl group from **288**. The dithiole **289** obtained can be coupled with the starting 2-morpholino-1,3-dithiolium salts **287** or dimerized in the presence of cupric acetate to the corresponding dimeric products **290**. Removal of the morpholino substituent by perchloric acid provided the cumulenic TTFs **292** and **293**.[127] So far, only the dications **292** and **293** could be isolated in fairly good yields (70–90%), the neutral forms being extremely unstable. Both positive charges beside more in the two 1,3-dithiolium moieties than in the corresponding ethanediylidene units (Scheme 80).

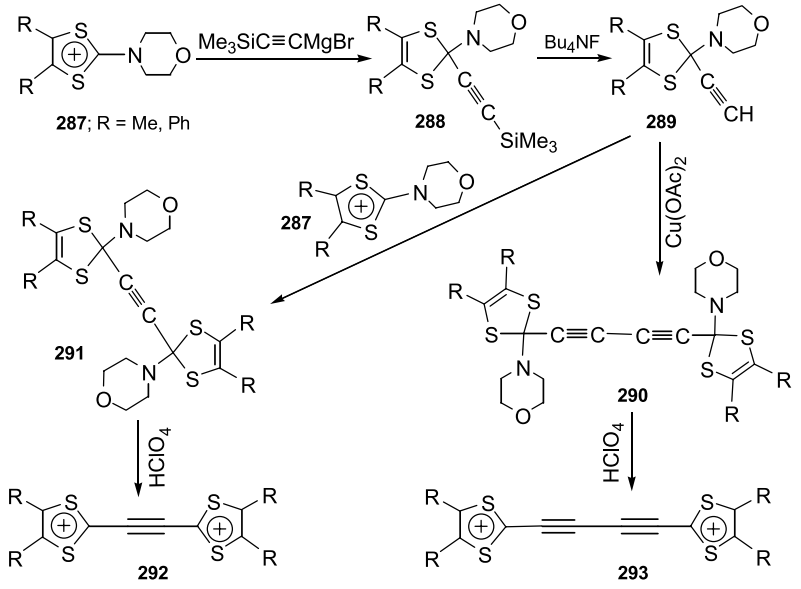
Probably, π-conjugation between the 1,3-dithiolium units is less effective through an acetylenic bond than through an olefinic bond using a Wittig–Horner reaction, TTF derivatives are obtained with double bonds of olefinic and aromatic character between the two 1,3-dithiol-2-ylidene moieties in 40–90% yield.[128]

8.3. Electrochemical oxidation of dithiafulvalenes

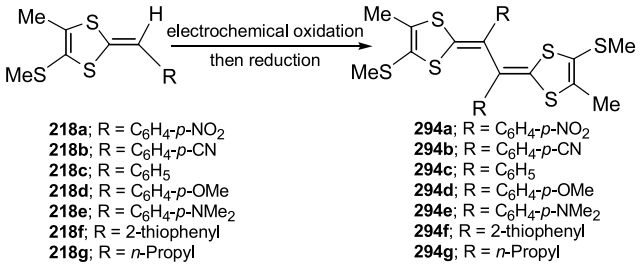
The intramolecular oxidative dimerization of 1,4-dithiafulvalene to yield the dication of the corresponding



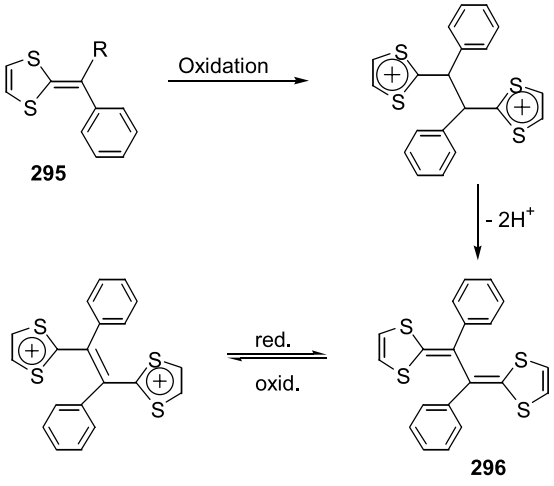
Scheme 79.



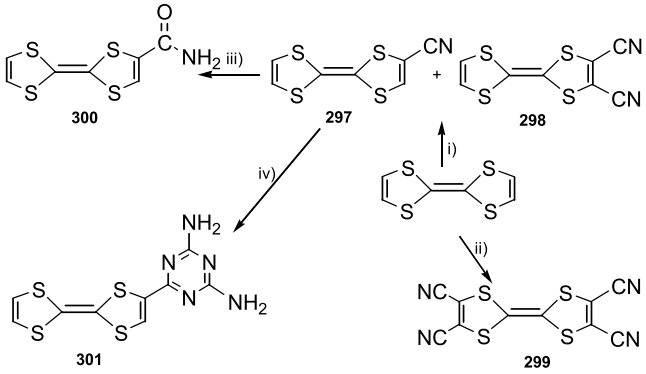
Scheme 80.



Scheme 81.



Scheme 82.



i) 1. LDA (1.1 eq.), Et_2O, - 78°C, 2. TsCN (1.1 eq.). ii) 1. LDA (4.4 eq.), Et_2O, - 78°C, 2. TsCN (4.4 eq). iii) NaOEt, EtOH, 25°C, 65%. iv) dicyanodiamide, reflux, 66%.

Scheme 83.

extended TTF system has been reported previously[129] and a similar process is thought to occur in the electrochemical polymerization of tris(1,4-dithiafulvalene) derivatives.[130] Lorcy and co-workers[33c] have reported the isolation of neutral systems **294** from monomer units **218** by a two-step electrochemical oxidation followed by reduction and concluded that the reaction involved dimerization of the cationic radical **218** (Scheme 81).

The mechanism of the electrochemical oxidation of dithiafulvalenes was explained by Fourmigué et al.[130] according to the steps shown in Scheme 82.

9. Reactions of tetrathiafulvalenes

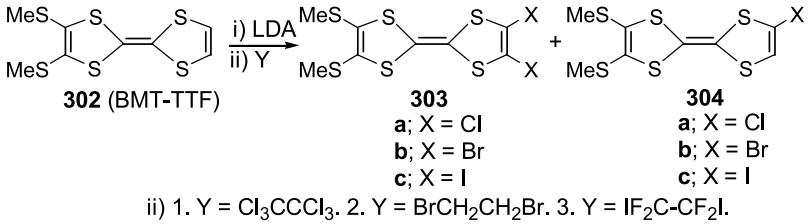
9.1. Reaction with LDA to form 4,5-disubstituted derivatives

TTF was monolithiated with lithium diisopropylamide using a procedure described by Green.[131] Addition of *p*-toluenesulfonyl cyanide to the lithiated species afforded the derivatives **297** (75%) and **298** (4%). The formation of a small amount of **298** presumably occurs due to a disproportionation of the mono-anion. The synthesis of **299** was achieved by the addition of excess *p*-toluenesulfonyl cyanide to tetralithio-TTF. The hydrolysis of **297** using excess sodium ethoxide in ethanol gave 4-amido-TTF **300** (65%). The reaction of **297** with dicyanodiamide under basic conditions gave the diaminotriazine derivative **301** in a respectable yield (66%) (Scheme 83).[131]

9.2. Halogenation of TTFs using LDA

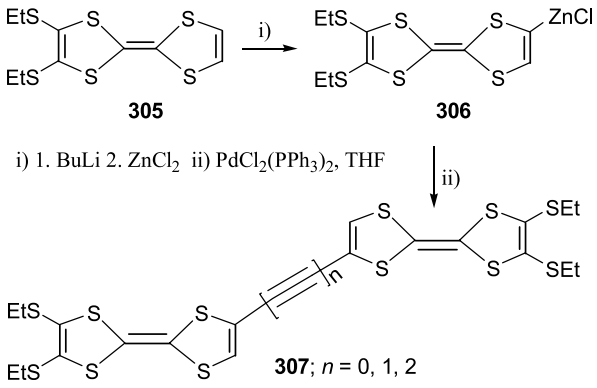
Synthesis of the halogenated BMT-TTF derivatives **303a–c** and **304a–c** was carried out by using lithiation of **302** with lithium diisopropylamide (LDA), followed by treatment with halogenating reagents.[132] Although the reaction of ethylenedithiotetrathafulvalene (EDT-TTF) with LDA led to the cleavage of the ethylenedithio ring, the treatment of BMT-TTF **302** with LDA produced the corresponding lithio derivative without decomposition. Thus, the reaction of **302** with LDA in THF at −78 °C followed by hexachloroethane at −78 °C to room temperature produced the dichloride **303a** in 49% yield, along with traces of the monochloride **304a**. The reaction depends upon the halogenating reagent and the equivalent amount of LDA (Scheme 84).[132]

The reaction of the BET-TTF derivative **305** with *n*-BuLi at −78 °C in THF, followed by treatment with $ZnCl_2$, afforded the organozinc intermediate **306**. A homocoupling reaction of **306** with bisditriphenylphosphinylpalladium chloride

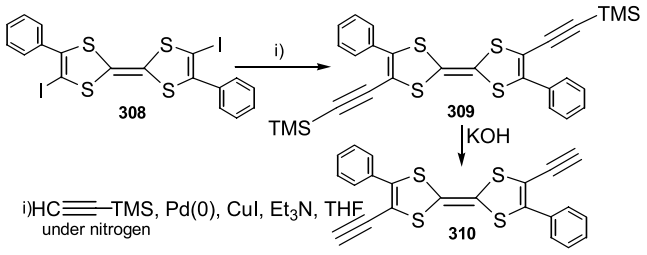


ii) 1. Y = Cl_3CCCl_3. 2. Y = $BrCH_2CH_2Br$. 3. Y = $IF_2C\text{-}CF_2I$.

Scheme 84.



Scheme 85.



Scheme 86.

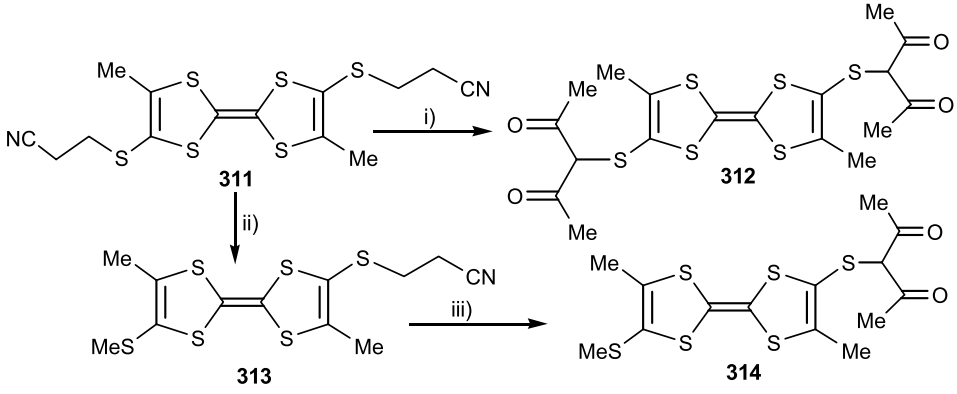
$PdCl_2(PPh_3)_2$ at room temperature in THF produced the bis-TTF derivatives **307** ($n=0$–2) in 27% overall yield based on **305**, as shown in Scheme 85.[133]

9.3. Reaction with trimethylsilylacetylene

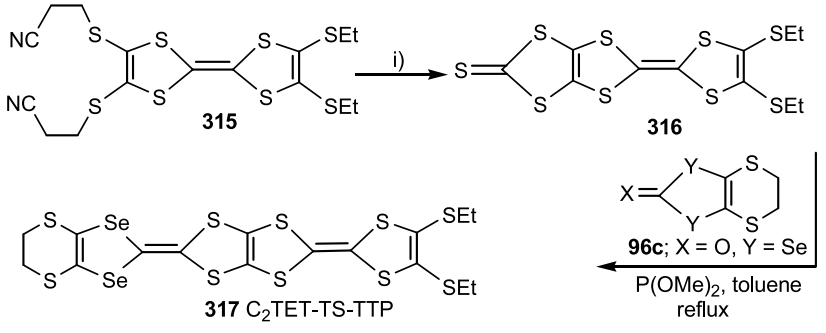
The reaction of *trans*-2,6-diiodo-3,7-diphenyltetrathiafulvalene **308** with trimethylsilylacetylene in the presence of $Pd(PPh_3)_4$, CuI and Et_3N in THF gave the symmetrical 2,6-bis[2-(trimethyl-silyl)ethynyl]-3,7-diphenyltetrathiafulvalene **309** in 70% yield. Treatment of **309** with aqueous KOH easily generated **310** (Scheme 86).[134]

9.4. Reaction with chloroacetylacetone

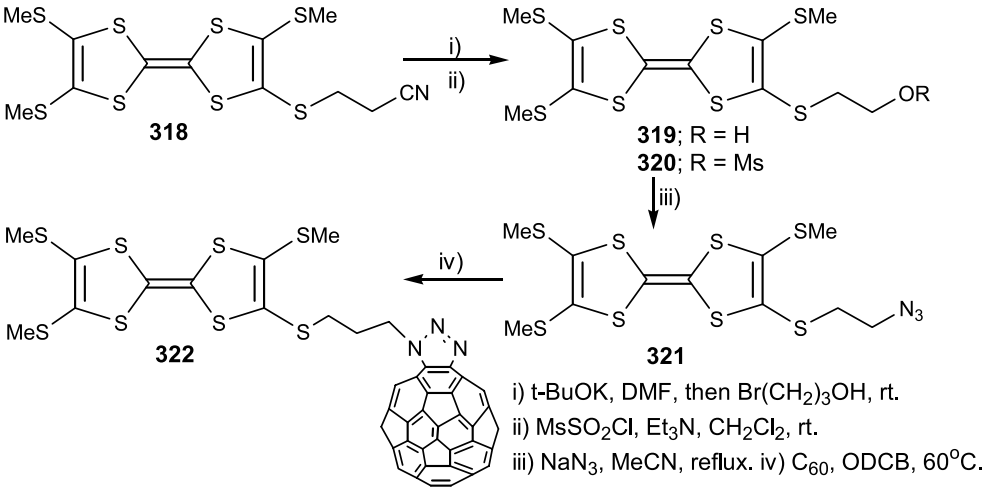
The mono-acetylacetone TTF **314** and the di-acetylacetone **312** were synthesized according to the method described in the literature. Selective monodeprotection of bis-cyanoethylthio TTF **311** by the addition of 1 equiv of base followed by alkylation of the monothiolate thus formed led to the formation of **313**. Deprotection of the second cyanoethylthio group via the same procedure and subsequent quenching with chloroacetylacetone gave the TTF **314** in 88% yield.[135] Similarly, TTF **312** was obtained by the deprotection of **311** followed by alkylation using chloroacetylacetone (Scheme 87).



Scheme 87.



Scheme 88.



Scheme 89.

9.5. Reaction with 1,3-diselenol-2-one derivatives

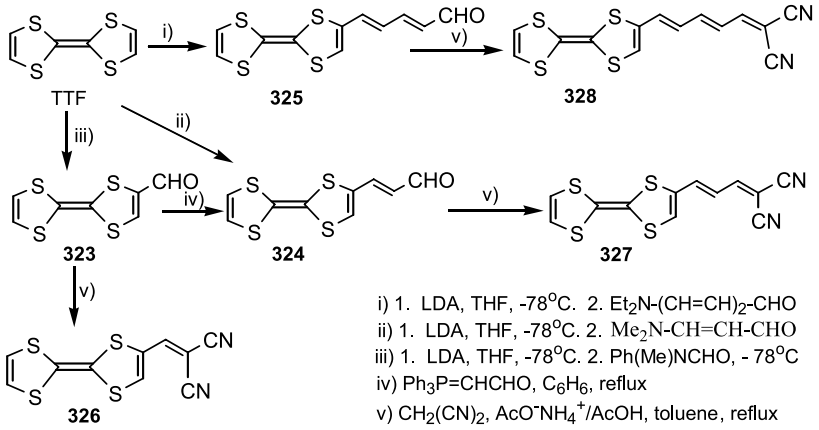
Treatment of 2,3-bis(2-cyanoethylthio)-6,7-bis(ethylthio)-TTF **315** with excess cesium hydroxide monohydrate in acetone in the presence of $ZnCl_2$ and tetrabutylammonium bromide followed by the addition of 1,1′-thiocarbonyldimidazole afforded the corresponding TTF **316**.[136] Refluxing of **316** with the compound **96c** (X=O, Y=Se) in toluene in the presence of trimethyl phosphite gave the target compound C_2TET-TS-TTP **317**, Scheme 88.[136]

9.6. Reaction with C_{60} derivative

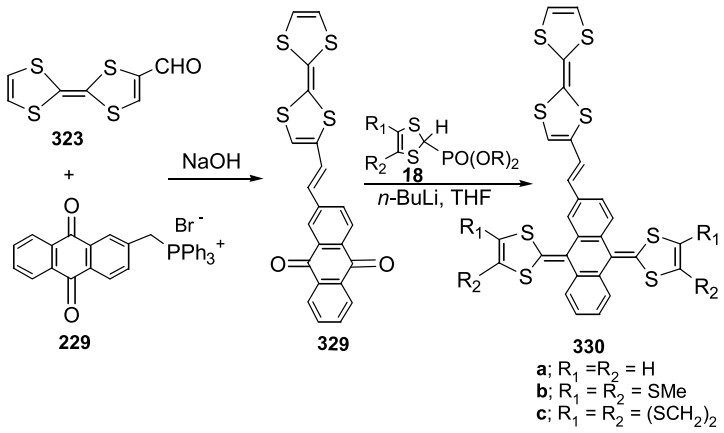
Martin et al. reported that the TTF derivative **322** could be obtained from the previously reported compound **318** in three steps, as shown in Scheme 89.[137] In particular, deprotection of compound **318** with *t*-BuOK in DMF afforded the thiolate, which was then reacted with 3-bromopropanol forming compound **319** (90% yield). Mesylation of **319** gave **320** in 89% yield, which on treatment with activated NaN_3 in refluxing acetonitrile furnished the azido derivative **321** in 67% yield. Finally, reaction of C_{60} with azide **321** in *o*-dichlorobenzene (ODCB) at 60 °C overnight led to the TTF derivative **322** in 54% yield (Scheme 89).

9.7. Formylation of tetrathiafulvalenes

Martin and co-workers reported that the synthesis of tetrathiafulvalene-π-acceptor (TTF-π-A) derivatives has been carried out by the reaction of appropriately functionalized acceptor moieties with formyl-TTF and its vinylogues.[138] The synthesis of formyl-TTF **323** was first reported by Green[131] via the reaction of monolithio-TTF with dimethylformamide. Later, Garin, Bryce and co-workers thoroughly investigated this reaction with a variety of formylating reagents in order to increase the yields and optimize the preparation of formyl-TTF **323**.[139] Upon condensation of formyl-TTF **323** with malononitrile, the TTF-π-acceptor **326** was obtained as a D-π-A system. A subsequent Wittig reaction of formyl-TTF **323** with phosphorane led to the formyl-TTF vinylogue **324** with an overall yield of 51% based on TTF. The formyl vinylogue **324** when reacted with malononitrile furnished the TTF-π-acceptor **327** in good yield. Subsequent reaction of the monolithiated product of TTF with LDA in THF at −78 °C with the formylating agent Et_2N–$(CH{=}CH)_2$–CHO afforded the vinylogue **325**, which upon condensation with malononitrile gave the tetrathiafulvalene-π-acceptor (D-π-A) **328**. The detailed reactions of the TTF with different formylating reagents along with the reaction conditions are presented in Scheme 90.



Scheme 90.



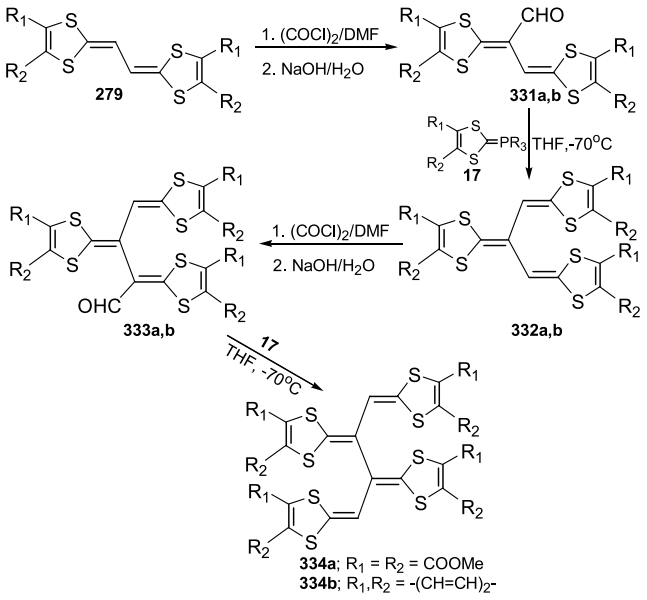
Scheme 91.

9.8. Reaction with anthraquinone derivatives

The reaction of formyl tetrathiafulvalene **323** with the phosphonium salt **229** under basic conditions was investigated by Martin et al.[140] to give the olefination product 2-(tetrathia-fulvalenylvinyl)-9,10-anthraquinone **329** in 90% yield, which upon cross-coupling with the phosphonate esters **18** afforded the tetrathiafulvalene-extended-tetrathiafulvalenes (TTF-ex-TTF) **330a–c** (Scheme 91).

10. Dendralene and radialene tetrathiafulvalene analogues

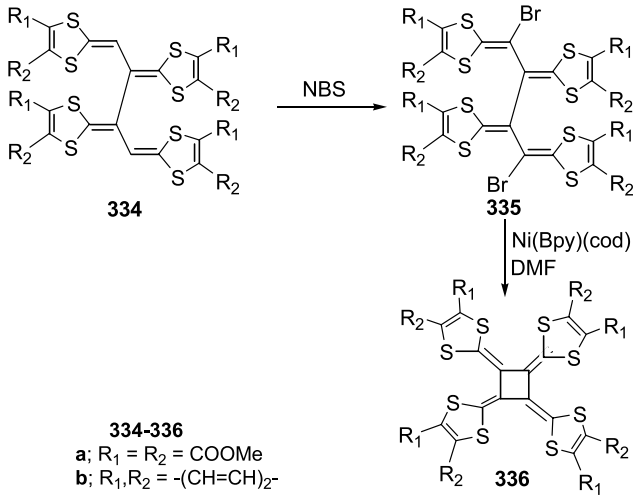
Treatment of tetrathiafulvalene derivatives **279** with oxalyl chloride in DMF at 0 °C followed by subsequent hydrolysis of the reaction mixture with sodium hydroxide in a chloroform/water mixed solvent gave the corresponding 1-formyl derivatives **331a**,**b**. The reaction of the formyl compounds **331a**,**b** with 1,3-dithiole-2-ylidene-tri-*n*-butyl-phosphoranes **17** afforded **332a**,**b** in 83 and 92% yield, respectively. In similar manner, formylation of **332a**,**b** gave the formyl derivatives **333a**,**b** in good yields. The formyl derivatives **333a**,**b** were allowed to cross-couple with **17** in THF at −78 °C to produce the dimeric products of the corresponding tetrathiafulvalenes **334a**,**b** in 89 and 73% yield, respectively (Scheme 92).[98,141]



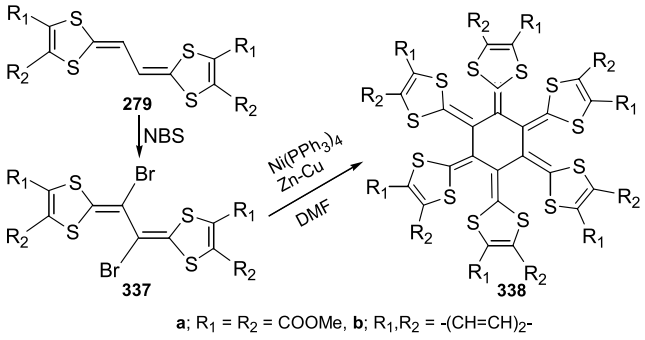
Scheme 92.

Yoshida et al.[141] have synthesized several tetrathiafulvalene analogues containing two or more 1,3-dithiol-2-ylidene moieties separated by conjugated double bonds such as dendralenes and radialenes in low yields. Bromination of **334**, which was obtained, by two consecutive Vilsmeier reactions with oxalyl chloride in DMF and a Wittig reaction, from TTF **279**, using *N*-bromosuccinimide (NBS) in CH_2Cl_2 at room temperature afforded the 1,4-dibromo derivatives **335** in quantitative yields. Treatment of the 1,4-dibromo derivatives **335** with a zero-valent Ni(bpy)(cod)-complex (bpy = 2,2-bipyridyl, cod = 1,5-cyclooctadiene) in DMF at room temperature gave the [4]-radialenes **336** in very low yield (3%) (Scheme 93).[141]

Bromination of **279** with N-bromosuccinimide (NBS) afforded the dibromo derivatives **337** in good yields. An intramolecular reductive coupling reaction using an $Ni(PPh_3)_4$ complex and a Zn–Cu couple in the presence of DMF as the solvent gave the corresponding hexakis(1,3-dithiol-2-ylidene)cyclohexanes **338** (Scheme 94).[142]



Scheme 93.



Scheme 94.

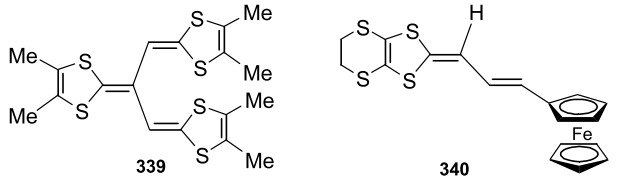


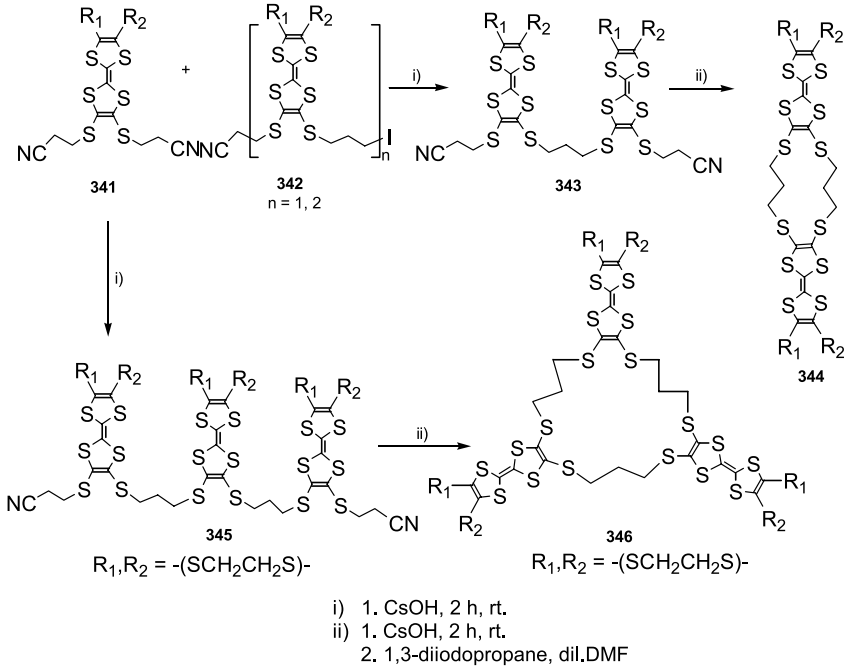
Chart 17.

New [3]- and [4]-dendralenes and [6]-radialenes bearing electron-donor 1,3-dithiole **339** and ferrocene substituents **340** have been also synthesized and characterized (Chart 17).[142b]

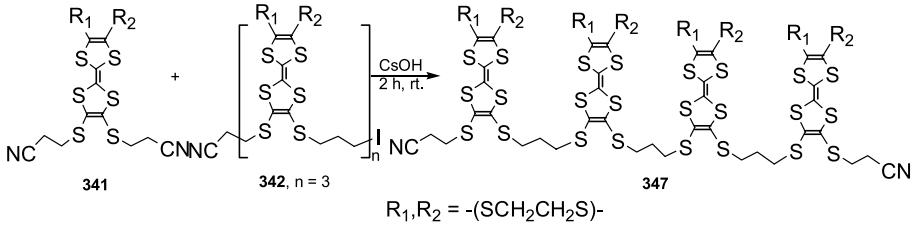
11. Dimeric, trimeric, tetrameric, dendrimeric and oligomeric tetrathiafulvalenes

The syntheses of dimeric TTFs **346** and trimeric TTFs **335** were achieved by the reaction of the dithiolate anions formed from the dicyanoethylthio TTF **341** with the 2-iodopropyl-tetrathiafulvalene derivatives **342** in DMF as the solvent.[143] Reaction of substituted TTFs **341** with **342** ($n=1$) in the presence of CsOH in DMF gave **343**, which cyclized to the dimeric products **344** in good yield. In the same manner, the reaction of **341** with **342** ($n=2$) gave the corresponding **345** which upon cyclization using 1,3-diiodopropane afforded the trimeric products **346** (Scheme 95).[143]

Similarly, the reaction of **341** with the trimeric TTF **342** ($n=3$) in an aqueous solution of CsOH gave the tetrameric product **347** (R_1, $R_2=SCH_2CH_2S$) (Scheme 96).[143]



Scheme 95.



Scheme 96.

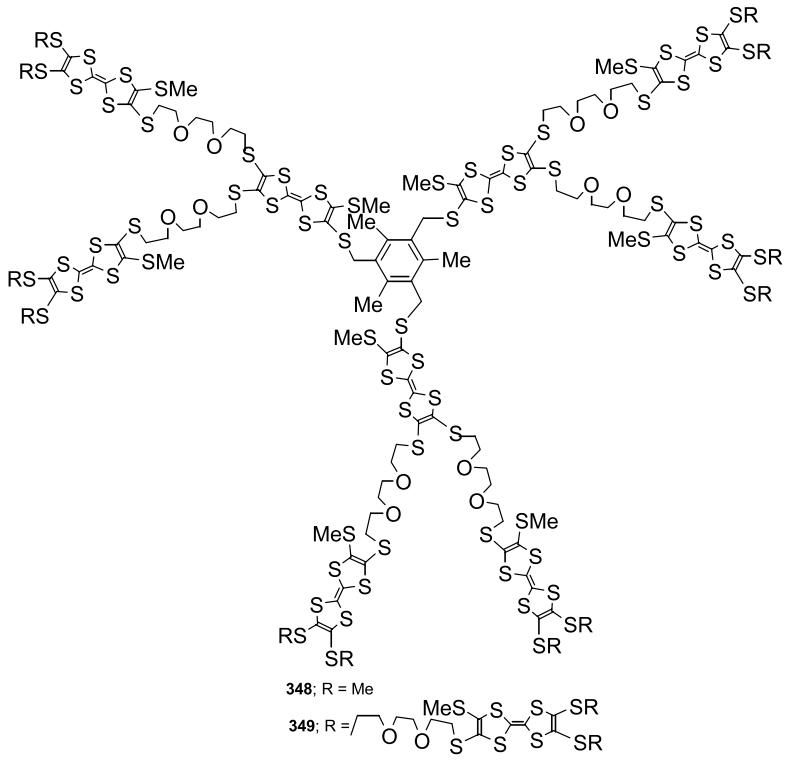


Chart 18.

A number of dendrimers and oligomers related to tetrathiafulvalene analogues have been synthesized and characterized by Bryce et al.[143b] The electrochemical properties of these dendrimers **348** and **349** were also studied using cyclic voltammetry. The redox behavior of the dendrimers exhibited two-oxidation potentials associated with two reductions at $E^{ox1}=0.55$ V and $E^{ox2}=0.86$ V (Chart 18).

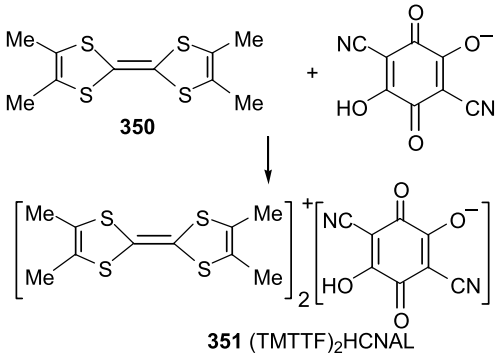
12. Applications and uses of tetrathiafulvalenes

Molecular sensors based on TTF have been reported recently. Hansen and Becher have reviewed the properties and uses of many tetrathiafulvalene derivatives as attractive building blocks, new donors, molecular shuttles, NLO materials, organic ferromagnets, sensors, conducting polymers, and electroactive Langmuir–Blodgett (LB) films and also their C_{60} complexes.[144]

12.1. Reaction with TCNQ to form CT complexes

Tetramethyltetrathiafulvalene **350** reacts with 2,5-dicyano-3,6-dihydroxy-1,4-benzoquinone H_2CNAL in THF/CH_2Cl_2 (2:1 ratio) to form a charge-transfer complex $(TMTTF)_2$-HCNAL **351** as single black crystals, which showed semiconductive behavior (Scheme 97).[145]

The TTF-TCNQ salts **352** and **353** were synthesized according to the procedure described by Bryce et al.[146] The behavior of modified TTF-TCNQ salts as potential mediators was compared to the unmodified TTF-TCNQ. The modified TTF-TCNQ formed a smooth well-defined film attached to the electrode surface. The unmodified TTF-TCNQ salt formed microcrystalline deposits that did not adhere firmly to the electrode surface (Chart 19).[146]



Scheme 97.

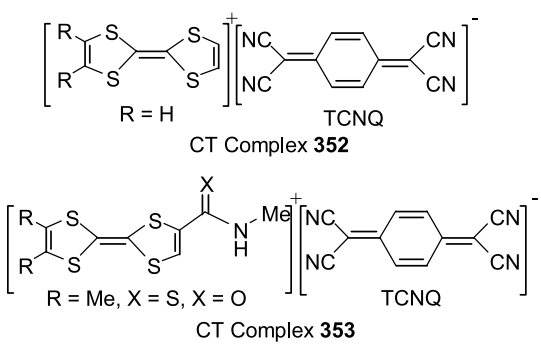
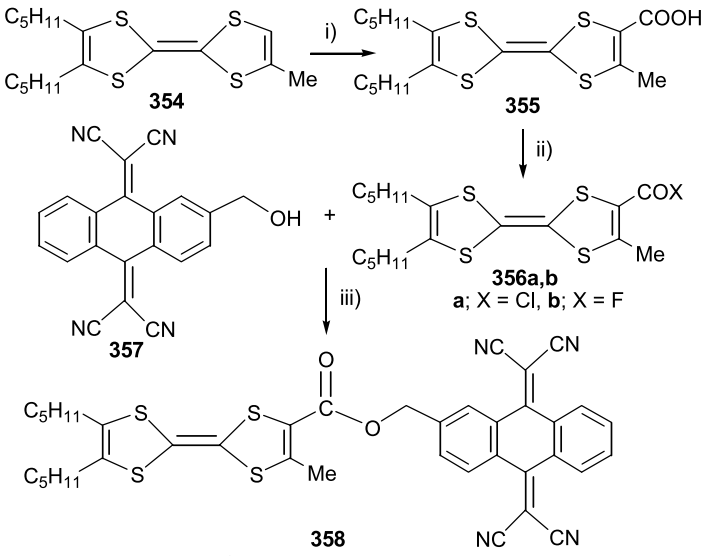


Chart 19.



Scheme 98.

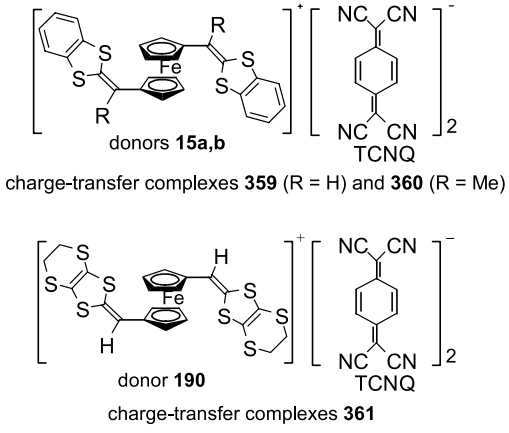


Chart 20.

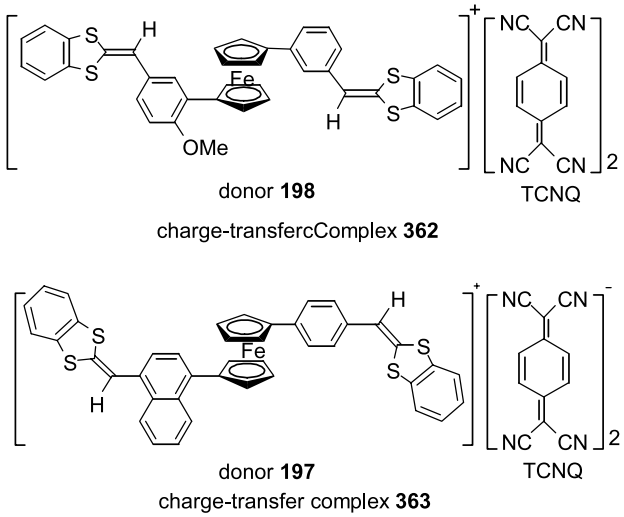


Chart 21.

12.2. Reaction with TCNAQ derivatives

Bryce et al.[147] reported that the tetrathiafulvalene derivatives underwent a reaction with TCNAQ or with its related TCNAQ-CH_2OH **357** to form the charge-transfer complex **358** as a brown crystalline solid in 50% yield. Lithiation of TTF **354** with LDA in THF at −78 °C followed by reaction with carbon dioxide gave the carboxylic acid derivative **355** in 61% yield. Conversion into the carbonyl chloride **356a** (X=Cl) and carbonyl fluoride **356b** (X=F) was readily achieved by reaction with oxalyl chloride and with cyanuric fluoride in pyridine, respectively. Reaction of **356a**,**b** with TCNAQ afforded the target molecule **358** (Scheme 98).[147]

The CT complexes **359**, **360** and **361** were obtained from the reaction of donors **15a**,**b** or **190** with the well-known organic acceptor TCNQ in dichloromethane at reflux temperature in good yields as dark-green crystals (Chart 20).[4,13]

Similarly, the CT complexes **362** and **363** were obtained from the reaction of the conjugated TTFs **197** or **198** with TCNQ in refluxing dichloromethane for a long period. The electrical conductivity measurements on **359** and **361** showed a substantial conductivity ($\sigma=0.2$ S cm^{-1} and $\sigma=0.26$ S cm^{-1}, respectively), the CT complex **360** exhibited less conductivity ($\sigma=4.8\times10^{-4}$ S cm^{-1}), whilst the CT complexes **362** and **363** were found to act essentially as insulators ($\sigma<10^{-10}$ S cm^{-1}) (Chart 21).[4,13]

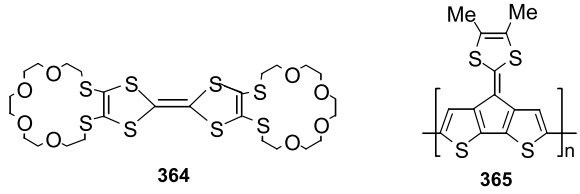


Chart 22.

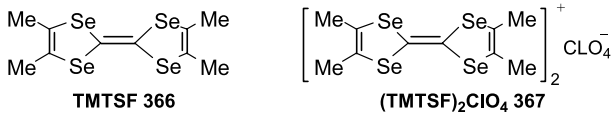


Chart 23.

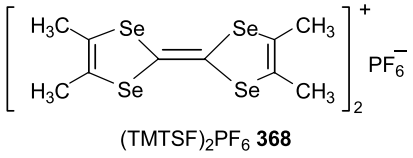


Chart 24.

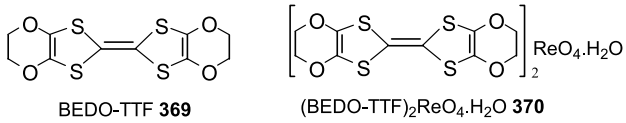


Chart 25.

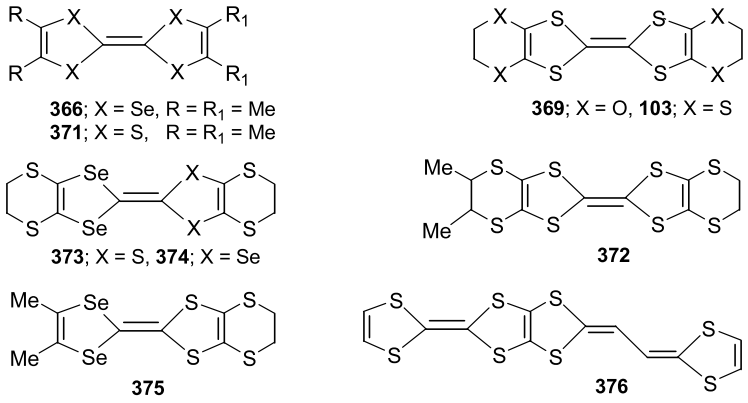


Chart 26.

12.3. Chemical sensors

Several TTFs were used as chemical sensors and the cation-sensitive TTFs could be divided into planar TTF derivatives with annelated macrocyclic moieties and distorted macrocyclic TTF systems. Planar derivatives which include TTF-crown ethers and TTF-thiacrown ethers such as TTF **364** and conducting polymers **365** have been investigated for their potential use as electroactive cation sensors (Chart 22).[148,149]

12.4. Superconductor materials

With regard to the development of new TTF derivatives in the search for electrically conducting materials, some alternatives to the study of single crystals have been used to grow layers of CT complexes, such as the formation of LB films or chemical vapor deposition. The combination of TTF donors, for example, **366** with nonorganic anions (ClO4, PF6, etc.), which serve as acceptors led to the formation of CT complexes. The $(TMTSF)_2ClO4$ **367** was synthesized as the first organic material that was superconducting at ambient pressure. Although, it has a relatively low superconducting transition temperature (1.2 K), the interest in superconductivity and other rather unusual properties in organic materials exploded after this discovery (Chart 23).[150]

The first organic superconductor, $(TMTSF)_2PF_6$ **368** with critical temperature $T_c = 1.4$ K under a hydrostatic pressure of 12 kbar with a transition temperature of 0.9 K, was discovered in 1980 by Bechgard et al. (Chart 24).[151] The salts based on TMTSF (Bechgard salts) are quasi-1-dimensional (q-1D) conductors, while salts based on ET are quasi-2-dimensional (q-2D) conductors, because of the strong in-plane intramolecular interactions due to S···S contacts.

A superconductor material like $(BEDO\text{-}TTF)_2ReO_4.H_2O$ **370** consists of layers obtained from the reaction of the BEDO-TTF molecule **369** and $ReO_4.H_2O$. The resulting complex was found to be a superconducting material at a critical temperature of about 2 K (Chart 25).[152]

Recently, a number of the TTF derivatives **103**, **359**, **362** and **364–369** have been investigated as superconducting salts.[153] In addition, a series of TTF derivatives, as shown in Chart 26, were examined as superconducting materials and alloys. Superconducting salts based on these molecules showed a negative pressure effect. This means that the T_c of the corresponding superconductors decreases and approaches 0 K under high pressure and the materials remain metallic. In contrast to the effects of hydrostatic pressure, however, uniaxial stress increases T_c.[154] There is a borderline between real metals where the electronic motion

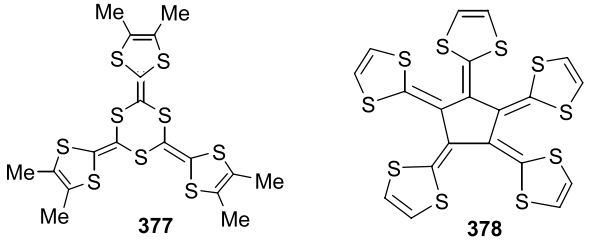


Chart 27.

is wave like and conductors where the electronic motion is rather of a hopping type.

12.5. Ferromagnets

Hansen and Becher[144] reported that the dithiol (DT) unit has found use in attempts to produce organic ferromagnets. The attempts have been directed towards systems with an odd-fold axis of symmetry. Ferromagnetism, which is another very important and useful physical property, is a special state of complete spin alignment throughout the bulk. Several theoretical models have already been proposed for achieving a linear-chain ferromagnetic coupling in an organic solid. Among the many systems synthesized which may be suitable for this purpose are the two DT-based systems **377** by Cava et al.[155] and **378** by Yoshida et al.[156] Although genuine bulk ferromagnetism is difficult to achieve in an organic material, there is reason to believe that the DT unit may prove useful in these types of advanced materials (Chart 27).

12.6. TTF derivatives as NLO materials

Recent advances in polymeric electro-optic materials and fabrication techniques for devices have significantly increased the potential incorporation of these materials and devices into modern high-bandwidth (fiber and wireless) telecommunication, information-processing and radar systems.[1e] Push–Pull systems of general structure D-π-A are being actively studied as NLO chromophores, since they can exhibit large quadratic molecular hyperpolarizabilities (β). These are electro-optic materials, the refractive index of which can be changed by the application of an electric field, and which are of interest as a result of their potential use in areas such as optical modulation, molecular switching, optical memory, and frequency doubling. The first NLO materials containing the TTF unit as the donor moiety in D-π-A systems such as **324** and **327** were reported in 1998 by Martin et al.[157] The influence of different acceptors and spacers connected to TTF has been also studied to optimize the nonlinear optical response of these materials. It was recognized that using stronger electron acceptors attached to the TTF systems such as **379** and **380** resulted in an increase in the NLO properties (Chart 28).[1e]

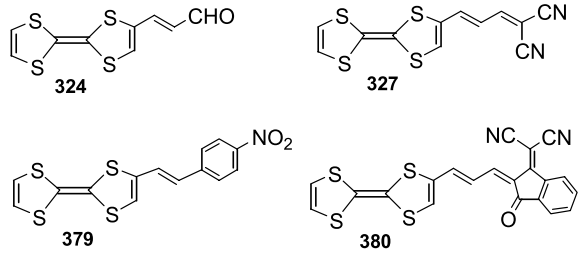


Chart 28.

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Biographical sketch

Abd El-Wareth Sarhan was born in 1962 in Assiut Egypt. He received his BSc and MSc degrees from Assiut University, Egypt. The MSc degree was supervised by Prof. A. M. Mahmould and H. A. H. El-Sherief, Professors of organic chemistry. He completed his doctoral thesis in 1994 as an Arab Student Aid International (ASAI) scholarship holder supported by H. R. H. Prince Turk bin Abdul Aziz in University of Hannover (Germany) under the direction of Prof. Dr. H. M. R. Hoffmann, PhD & DSc. His three years works at University of Hannover focused on the [4+3]cycloaddition reactions. He was then appointed as Lecturer of Organic Chemistry in Assiut University. He continued his research on [4+3]cycloaddition reactions and heterocyclic synthesis of new biological compounds along with teaching and supervising the graduates and postgraduates students. In 1997 moved to University of Linz, Austria as a post doctoral fellow in Prof. Dr. Heinz Falk's group at the institute of organic chemistry supported by Austrian academy of science (OÄD) where he worked on hypericin chemistry. He returned to Assiut University and awarded a best research prize followed by a Shoman Foundation Prize (Jordan-Amman) for young Arabian scientists in 1998. In 1999 he was promoted to be an associate professor of organic chemistry at the same university. His research interests concentrate on the development and study of new reactions for organic synthesis and heterocyclic chemistry. From 2000 to 2003, he was awarded a staff member position at Yamagata University, Faculty of Engineering working in materials chemistry and ferrocene-tetrathiafulvalenes organometallics joining the Professor Taeko Izumi group. He participated in many national and international conferences and is an active member in several scientific organizations. In 2004, he was promoted to be Professor of organic chemistry at Assiut University and awarded a visiting professorship at University of Hannover with Professor Holger Butencheon, Dean of Faculty of Chemistry.

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Synthesis of highly hindered polyanionic chelating ligands

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Abstract—Practical and efficient protocols to obtain highly hindered polyanionic chelating ligands based on *bis*-(3,5-di-*tert*-butyl-2-hydroxybenzamido) compounds are reported here. *N*-3,5-di-*tert*-Butylsalicyloyloxysuccinimide was treated with aliphatic diamines to form aliphatic hydrocarbon-linked *bis*-amides **4a**–**4g**. Aromatic diamines required more powerful electrophile, thus the corresponding benzylated acid chloride was used to form aromatic hydrocarbon-linked *bis*-amides **8a**–**8d**. The yields ranged from good to very good and showed that choosing the right acylating agent is a key point in this synthesis. All the compounds were characterized by elemental analysis, IR, MS and NMR.

1. Introduction

During the last few years, chelating agents have reached incredible levels of importance due to the remarkable applications that they have found in metal complexes catalysis.[1] Carboxamido ligands are interesting because it has been shown that they are highly resistant to oxidative degradation.[2] The success of metal complexes in enantioselective catalysis depends, among other characteristics, on the ability of the systems to tolerate very oxidative environments.[2d] Amides work much better than other ligands such as imines or phosphines, as reactions can be followed from their turnover frequencies (TOF). TOF over 100 have been described for *bis*-amides while for Schiff bases they reach only 30 in the best cases. However, amide-based ligands are less known than imines or phosphines. Polyanionic chelating ligands have been used in the synthesis of chromium, manganese, iron, cobalt, nickel and copper complexes with unusual geometries, oxidation states and spin states.[2,3] These characteristics are a consequence of their strong ability to donate electron density.[2c] Ligands containing voluminous groups have become central in catalytic asymmetric synthesis since they allow discrimination between different substrates and even between faces of a substrate that is approaching the active site.[4] Our goal is to obtain ligands that combine these two characteristics. We described the synthesis of *N*,*N*-disubstituted-3,5-di-*tert*-butyl-2-hydroxybenzamides using the corresponding acid chloride, some years ago.[5] This procedure, however did not afford any *bis*-amide when it was tried with either aliphatic or aromatic diamines. The reaction between salicyloyl chloride and diamines, the obvious method, has been described and a few *bis*-amides have already been reported.[1h,6] However, substitution in the aromatic moiety of the acid was different from the one reported here. To our knowledge, *bis*-3,5-di-*tert*-butyl-2-hydroxybenzamides have never been described by other authors. *N*-hydroxysuccinimide esters have been used to obtain *tris*-amides.[7] These esters are acylating agents which can be used under very mild conditions, usually providing good yields. It was decided to explore this approach to obtain *bis*-(3,5-di-*tert*-butyl-2-hydroxybenzamides) using several diamines.

2. Results and discussion

The synthetic route that was followed in the first trials[8] is shown in Scheme 1. The yields were rather low, however, we report here some modifications in the procedure, that improved the yields up to 75%. Dimethylformamide was used instead of acetone as solvent.

The starting ester **1** can be obtained in an almost quantitative yield.[5] The succinimide ester **3** is also easily obtained and readily crystallized. Since **3** is a fairly stable compound, it can be stored and used whenever needed. Furthermore, the *bis*-amides **4** are also readily purified by crystallization. The physical characteristics and the analytical data that confirm the compounds are presented in the Section 4. The infrared spectra show two characteristic absortions over 3000 cm^{-1} for NH and OH stretching. The C=O absortion is shifted to lower wavenumber compared to the succinimide ester **3**. The ^1H NMR spectra show two important low field signals,

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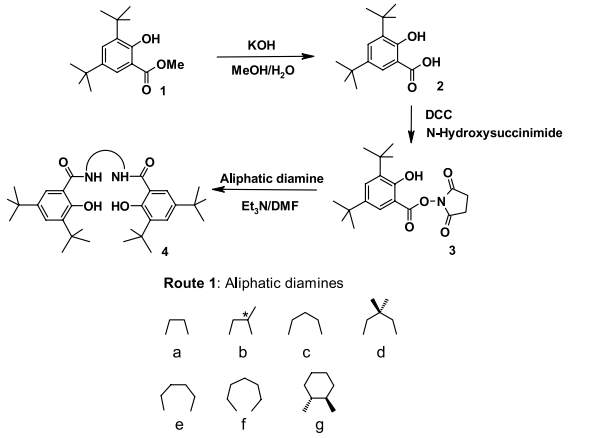
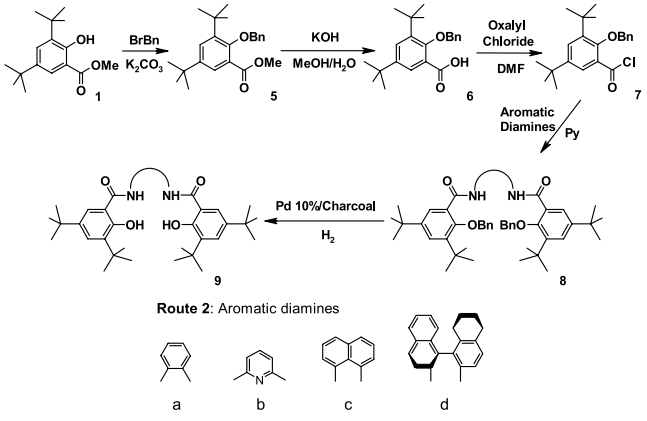


Scheme 1.

the first, between 12 and 12.5 ppm for OH (2H), the second, below 7 ppm for NH (2H). The NH signal is broad and the multiplicity is not well resolved. The melting points, as expected for amides, are high.

Unfortunately, the procedure has a serious drawback that precludes its generality. It does not work with aromatic diamines. Since the reaction proceeds in alkaline medium, the actual reagent is a phenoxyde ion. Therefore, electrophilicity at the carboxylic carbon diminishes. The compound would become less reactive towards weaker nucleophiles such as aromatic diamines. These statements were confirmed by calculating the local electrophilicity index at the reacting atom. This local philicity contains information about the global electrophilicity, Fukui's function and provides additional knowledge of electronegativity as well as the local and global softness.[9] Scheme 2 shows the modification that was made to overcome the difficulty.



Scheme 2.

In the first trials to enhance the electrophilicity at the carboxylic carbon, compound **3** was benzylated. The product is obtained in good yield, however, it did not react with aromatic diamines, being isolated unchanged. Finally, the benzylated acid chloride **7** did react with aromatic diamines. The *bis*-amides **8** were debenzylated by hydrogenolysis using Pd/C with a continuous stream of hydrogen and good stirring at 40 °C.[10] Even though the yields of amides were only moderate to good, the procedure is still easy to be carried out. Besides benzylation, acetylation and methylation were also tried without success. Authors that used methylation to protect the phenolic hydroxyl of other salicylic acid derivatives, failed in the deprotection step.[1h] The IR spectra of the *bis*-amides **9** show the same characteristic absorption bands above mentioned. The ^{1}H NMR spectra of compounds **9**, show signals at 8.5 ppm for the aromatic amides NH.

Amides (**4** and **9**) were dried at room temperature in a vacuum oven after crystallization and filtration. The samples were then analyzed by thermogravimetry. Only one mass loss of 97% was observed at 250 °C. Below that temperature no mass loss regions were observed, showing the absence of water. This result accounts for the sharp coincidence between calculated and experimental values of elemental analysis. This behavior has been reported by other authors.[11]

From the results, it can be seen that choosing the right acylating system depends on the reactivity of the nucleophile. When the extremely reactive chloride of acid **2** reacts with aliphatic diamines, unwanted secondary reactions are favored[12] and the final product becomes very difficult to isolate from the reacting mixture. A 'milder' electrophile such as **3**, affords the products without difficulties, provided that 'good' nucleophiles are used. In fact, compound **3** does not react with aromatic diamines, owing to their lower reactivity. A stronger acylating agent is required in that case, even stronger than the chloride of acid **2**, as it is the case with the benzylated chloride **7**. The reactivity of this compound that does not have acidic protons remains unchanged in alkaline medium.

Co(III) complexes are currently being obtained in our laboratory and we are working to characterize them. In order to obtain the tetraanion, the ligands are deprotonated by treatment with *n*-butyllithium. Anhydrous $CoCl_2$ is added and then oxygen is bubbled trough the solution during 2 h. The characteristic bands associated with NH and OH stretching are not observed in the IR spectra of the complexes. Besides, the stretching band corresponding to the amide carbonyl is shifted to higher frequencies with respect to the free ligand. Far IR spectra show a signal around 550 cm^{-1} corresponding to the Co–N stretching.

3. Conclusion

In summary, we have described convenient procedures to obtain both aliphatic and aromatic *bis*-amides derived from 3,5-di-*tert*-butyl-2-hydroxybenzoic acid. The procedures are easily carried out in good yields. Some of the synthesized chelating molecules here described have a very hindered coordinating center. These ligands are promising species to be used in asymmetric catalysis.[4,13,14] These polyanionic chelating molecules have two carboxamido and two phenolic groups, both of them strong electron donors, therefore it is quite likely that they will be able to stabilize high valence complexes with transition metals.[2,3] Both, chiral and nonchiral molecule can find many applications.[15] Our

final goal is to try them in enantioselectively catalyzed reactions.

4. Experimental

The compounds synthesized were characterized using FTIR (Nicolet, Magna 550, KBr discs). ^{13}C and ^{1}H NMR (Bruker AC 250P; 62.9 and 250 MHz, respectively, TMS as internal standard). The solvent was $CDCl_3$, except when otherwise stated. ^{1}H–^{13}C correlation spectra and DEPT were also used for signal assignment. High resolution mass spectra were obtained (VG Autospec Micromass with magnetic sector) using the electronic impact technique (70 eV, 230 °C). Melting points (in Celsius degrees) were obtained in a Kofler Microscope and are uncorrected. Elemental analyses were obtained in a Fison EA 1108 Analyzer. Infrared values (ν) are quoted in reciprocal centimeters (cm^{-1}), NMR chemical shifts (δ) are quoted in ppm. Racemic 1,2-propanediamine was used. Racemic *trans*-1,2-cyclohexanediamine[16] and racemic 2,2′-diamine-1,1′-binaphthyl[17] were resolved as reported.

4.1. Synthesis of aliphatic bis-amides

4.1.1. *N*-3,5-di-*tert*-Butylsalicyloyloxysuccinimide (3). 3,5-di-*tert*-Butylsalicylic acid **2** (20 g, 0.083 mol) and *N*-hydroxysuccinimide (8.9 g, 0.088 mol) were dissolved in 300 ml of dioxane. The solution was cooled to 10 °C and dicyclohexylcarbodiimide (19.5 g, 0.094 mol) dissolved in 300 ml of the same solvent, was slowly dropped. The reaction mixture was stirred for 24 h at room temperature. The urea was separated by filtration and the filtrate evaporated to dryness. The white solid was recrystallized from ethanol. Yield: 74%, mp: 168–170°. Anal. Elem. $C_{19}H_{25}NO_5$: Calcd C, 65.69, H, 7.25, N, 4.03. Found. C, 65.67, H, 7.23, N, 4.05. ^{1}H NMR: 10.12 (s, 1H, OH), 7.83, 7.76 (d, d, $J=2.45$ Hz, 2H, CH arom.), 2.93 (s, 4H, CH_2–C=O), 1.42, 1.31 (s, s, 18H, CMe_3). ^{13}C NMR: 169.1 (2C, C=O, imide), 166.3 (1C, C=O, ester), 159.7, 141.5, 137.8, 133.3, 123.4, 107.1 (6C, arom.). MS: M^+ 347.16 (347.40). FT-IR: 3285 (OH), 2959 (CH), 1737 (C=O), 1598 (C=C).

4.2. *bis*-Amides (4a–4f). General method

To a solution of *N*-3,5-di-*tert*-butylsalicyloyloxysuccinimide (2.0 g, 5.6 mmol) and the corresponding diamine (2.8 mmol) in 15 ml of DMF, 5 ml of Et_3N and a catalytic amount of DMPA were added. The reaction mixture was stirred for 12 h at room temperature and then poured into ice/10% HCl. The mixture was extracted with 50 ml of ethyl acetate and the aqueous layer was extracted again. The organic extracts were combined, washed with brine, dried over Na_2SO_4 and rotovapped. The solid was recrystallized from ethanol.

4.2.1. 1,2-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-ethane (4a). Yield: 72%, mp: 235–236°. Anal. Elem. $C_{32}H_{48}N_2O_4$: Calcd C, 73.23, H, 9.24, N, 5.34. Found. C, 73.22, H, 9.25, N, 5.35. ^{1}H NMR: 12.67 (s, 2H, OH), 7.60 (s, broad, 2H, NH), 7.46, 7.30 (d, d, $J=2.03$ Hz, 4H, arom.), 3.71 (s, 4H, CH_2N), 1.41, 1.31 (s, s, 36H, CMe_3). ^{13}C NMR: 172.8 (2C, C=O), 158.9, 140.2, 138.1, 129.2, 119.7, 112.5 (12C, arom.), 40.7 (2C, CH_2N), 35.2, 34.3 (4C, CMe_3), 31.4, 29.4 (12C, CMe_3). MS: M^+ 524.35 (524.78). FT-IR: 3335 (OH), 2958 (C–H), 1541 (C=O).

4.2.2. 1,2-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-propane (4b). Yield: 77%, mp: 223–225°. Anal. Elem. $C_{33}H_{50}N_2O_4$: Calcd C, 73.56, H, 9.37, N, 5.20. Found. C, 73.59, H, 9.37, N, 5.16. ^{1}H NMR: 12.75, 12.60 (s, s, 2H, OH), 7.45 (s, broad 3H, 2H arom. and NH α to CH_2), 7.35 (d, $J=6.55$ Hz, 1H, NH α to CH), 7.24 (d, $J=2.48$ Hz, 2H, arom.), 4.37, 3.72, 3.52 (m, m, m, 3H, CH and CH_2), 1.39 (s, 18H, CMe_3), 1.35 (d, $J=6.66$ Hz, 3H, CH_3 β to N), 1.30 (s, 18H, CMe_3). ^{13}C NMR: 172.8, 172.2 (2C, C=O), 158.9, 158.8, 140.1, 138.2, 138.1, 129.9, 129.2, 119.5, 112.5 (12C, arom.), 47.3 (1C, CH α to N), 46.2 (1C, CH_2 α to N), 35.2, 34.3 (4C, CMe_3), 31.4, 29.3 (12C, CMe_3), 18.3, (1C, Me β to N). MS: M^+ 538.38 (538.81). FT-IR: 3410 (NH), 3370 (OH), 2957 (CH), 1536 (C=O).

4.2.3. 1,3-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-propane (4c). Yield: 76%, mp: 218–220°. Anal. Elem. $C_{33}H_{50}N_2O_4$: Calcd C, 73.56, H, 9.37, N, 5.20. Found. C, 73.60, H, 9.38, N, 5.25. ^{1}H NMR: 12.73 (s, 2H, OH), 7.49 (d, $J=2.18$ Hz, 2H, arom.), 7.40 (t, not well resolved, 2H, NH), 7.38 (d, $J=2.18$ Hz, 2H, arom), 3.57 (m, 4H, CH_2N), 1.83 (broad signal, 2H, CH_2 β to N), 1.44, 1.34 (s, s, 36H, CMe_3). ^{13}C NMR: 172.0 (2C, C=O), 158.8, 140.1, 138.2, 129.5, 113.0, (12C, arom.), 35.5 (2C, CH_2N), 35.2, 34.3 (4C, CMe_3), 31.4 (6C, CMe_3), 29.5 (1C, CH_2 β to N), 29.4 (6C, CMe_3). MS: M^+ 538.26 (538.81). FT-IR: 3410 (NH), 3369 (OH), 2957 (CH), 1535 (C=O).

4.2.4. 1,3-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-2,2-di-methylpropane (4d). Yield: 83%, mp: 251–252°. Anal. Elem. $C_{35}H_{54}N_2O_4$: Calcd C, 74.15, H, 9.62, N, 4.94. Found. C, 74.17, H, 9.60, N, 4.93. ^{1}H NMR: 12.71 (s, 2H, OH), 7.62 (t, $J=6.42$ Hz, 2H, NH), 7.52, 7.44 (d, $J=2.17$ Hz, 4H, arom.), 3.29 (d, $J=6.70$ Hz, 4H, CH_2N), 1.45, 1.37 (s, s, 36H, CMe_3), 1.04 (s, 6H, CH_3). ^{13}C NMR: 171.9 (2C, C=O), 158.8, 140.1, 138.1, 129.0, 119.4, 113.0 (12C, arom.), 46.4 (2C, CH_2N), 37.1 (1C, $C(CH_3)_2$), 35.2, 34.3 (4C, CMe_3), 31.2, 29.3 (12C, CMe_3), 23.8 (2C, CH_3). MS: M^+ 566.41 (566.87). FT-IR: 3317 (NH), 3270 (OH), 2958 (CH), 1553 (C=O).

4.2.5. 1,4-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-butane (4e). Yield: 72%, mp: 248–249°. Anal. Elem. $C_{34}H_{52}N_2O_4$: Calcd C, 73.86, H, 9.50, N, 5.07. Found. C, 73.90, H, 9.49, N, 5.07. ^{1}H NMR: 12.64 (s, 2H, OH), 7.46, 7.19 (d, d, $J=2.3$ Hz, 4H, arom.), 6.76 (t, broad, not well resolved, 2H, NH), 3.53 (m, not well resolved, 4H, CH_2N), 1.75 (broad signal, 4H, CH_2 β to N), 1.42, 1.30 (s, s, 36H, CMe_3). ^{13}C NMR: 171.6 (2C, C=O), 158.7, 139.1, 128.8, 119.1, 113.1 (12C, arom.), 39.4 (2C, CH_2N), 35.2, 34.3 (4C, CMe_3), 31.4, 29.3 (12C, CMe_3), 26.8 (2C, CH_2 β to N). MS: M^+ 552.29 (552.84). FT-IR: 3397 (NH, OH), 2956 (CH), 1542 (C=O).

4.2.6. 1,5-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-pentane (4f). Yield: 73%, mp: 215–217°. Anal. Elem. $C_{35}H_{54}N_2O_4$: Calcd C, 74.15, H, 9.62, N, 4.94. Found. C, 74.19, H, 9.61, N, 4.93. ^{1}H NMR: 12.69 (s, 2H, OH), 7.45, 7.12 (d, d, $J=2.28$ Hz, 4H, arom.), 6.40 (t, not well

resolved, 2H, NH), 3.45 (m, 4H, CH_2N), 1.71 (m, 4H, CH_2 β to N), 1.48 (m, 2H, CH_2 γ to N), 1.42, 1.30 (s, s, 36H, CMe_3). ^{13}C NMR: 171.3 (2C, C=O), 158.7, 139.9, 138.2, 128.8, 118.9, 113.3 (12C, arom.), 39.6 (2C, CH_2N), 35.2, 34.3 (4C, *C*Me_3), 31.4, 29.3 (12C, C*Me*$_3$), 29.3 (2C, CH_2 β to N), 24.4 (1C, CH_2 γ to N). MS: M^+ 566.39 (566.87). FT-IR: 3403 (NH, OH), 2958 (CH), 1536 (C=O).

4.2.7. (*R*,*R*)-1,2-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido) cyclohexane (4g). (*R*,*R*)-Cyclohexane-1,2-diammonium mono-(+)-tartrate salt (0.70 g, 2.8 mmol), K_2CO_3 (0.81 g, 5.8 mmol) and 30 ml of EtOH/H_2O (5:1) were placed in a 100 ml one-necked round-bottomed flask equipped with a reflux condenser. The mixture was stirred and heated at 80 °C for 30 min. Then, it was cooled to room temperature and compound **3** (2.0 g, 5.6 mmol) and DMPA were added. Stirring was continued for 12 h. The work up was the same described in the general method for *bis*-amides. Yield: 62%, mp: 238–242° (amorphous solid). Anal. Elem $C_{36}H_{54}N_2O_4$: Calc. C, 74.69, H, 9.42, N, 4.84. Found. C, 74.72, H, 9.42, N, 4.86. ^1H NMR: 12.76 (s, 2H, OH), 7.44, 7.20 (d, d, 4H, J=2,0 Hz, arom.), 7.03 (t, not well resolved, 2H, NH), 3.95 (broad signal, 2H, CHN), 2.22 (broad signal, 2H, CH_2 β N), 1.92 (broad signal, 2H, CH_2 β N), 1.39, 1.31 (s, s, complex signal, 40H, CMe_3 and CH_2 γ N). ^{13}C NMR: 171.8 (2C, C=O), 158.7, 139.9, 137.8, 128.9, 119.3, 112.3 (12C, arom.), 54.0 (2C, CHN), 34.9, 34.1 (4C, *C*Me_3), 31.9 (2C, CH_2 β to N), 31.2, 29.1 (12C, C*Me*$_3$), 24.4 (2C, CH_2 γ to N). MS: M^+ 578.39 (578.88). FT-IR: 3348 (OH), 3296 (NH), 2955 (CH), 1550 (C=O).

4.3. Synthesis of aromatic bis-amides

4.3.1. Methyl 3,5-di-*tert*-butyl-2-benzyloxybenzoate (5). In a 100 ml one-necked round-bottomed flask methyl 3,5-di-*tert*-butylsalicylate (10 g, 0.038 mol), benzyl bromide (5.0 ml, 0.042 mol, 7.1 g) and K_2CO_3 (5.2 g, 0.038 mol) in 40 ml of DMF were stirred during 48 h at room temperature. The mixture was then poured into 500 ml of ice, stirred some minutes and filtered. The white solid was recrystalizated from ethanol. Yield: 90%, mp: 81–83°. Anal. Elem. $C_{23}H_{30}O_3$: Calcd C, 77.95, H, 8.54. Found. C, 78.01, H, 8.59. ^1H NMR: 7.62, 7.54 (d, d, J=2.54 Hz, 2H, arom.), 7.49–7.33 (complex signal, 5H, benzyl group), 4.91 (s, 2H, CH_2-phenyl), 3.80 (s, 3H, OCH_3), 1.41, 1.33 (s, s, 18H, CMe_3). ^{13}C NMR: 168.7 (1C, C=O), 155.6, 145.2, 142.8, 137.5, 128.3, 128.1, 127.6, 127.0, 126.1, 124.7 (12C, arom.), 76.5 (1C, CH_2-phenyl), 52.2 (1C, OCH_3), 35.4, 34.5 (2C, *C*Me_3), 31.3, 30.7 (6C, C*Me*$_3$). MS: M^+ 354.11 (354.50). FT-IR: 2956 (CH), 1728 (C=O), 1226 (C–O).

4.3.2. 3,5-di-*tert*-Butyl-2-benzyloxybenzoic acid (6). To a solution of **5** (10.1 g, 0.030 mol) in 150 ml of methanol, KOH (6.7 g, 0.11 mol) dissolved in 50 ml of water was added. The resulting mixture was refluxed with stirring during 4 h and then poured into 500 ml of an ice-10% NaOH mixture, stirred and filtered. The white solid was recrystallized from ethanol. Yield: 75%, mp: 173–175°. Anal. Elem. $C_{22}H_{28}O_3$: Calcd C, 77.67, H, 8.31. Found. C, 76.79, H, 8.19. ^1H NMR: 11.31 (s, 1H, OH), 7.91, 7.63 (d, d, J= 2.41 Hz, 2H, arom.), 7.49–7.36 (complex signal, 5H, benzyl group), 4.97 (s, 2H, CH_2-phenyl), 1.46, 1.34 (s, s, 18H, CMe_3). ^{13}C NMR: 170.6 (1C, C=O), 156.1, 146.3, 143.1, 136.5, 129.8, 128.5, 128.1, 127.7, 127.5, 123.4 (12C, arom.), 78.0 (1C, CH_2-phenyl), 35.6, 34.7 (2C, *C*Me_3), 31.3, 31.0 (6C, C*Me*$_3$). MS: M^+ 340.16 (340.47). FT-IR: 3433 (OH), 2910 (CH), 1691 (C=O).

4.4. Benzylated *bis*-amides (8a–8d). General method

To a solution of **6** (2.5 g, 7.3 mmol) in CH_2Cl_2 and cooled to 0 °C, oxalyl chloride (1.3 ml, 0.015 mol, 1.9 g) and a catalytic amount of DMF were added. The mixture was stirred during 4 h at room temperature. When the reaction was finished the solvent was removed under reduced pressure in a rotary evaporator and the solid was treated with some extra CH_2Cl_2 and again evaporated. This treatment was repeated one more time. The residue was redissolved in 30 ml of CH_2Cl_2 and cooled to 0 °C. To this solution 5 ml of pyridine and a catalytic amount of DMPA were added. The diamine was dissolved in 20 ml CH_2Cl_2 and dropped into the cooled solution. The mixture was stirred during 12 h and then it was refluxed during 4 h. The solution was finally poured into 500 ml of an ice–10% NaOH mixture and filtered. The solid was recrystallized from ethanol.

4.4.1. 1,2-*bis*-(3,5-di-*tert*-Butyl-2-benzyloxybenzamido) benzene (8a). Yield: 77%, mp: 196–197°. Anal. Elem. $C_{50}H_{60}N_2O_4$: Calcd C, 79.74, H, 8.05, N, 3.72. Found. C, 80.02, H, 8.00, N, 3.69. ^1H NMR: 8.97 (s, 2H, NH), 7.61, 7.48 (d, d, J=2.57 Hz, arom.), 7.37–7.25, 7.02 (complex signals, 12H, benzyl and phenyl groups), 4.97 (s, 4H, CH_2-phenyl), 1.43, 1.27 (s, s, 36H, CMe_3). ^{13}C NMR: 166.5 (2C, C=O), 153.5, 146.5, 142.4, 136.6, 130.5, 128.7, 128.4, 127.7, 127.5, 126.8, 126.1, 125.9, 124.7 (26C, arom.), 77.2 (2C, CH_2-phenyl), 35.4, 34.6 (4C, *C*Me_3), 31.3, 30.9 (12C, C*Me*$_3$). MS: M^+ 752.39 (753.08). FT-IR: 3066 (NH), 2958 (CH), 1660 (C=O).

4.4.2. 2,6-*bis*-(3,5-di-*tert*-Butyl-2-benzyloxybenzamido) pyridine (8b). Yield: 65%, mp: 209–211°. Anal. Elem. $C_{49}H_{59}N_3O_4$: Calcd C, 78.04, H, 7.90, N, 5.57. Found. C, 78.91, H, 7.95, N, 5.41. ^1H NMR: 9.06 (s, 2H, NH), 8.03 (d, J=8.0 Hz, 2H, CH py), 7.84 (d, J=2.35 Hz, 2H, arom.), 7.71 (t, J=8.55 Hz, 1H, CH py), 7.59 (d, J=2.37 Hz, 2H, arom.), 7.37 (d, J=7.48 Hz, 4H, benzyl group), 7.18 (t, J= 7.41 Hz, 4H, benzyl group), 7.03 (t, J=7.28 Hz, 2H, benzyl group), 4.82 (s, 4H, CH_2-phenyl), 1.37, 1.15 (s, s, 32H, CMe_3). ^{13}C NMR: 165.7 (2C, C=O), 153.6, 149.5, 146.9, 143.0, 140.9, 136.1, 128.6, 128.2, 127.9, 127.8, 127.6, 126.5, 110.0 (29C, arom.), 77.8 (2C, CH_2-phenyl), 35.6, 34.7 (4C, *C*Me_3), 31.4, 31.1 (12C, C*Me*$_3$). MS: M^+ 753.41 (754.07). FT-IR: 3375 (NH), 2959 (CH), 1675 (C=O).

4.4.3. 1,8-*bis*-(3,5-di-*tert*-Butyl-2-benzyloxybenzamido) naphthalene (8c). Yield: 51%, mp: 204–206°. Anal. Elem. $C_{54}H_{62}N_2O_4$: Calcd C, 80.75, H, 7.80, N, 3.49. Found. C, 81.01, H, 7.91, N, 3.42. ^1H NMR: 9.46 (s, 2H, NH), 7.59–7.47, 7.17–7.11 (complex signals, 16H, benzyl and phenyl groups), 7.53, 7.39 (d, d, J=2.32 Hz, 4H, arom.), 4.79 (s, 4H, CH_2–phenyl), 1.30, 1.18 (s, s, 32H, CMe_3). ^{13}C NMR: 166.8 (2C, C=O), 153.0, 146.5, 142.2, 136.3, 135.4, 132.3, 129.0, 128.3, 127.7, 126.6, 126.3, 125.9, 125.2, 121.7 (34C, arom.), 76.9 (2C, CH_2–phenyl), 35.4, 34.6 (4C, *C*Me_3), 31.4, 30.9 (12C, C*Me*$_3$). MS: M^+

802.67 (803.14). FT-IR: 3338, 3342 (NH), 2957 (CH), 1662 (C=O).

4.4.4. (*R*)-2,2′-*bis*-(3,5-di-*tert*-Butyl-benzyloxybenzamido)-1,1′-binaphthyle (8d). Yield: 54%. mp: 194–196 °C. Anal. Elem. $C_{64}H_{68}N_2O_4$: Calcd C, 82.71,H, 7.39, N, 3.02. Found. C, 83.01, H, 7.83, N, 2.98. ^{1}H NMR: 8.35 (d, J=8.97 Hz, 2H, arom.), 7.97 (s, 2H, NH), 7.89 (d, J=9.0 Hz, 2H, binaph.), 7.76 (d, J=8.2 Hz, 2H, arom.), 7.26–6.91 (complex signal, 10H, benzyl and binaph.) 4.61, 4.59 (s, s, 4H, CH_2–phenyl), 1.08, 1.05 (s, s, 36H, CMe_3). ^{13}C NMR: 166.9 (2C, C=O), 153.4, 145,6, 142.3, 136.7, 135.2, 132.3, 131.3, 129.7, 128.9, 128.1, 127.8, 127.7, 127.2, 126.9, 125.4, 125.0, 124.5, 122.2, 122.0 (22C, arom.), 76.7 (2C, CH_2–Phenyl), 35.2, 34.3 (4C, *C*Me_3), 31.2, 30.6 (12C, C*Me*$_3$). MS: M^+ 928.70 (929.30). FT-IR: 3391, 3353 (NH), 2959 (CH), 1676 (C=O).

4.5. Hydrogenolysis. General procedure

A solution of the corresponding bis-amide (1–1.5 mmol) in 5 ml of toluene was diluted with 100 ml of absolute ethanol and debenzylated at 40 °C over a 10% Pd/C catalyst. A continuous stream of H_2 was passed trough the suspension until no *O*-benzylated material was detected by TLC. The reaction mixture was filtered through Celite and evaporated under reduced pressure. The solid was recrystallized from ethanol.

4.5.1. 1,2-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-benzene (9a). Yield: 79%, mp: 251–253°. Anal. Elem. $C_{36}H_{48}N_2O_4$: Calcd C, 75.48, H, 8.46, N, 4.89. Found. C, 75.70, H, 8.55, N, 4.78. ^{1}H NMR (DMSO): 12.95 (s, 2H, OH), 10.36 (s, 2H, NH), 7.78, 7.71, 7.49 (broad signals, 8H, arom.), 1.45, 1.29 (s, s, 36H, CMe_3). ^{13}C NMR (DMSO): 171.6 (2C, C=O), 159.3, 140.0, 138.1, 135.1, 130.0, 129.1, 127.1, 125.9, 126.4, 119.5, 112.3 (22C, arom.), 35.2, 33.91 (4C, *C*Me_3), 31.1, 29.4 (12C, C*Me*$_3$). MS: M^+ 572.30 (572.82). FT-IR: 3302 (NH, OH), 2958 (CH), 1529 (C=O).

4.5.2. 2,6-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-pyridine (9b). Yield: 45%. mp: 287–289°. Anal. Elem. $C_{35}H_{47}N_3O_4$: Calcd C, 73.26, H, 8.27, N, 7.32. Found. C, 72.91, H, 8.18, N, 7.19. ^{1}H NMR: 12.22 (s, 2H, OH), 8.34 (s, broad, 2H, NH), 8.00 (d, J=8.0 Hz, 2H, CH py), 7.78 (t, J=7.80 Hz, 1H, CH py), 7.48 (d, J=2.07 Hz, 2H, arom.), 7.28 (d, J=2.02 Hz, 2H, arom.), 1.38, 1.29 (s, s, 36H, CMe_3). ^{13}C NMR: 169.8 (2C, C=O), 159.4, 149.1, 141.0, 140.4, 138.6, 130.0, 119.2, 112.9, 110.7 (17C, arom.), 35.3, 34.4 (4C, *C*Me_3), 31.5, 29.3 (12C, C*Me*$_3$). MS: M^+ 573.35 (573.81). FT-IR: 3382 (NH), 2961 (CH), 1673 (C=O).

4.5.3. 1,8-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido) naphthalene (9c). Yield: 58%, mp: 291–293°. Anal. Elem. $C_{40}H_{50}N_2O_4$: Calcd C, 77.13, H, 8.11, N, 4.50. Found. C, 77.18, H, 8.10, N, 4.48. ^{1}H NMR: 12.48 (s, 2H, OH), 8.61 (s broad, 2H, NH), 7.93, 7.90 (d, d, J=1.89 Hz, 2H, napht.), 7.52 (complex signal, 4H, naph.), 7.35, 6.99 (d, d, J=2.14 Hz, 4H, arom.), 1.39, 0.93 (s, s, 36H, CMe_3). ^{13}C NMR: 170.2 (2C, C=O), 158.2, 139.8, 136.6, 134.7, 128.5, 127.1, 126.7, 121.9, 113,5 (18C, arom.), 34.7, 34.0 (4C, *C*Me_3), 31.2, 29.2 (12C, C*Me*$_3$). MS: M^+ 622.34 (622.88). FT-IR: 3439, 3305 (NH, OH), 2958 (CH), 1590 (C=O).

4.5.4. (*R*)-2,2′-*bis*-(3,5-di-*tert*-Butyl-2-hydroxybenzamido)-1,1′-binaphthyle (9d). Yield: 51%. mp: 136–148° (amorphous solid). Anal. Elem. $C_{50}H_{56}N_2O_4$: Calcd C, 80.17, H, 7.55, N, 3.74. Found. C, 80.15, H, 7.45, N, 4.01. ^{1}H NMR: 12.24 (s, 2H, OH), 8.85 (d, J=9.09 Hz, 2H, arom.), 8.16 (d, J=9.09 Hz, 2H, arom.), 8.08 (d, J=8.10 Hz, 2H, binaph.), 7.93 (s, 2H, NH), 7.53–7.22 (complex signal, 6H, binaph.), 6.18 (d, J=1.53 Hz, 2H, binaph.), 1.36, 0.97 (s, s, 18H, CMe_3). ^{13}C NMR: 169.5 (2C, C=O), 159.0 (2C, C–NH, binaph.), 140.1, 138.1, 134.8, 132.1, 131.3, 130.5, 129.2, 128.6, 128.0, 126.0, 124.6, 120.8, 119.9, 119.0, 113.1 (30C, arom.), 35.1, 33.8 (4C, *C*Me_3), 31.1, 29.2 (12C, C*Me*$_3$). MS: M^+ 748.40 (749.04). FT-IR: 3415 (NH, OH), 2956 (CH), 1592 (C=O).

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1-(4-Nitrophenoxycarbonyl)-7-pyridin-4-yl indolizine: a new versatile fluorescent building block. Application to the synthesis of a series of fluorescent β-cyclodextrins

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Abstract—The synthesis of a series of new fluorescent building blocks **1a–d** incorporating a pyridinoindolizine unit and two potentially reactive sites is described. The reaction of **1a–d** with the mono-6-amino-6-deoxy-β-cyclodextrin provides the corresponding fluorescent water soluble hosts **2a–d** in good yield. The sensor properties of **2a–d** in the presence of 1-adamantanol is described.

1. Introduction

Designing functionalisable fluorescent organic compounds which can be used as building blocks for the synthesis of new chromogenic derivatives with distinctly different physical and/or chemical properties is a great interest to biologists[1] and organic materials chemists.[2] Such reactive fluorophores are, for example, widely employed as fluorescent labels in the study of complex biological systems (DNA hybridisation)[3] and in analytical HPLC derivatisation reactions[4] in order to overcome the problem of low detection limits. It has been shown that the presence of a functionality on the fluorescent backbone could also offer the opportunity to modify their solubility by introducing long chain or ionic moieties with the aim to improving the solubility in organic solvents and water, respectively.[5]

The attachment of fluorophores to synthetic receptors has also received considerable interest over the last few years, in endeavours to furnish new fluorescent sensors.[6] In particular, fluorescent cyclodextrins have generated considerable interest from the synthetic community as witnessed by recent articles dealing with their synthesis and emphasizing their sensory,[7] but also their biochemical[8] and photoelectronic[9] properties. On the other hand, indolizinic derivatives are of interest as biologically active products and are well known to exhibit a variety of pharmacological effects including cardiovascular,[10] anti-inflammatory activities[11] but also antioxidant properties.[12] In addition to exhibiting a spectrum of pharmacological effects, synthetic indolizinic derivatives are also well known for their fluorescence properties and some of them have already been used as dyes[13] and biological markers.[14]

Considering the well known fluorescence properties of indolizine derivatives, the incessant need for new reactive fluorophores and the increasing importance of fluorescence spectroscopy in both biological and supramolecular recognition fields, we were interested on the synthesis on new fluorescent building blocks including an indolizinic unit bearing two potential different reactive functions, *e.a* a 4-nitrophenoxycarbonyl leaving group (site A) and a free pyridinic moiety (site B), as sites for further structural modifications (Fig. 1).

Herein, we describe the convenient synthesis and the characterisation of the new type fluorescent building block **1** and its successful incorporation into the primary face of the β-cyclodextrin through the reactivity of the nitrophenylester group (site A). Fluorescence properties of graft compounds **2a–d** are also described through, notably, the evaluation of their sensitivity factors in the presence of 1-adamantanol.

2. Results and discussion

2.1. Synthesis and characterisation

Scheme 1 displays the strategy involved for the preparation

Keywords: β-Cyclodextrins; Fluorophores; Indolizinic derivatives.
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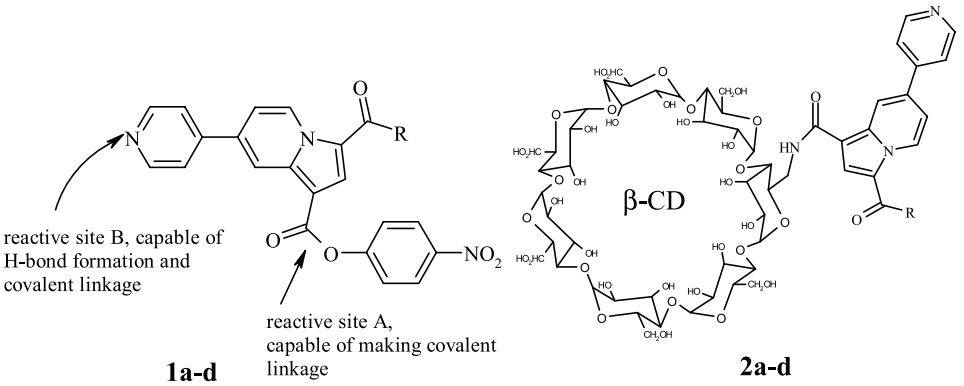
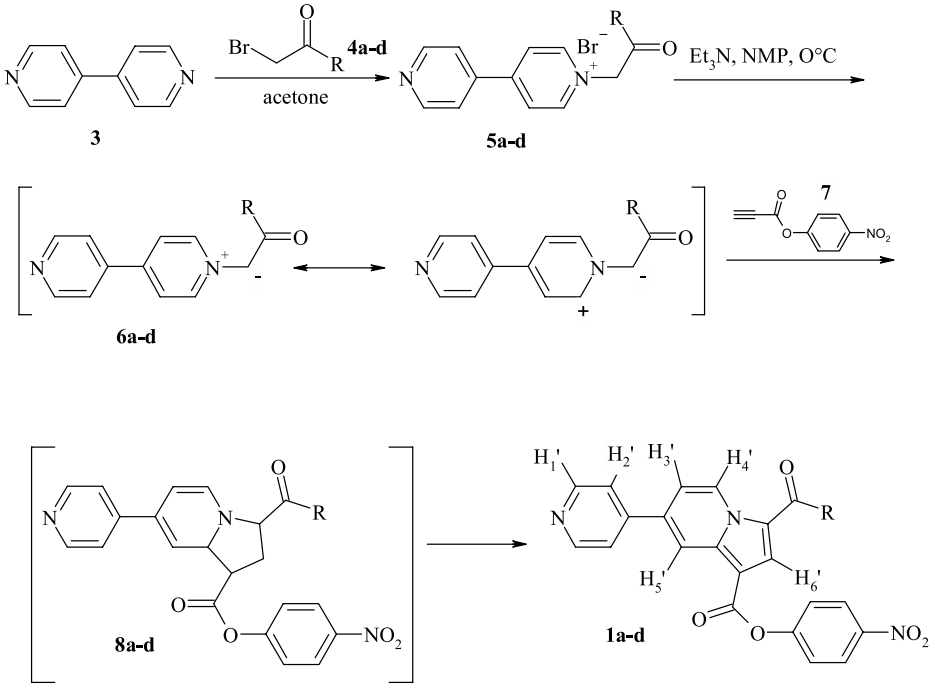


a: R = C_6H_4; **b**: R =4-Me-C_6H_4; **c**: R = 4-MeO-C_6H_4; **d**: R = 4-Cl-C_6H_4

Figure 1. The new fluorescent building block 1 and its corresponding β-cyclodextrin fluorescent sensor **2**.



Scheme 1. Synthesis of **1a**–**e**.

of the new reactive fluorophore **1**. The literature offers several methods for the construction of the indolizinic unit.[15] Among them, due to the easy access of 1,3 dipoles derived from cycloimmonium salts and the wide range of dipolarophiles commercially available, the 1,3-dipolar cycloaddition of pyridinium ylide derivatives with activated double or triple bonds has been shown to be a highly effective and powerful strategy to build this pentatomic framework.[16]

Thus, the salt method[17] has been applied in order to obtain the bipyridinium ylides **6**. Quaternization of the bipyridine **3** at room temperature in dry acetone with the commercially available 4-substituted ω-bromoacetophenones **4a**–**d** gave the corresponding monosalts **5a**–**d** in high yields. Next these salts in the presence of triethylamine (TEA) form the monosusbstituted carbanions ylides **6a**–**d** 'in situ' which undergo a 1,3-dipolar cycloaddition reaction with the electron-deficient compound **7** to give primary cycloadducts **8a**–**d** which spontaneously furnish, after rearomatisation, finals compounds **1a**–**d**, in good yields (Table 1). It should be noted, that, to the best of our knowledge, the dipolarophile **7** was used for the first time in this type of chemical transformation. Moreover the presence of the leaving group (4-NO_2PhO–) in its structure does not affect the yield compared to other dipolarophiles previously used.[16b,k] Thus, this activated dipolarophile could offer various applications with the aim to functionalising other heterocyclic frameworks. The structure of **1a**–**d** were deduced from their spectroscopic data. IR spectra of **1a**–**d** showed three characteristic absorption bands at ≈1610, 1725, 1520 cm^{-1} ascribed to ν (C=O), ν (O–C=O) and ν (NO_2), respectively. The C^{13} spectra exhibited two signals ≈185 and 160 ppm for **1a**–**d**, which confirm the presence of a ketone and a carboxylic acid derivative, respectively. Examination of the crude reaction mixture by 400 MHz ^{1}H

Table 1. Emission variations of **2a–d**, measured in phosphate buffer (pH=7.0, 25 °C) with [**2a–d**]$_0$=0.01 mM and [1-adamantanol]=0.1 mM

Compound	Yield (%)	$\Delta I/I_0$	λ_{exc} (nm)	K_b (M^{-1})
1a	49	—	—	—
1b	53	—	—	—
1c	57	—	—	—
1d	46	—	—	—
2a	52	0.449	274	79,500
2b	54	0.306	273	91,200
2c	58	0.094	275	192,000
2d	38	0.321	276	127,600

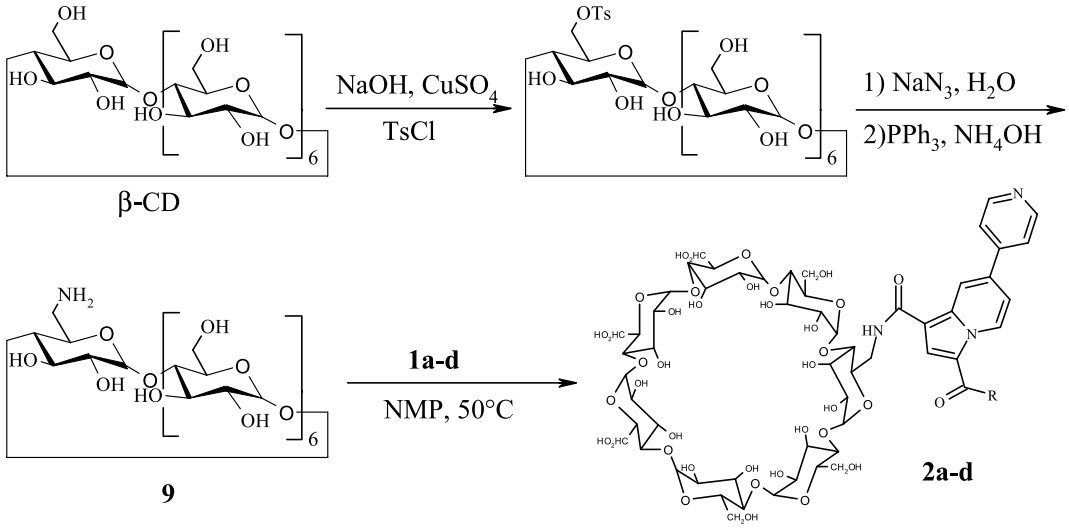
NMR spectroscopy revealed the formation of **1a–d** as a single regioisomer. The assignments of most of the proton signals were performed using 1D NMR experiment (see Section 4) and the complete structure elucidation, including the determination of the relative regiochemistry, were secured through two-dimensional techniques (COSY-LR and NOE). The absence in the COSY-LR spectra and in NOESY experiments of crossed signals between H'_5 and H'_6 allowed the unambiguous assignment of the regiochemistry of **1a–d**.

The mono-6-amino-6-deoxy-β-cylodextrin **9** was synthesised via a three step process involving a preliminary regioselective tosylation into the primary face of βCD,[18] following, by the displacement of the tosyl leaving group with NaN_3[19] and the reduction of the azido group via the Staüdinger reaction.[20] (Scheme 2) Then, the mono-6-amino-6-deoxy-β-cylodextrin **9** was treated with **1a–d** in NMP (*N*-Methylpyrrolidone) at 50 °C to give the corresponding fluorescent β-CD. Crude **2a–d** were isolated by precipitation from acetone and then successively purified using Sephadex CM25 and G15 chromatography, respectively. Analysis of **2a–d** by FTIR, NMR, ESIMS and elemental analysis are in agreement with the proposed structures and with the literature data. The NMR spectra of **2a–d** display the characteristic signal of the amide proton around 8.2 ppm and the ^{13}C spectra show clearly two chemical shift values near 164 and 180 ppm belonging to the CONH and the COAr groups, respectively. To obtain further evidence about the initial geometry, 2D-ROESY experiments have been performed in D_2O for all fluorescent compounds **2a–d**. All Roesy spectra do not display NOE cross peaks between the H-3 and H-5 protons of thecyclodextrin part and aromatics protons of the pyridino-indolizinic moiety, which indicate distinctly that the fluorophore arm is located outside the cavity. In a previous paper,[21] we described for the first time the reactivity of cycloimmonium ylides with the electroactive propinamido-βCD. This new tool for the functionalisation of the primary face of the β-cyclodextrin has resulted in the synthesis of **2a–d**. Here, the new proposed method offers two major advantages, as it furnish significant higher yields (20–30% higher) and because it offers the possibility to graft directly this new fluorescent arm into another molecular scaffolds with the aim to obtain new fluorescent artificial receptors.

2.2. Fluorescence study

The purpose here is to check if the new fluorescent moiety appended to the β-cyclodextrin can induce change in fluorescence emission upon addition of a guest such 1-adamantanol in aqueous solution. 1-Adamantanol was chosen for its ability to strongly bind to β-CD and also due to its non-fluorescent nature, which will not interfere with subsequent fluorescence measurements.

Figure 2 shows the fluorescence spectra of **2a** (**2b–d** display the same fluorescent behaviour in studied concentrations) alone, and in the presence of various concentrations of 1-adamantanol in aqueous solution (phosphate buffer, pH=7.0), respectively. Upon addition of 1-adamantanol to an aqueous solution of **2a**, a decrease in the fluorescence



Scheme 2. Preparation of the fluorescent β-cyclodextrins **2a–d**.

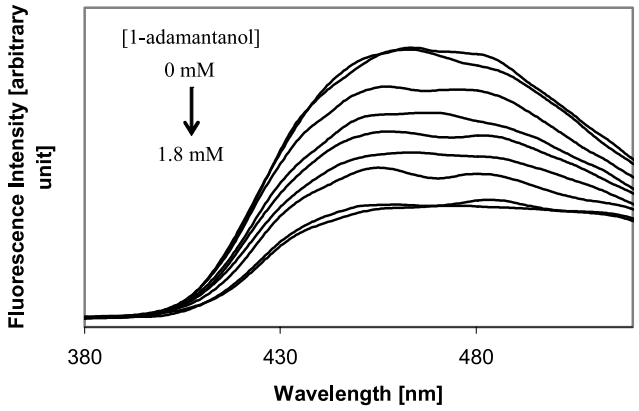


Figure 2. Emission spectra in phosphate buffer (pH=7.0, 25 °C) of **2a** (0.01 mM) at various concentrations of 1-adamantanol (0–1.8 mM).

intensity with a shift toward shorter wavelength were observed. The result obtained suggests that the pyridinoindolizine linker, which is attached onto the primary face of the β-cyclodextrin, is displaced into a more polar environment when the 1-adamantanol is added. To calculate the molecular recognition abilities of **2a–d**, the $\Delta I/I_0$ value was used as the sensitive factor, where $\Delta I = I_0 - I$; I and I_0 are the emission intensities in the presence and the absence of 1-adamantanol, respectively. Table 1 shows the $\Delta I/I_0$ values obtained with 1-adamantanol at 0.1 mM. **2a**,**b** and **2d** show a significant sensitivity factors when recorded in the presence of 1-adamantanol. Compared to the well known dansyl appended β-cyclodextrin derivative ($\Delta I/I_0 = 0.390$ in Phosphate Buffer, pH=7.0),[22] **2a** displays a comparable sensitivity factor ($\Delta I/I_0 = 0.449$) in the presence of 1-adamantanol. On the other hand, **2c** shows a surprisingly very low sensitivity. So in order to examine the possible correlation between the fluorescence variation and the bindings ability of the hosts, the binding constants have been calculated. The guest-induced fluorescence variation was employed to calculate the binding constants of the different hosts using the previously method reported by Ueno.[23] The results are shown in Table 1. While **2a**, **2b** and **2d** display almost the same binding behaviour, which is consistent with the corresponding sensitivity factors obtained, **2c** ($R = OCH_3$) has the strongest binding affinity and the lowest sensitivity factor. This means that the sensitivity value given for **2c** is relative, and not an absolute, measure of its sensory ability.

3. Conclusion

We have described in this paper the synthesis and the characterisation of a series of new functionalisable fluorophores. For their preparation, a new efficient activated dipolarophile was developed. The different fluorescence arms were connected to the primary face of the β-cyclodextrin leading corresponding fluorescent macrocycles in good yields. Fluorescent sensor properties were also proved through the variation of the fluorescence emission of **2a–d** upon addition of 1-adamantanol. The preparation, using the second reactive site B, of polymeric supramolecular systems bearing this new fluorescent moiety (with and without the cylodextrin moiety) is underway.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer with tetramethylsilane as internal standard. The abbreviations used are: s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were measured using a Platform II Micromass Apparatus. IR spectra were recorded using a Perkin–Elmer instrument. Melting points were obtained with a Reichert Thermopan apparatus and are uncorrected. Fluorescence spectra were recorded using a Perkin–Elmer LS50B spectrometer. Chromatographic separations were carried out on Aldrich G25 and G15. All reagents were used as purchased unless otherwise stated. Solvents were dried according to standard procedures.[24] All reactions were performed under N_2. The reagents were transferred by syringe

4.1.1. General procedure for the synthesis of 1-substituted-[4,4′] bipyridium bromides 5a–d. The ω-bromacetophenone compounds **4a–d** are commercially available. A solution of ω-bromacetophenone **4a–d** (8.8 mmol) in acetone (200 mL) was added at room temperature to a solution of bipyridine **3** (1.37 g, 8.8 mmol) in acetone (100 mL). The solution was warmed to 40 °C for 10 h. The crude product precipitated, filtered off and washed with acetone to give colourless solids.

^1H and C^{13} spectra of compound **5a**, **5c** were consistent with literature data.[25]

4.1.2. 1-(4-Methylbenzoylmethyl)-[4,4′]bipyridinium bromide (5b). Mp 350 °C. ^1H NMR (DMSO/TMS): δ= 2.46 (s, 3 H, CH_3), 6.54 (s, 2 H, CH_2N^+), 7.51 (d, J= 8.1 Hz, 2H, H_{meta}/CO), 8.01 (d, J=8.1 Hz, 2H, H_{ortho}/CO), 8.10 (d, J=5.8 Hz, 2H, H_{meta}/N), 8.78 (d, J=6.6 Hz, 2H, H_{meta}/N^+), 8.91 (d, J=5.8 Hz, 2H, H_{ortho}/N), 9.18 (d, J= 6.6 Hz, 2H, H_{ortho}/N^+); ^{13}C NMR (DMSO/TMS): δ=22.2, 66.6, 122.9, 126.0, 129.3, 130.6, 131.9, 141.7, 146.4, 147.7, 151.9, 153.8, 191.0; IR (KBr): $\tilde{\nu}$=3024 cm^{-1}, 2949, 1678, 1643, 1602, 1410, 804; MS (ES^+, cone 10); m/z (%): 289 (100) [M−Br]; $C_{19}H_{17}BrN_2O$: Calcd C 61.80, H 4.64, N 7.59; found C 62.02, H 4.72, N 7.46.

4.1.3. 1-(4-Chlorobenzoylmethyl)-[4,4′]bipyridinium bromide (5d). Mp 350 °C. ^1H NMR (DMSO/TMS): δ= 6.51 (s, 2 H, CH_2N^+), 7.78 (dd, J=8.6 Hz, 2H, H_{meta}/CO), 8.10 (m, 4H, H_{ortho}/CO+H_{meta}/N), 8.77 (d, J=6.9 Hz, 2H, H_{meta}/N^+), 8.91 (d, J=4.5 Hz, 2H, H_{ortho}/N), 9.14 (d, J= 6.9 Hz, 2H, H_{ortho}/N^+); ^{13}C NMR (DMSO/TMS): δ=66.0, 122.2, 125.3, 129.5, 130.3, 132.5, 140.0, 141.0, 147.0, 151.2, 153.3, 190.0; IR (KBr): $\tilde{\nu}$=3018 cm^{-1}, 2927, 1693, 1642, 1588, 1495, 795; MS (ES^+, cone 10); m/z (%):309 (100) [M−Br−2], 311 (100) [M−Br]; $C_{18}H_{14}BrClN_2O$: Calcd C 55.48, H 3.62, N 7.19; found C 55.62, H 3.73, N 7.05.

4.2. General procedure for the synthesis 3-(4-substitutedbenzoyl)-1-(4-nitrophenylcarbonyl)-7-pyridin-4-ylindolizines 1a–d

A solution of freshly distilled Et_3N (2.7 mmol) was added to

a stirred solution of **5a–e** (2.4 mmol) and 4-nitrophenylpropiolate **7**[26] (2.4 mmol) in dry NMP at 0 °C under N_2, in the absence of light. The reaction mixture was maintained at 0 °C over 2 days. The crude product precipitated, filtered and washed with a large amount of methanol.

4.2.1. 3-(Benzoyl)-1-(4-nitrophenoxycarbonyl)-7-pyridin-4-ylindolizine 1a. Mp 288–289 °C; ^{1}H NMR (DMSO+5% CF_3COOD/TMS): δ=7.60–7.74 (m, 5H, $H_{meta}/NO_2+H_{meta}/CO+H_{para}/CO$), 7.90 (d, J=6.6 Hz, 2H, H_{ortho}/CO), 8.00–7.85 (m, 2H, $H'_3+H'_6$), 8.37 (d, J=9.0 Hz, 2 H, H_{ortho}/NO_2), 8.60 (d, J=6.7 Hz, 2H, H'_2), 8.90 (s, 1H, H'_5), 9.08 (d, J=6.7 Hz, 2H, H'_1), 9.94 (d, J=7.9 Hz, 1H, H'_4); ^{13}C NMR (DMSO+5% CF_3COOD/TMS): δ=105.7, 114.5, 118.3, 123.4, 123.6, 124.5, 125.3, 128.6, 128.7, 128.9, 129.8, 132.4, 134.0, 138.7, 138.8, 143.0, 145.1, 152.5, 155.4, 160.6, 185.2; IR (KBr): $\tilde{\nu}$=3060 cm^{-1}, 1727, 1611, 1523, 1478, 1347, 861; MS (ES$^+$, cone 60); *m/z* (%): 464 (100) [M+H], 486 (40) [M+Na]; $C_{27}H_{17}N_3O_5$: Calcd C 69.97, H 3.70, N 9.07; found C 70.08, H 3.74, N 8.98.

4.2.2. 3-(4-Methylbenzoyl)-1-(4-nitrophenoxycarbonyl)-7-pyridin-4-ylindolizine 1b. Mp 260–261 °C; ^{1}H NMR (DMSO+5% CF_3COOD/TMS): δ=2.43 (s, 3H, CH_3), 7.42 (d, J=8.1 Hz, 2H, H_{meta}/CO), 7.63 (d, J=9.1 Hz, 2H, H_{meta}/NO_2), 7.80 (d, J=8.1 Hz, 2H, H_{ortho}/CO), 7.95 (d, J=7.3 Hz, 1H, H'_3), 7.97 (s, 1H, H'_6), 8.35 (d, J=9.1 Hz, 2H, H_{ortho}/NO_2), 8.59 (d, J=6.8 Hz, 2H, H'_2), 8.87 (s, 1H, H'_5), 9.08 (d, J=6.8 Hz, 2 H, H'_1), 9.96 (d, J=7.3 Hz, 1H, H'_4); ^{13}C NMR (DMSO+5% CF_3COOD/TMS): δ=21.4, 105.4, 114.4, 118.1, 123.4, 123.6, 124.1, 125.3, 128.5, 129.1, 129.3, 129.7, 134.1, 135.9, 138.7, 142.7, 143.6, 145.0, 151.7, 155.3, 184.8; IR (KBr): $\tilde{\nu}$=3072 cm^{-1}, 1725, 1600, 1522, 1464, 1345, 861; MS (ES$^+$, cone 60); *m/z* (%): 478 (100) [M+H], 500 (25) [M+Na]; $C_{28}H_{19}N_3O_5$: Calcd C 70.43, H 4.01, N 8.80; found C 70.87, H 4.14, N 8.71.

4.2.3. 3-(4-Methoxybenzoyl)-1-(4-nitrophenoxycarbonyl)-7-pyridin-4-ylindolizine 1c. Mp 272–273 °C; ^{1}H NMR (DMSO +5% CF_3COOD/TMS): δ=3.84 (s, 3H, CH_3), 7.15 (d, J=8.6 Hz, 2H, H_{meta}/CO), 7.64 (d, J=9.1 Hz, 2H, H_{meta}/NO_2), 7.87–7.94 (m, 3H, H'_3+H_{ortho}/CO), 7.95 (s, 1H, H'_6), 8.36 (d, J=9.1 Hz, 2H, H_{ortho}/NO_2), 8.59 (d, J=6.7 Hz, 2H, H'_2), 8.86 (s, 1H, H'_5), 9.07 (d, J=6.7 Hz, 2H, H'_1), 9.90 (d, J=7.6 Hz, 1H, H'_4); ^{13}C NMR (DMSO+5% CF_3COOD/TMS): δ=55.6, 105.6, 114.5, 118.4, 123.4, 123.9, 124.5, 125.4, 127.9, 129.9, 131.0, 131.6, 133.7, 138.6, 142.9, 142.7, 145.2, 152.3, 154.8, 155.2, 160.7, 184.4; IR (KBr): $\tilde{\nu}$=3078 cm^{-1}, 1723, 1597, 1520, 1478, 1345, 799; MS (ES$^+$, cone 60); *m/z* (%): 494 (100) [M+H], 516 (40) [M+Na]; $C_{28}H_{19}N_3O_6$: Calcd C 68.15, H 3.88, N 8.52; found C 68.23, H 3.92, N 8.43.

4.2.4. 3-(4-Chlorobenzoyl)-1-(4-nitrophenoxycarbonyl)-7-pyridin-4-ylindolizine 1d. Mp 255–256 °C; ^{1}H NMR (DMSO+5% CF_3COOD/TMS): δ=7.74 (m, 4H, $H_{meta}/NO_2+H_{meta}/CO$), 7.90 (d, J=8.3 Hz, 2H, H_{ortho}/CO), 7.96 (s, 1H, H'_3), 7.96 (s, 1H, H'_6), 8.35 (d, J=8.9 Hz, 2H, H_{ortho}/NO_2), 8.57 (d, J=6.0 Hz, 2H, H'_2), 8.86 (s, 1H, H'_5), 9.06 (d, J=6.0 Hz, 2H, H'_1), 9.94 (d, J=7.0 Hz, 1H, H'_4); ^{13}C NMR (DMSO+5% CF_3COOD/TMS): δ=105.7, 114.6, 118.1, 123.4, 123.6, 124.2, 125.3, 128.5, 128.9, 129.8, 130.9, 134.6, 137.2, 139.0, 143.5, 145.1, 151.8, 155.3, 160.5, 183.9; IR (KBr): $\tilde{\nu}$=3069 cm^{-1}, 1728, 1616, 1591, 1469, 1344, 798; MS (ES$^+$, cone 60); *m/z* (%): 498 (100) [M+H], 500 (32) [M+H+2], 520 (31) [M+Na], 522 (10) [M+Na+2]; $C_{27}H_{16}ClN_3O_5$: Calcd C 65.13, H 3.24, N 8.44; found C 65.23, H 3.11, N 8.51.

4.3. General procedure for the synthesis of *N*-(6A-deoxy-β-cyclodextrin-6a-yl)-1-amido-3-(4-substitutedbenzo-yl)-1-(4-nitrophenylcarbonyl)-7-pyridin-4-ylindolizines 2a–d.[21]

A solution of **1a–d** (1 mmol) in dry NMP (10 mL) was added dropwise to a stirred solution of **9** (1 mmol) in dry DMF (30 mL) at 50 °C under N_2. The reaction mixture was maintained at 50 °C over 24 h. The yellow solution was then poured in acetone (300 mL) and the crude compound collected by filtration. The latter was dissolved in water and the unreacted starting material **1a–d** was removed by filtration and the filtrate was poured again in acetone (300 mL). The resultant precipitate was passed through a CM-25 column by eluting with water. The fractions containing the fluorescent β-cyclodextrin were combined, concentrated in vacuum. Finally, the mixture was applied to gel filtration using Sephadex G-15 to give **2a–d** as fine yellow powders.

4.3.1. *N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-amido-3-benzoyl-7-pyridin-4-ylindolizine 2a. ^{1}H NMR (DMSO/TMS): 3.25–3.90 (m, 42H, *H*-2, *H*-4, *H*-3, *H*-5, *H*-6^{A,B}), 4.28–4.58 (m, 6H, –O*H*$_6$), 4.84–5.01 (m, 7H, *H*-1), 5.63–6.08 (m, 14H, –O*H*$_2$, –*OH*$_3$), 7.52–7.76 (m, 4H, *H*$'_3$, *H meta/CO*, *H para/CO*), 7.92 (d, J=8.3 Hz, 2H, *H ortho/CO*), 7.94 (d, J=5.9 Hz, 2H, *H*$'_2$), 8.21 (s, 1H, *H*$'_6$), 8.39 (m, 1H, N*H*), 8.73 (d, J=5.9 Hz, 2H, *H*$'_1$), 9.02 (s, 1H, *H*$'_5$), 9.92 (d, J=7.3 Hz, 1H, *H*$'_4$); ^{13}C NMR (DMSO-d_6, δ): 60.8, 60.9, 71.0, 72.8, 73.2, 74.0, 81.9, 82.3, 82.5, 82.7, 85.1, 102.7, 103.1, 113.8, 117.3, 121.2, 126.4, 128.7, 128.8, 129.3, 131.8, 150.8, 164.2, 185.4; *m/z* (%): 1481 (M+Na, 100), 1459 (M+1, 15); $C_{63}H_{83}N_3O_{36}\cdot 5H_2O$: Calcd C 48.87, H 6.05, N 2.71; found C 48.98, H 6.13, N 3.02.

4.3.2. *N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-amido-3-(4-methylbenzo yl)-7-pyridin-4-ylindolizine 2b. ^{1}H NMR (DMSO/TMS): 2.44 (s, 3H, –C*H*$_3$), 3.13–3.84 (m, 42H, *H*-2, *H*-3, *H*-4, *H*-5, *H*-6^{A,B}), 4.38–4.58 (m, 6H, –O*H*$_6$), 4.78–4.97 (m, 7H, *H*-1), 5.58–6.01 (m, 14H, -O*H*$_2$, *OH*$_3$), 7.14 (d, J=8.8 Hz, 2H, *H meta/CO*), 7.76 (dd, J=1.9, 7.4 Hz,1H, *H*$'_3$), 7.85 (d, J=5.8 Hz, 2H, *H*$'_2$), 7.89 (d, J=8.8 Hz, 2H, *H ortho*/CO), 8.15 (s, 1H, *H*$'_6$), 8.34 (m, 1H, N*H*), 8.73 (d, J=5.7 Hz, 2H, *H*$'_1$), 8.95 (s, 1H, *H*$'_5$), 9.84 (d, J=7.4 Hz, 1H, *H*$'_4$); ^{13}C NMR (DMSO): 21.9, 60.6, 60.9, 71.2, 73.2, 73.3, 73.9, 74.0, 82.1, 82.5 (2×), 85.0, 102.7, 102.7, 103.1, 114.6, 117.8, 121.6, 126.7, 129.3, 130.1, 151.5, 164.3, 185.2; *m/z* (%): 1495 (M+Na, 100); 1473 (M+1, 18); $C_{64}H_{85}N_3O_{36}\cdot 5H_2O$: Calcd C 49.20, H 6.13, N 2.69; found C 49.28, H 6.10, N 2.73.

4.3.3. *N*-(6^A-Deoxy-β-cyclodextrin-6^A-yl)-1-amido-3-(4-methoxybenzoyl)-7-pyridin-4-ylindolizine 2c. ^{1}H NMR (DMSO/TMS): 3.03–3.88 (m, 42H, *H*-2, *H*-3, *H*-4, *H*-5, *H*-6^{A,B}), 3.95 (s, 3H, –OC*H*$_3$), 4.33–4.59 (m, 6H, –O*H*$_6$), 4.78–4.97 (m, 7H, *H*−1), 5.54–6.07 (m, 14H, –O*H*$_2$, *OH*$_3$),

7.14 (d, $J=8.7$ Hz, 2H, *H meta/CO*), 7.73 (d, $J=7.4$ Hz, 1H, H'_3), 7.89 (d, $J=8.7$ Hz, 2H, *H ortho/CO*), 8.21 (s, 1H, H'_6), 8.23 (d, $J=6.1$ Hz, 2H, H'_2), 8.40 (m, 1H, N*H*), 8.88 (d, $J=6.1$ Hz, 2H, H'_1), 9.03 (s, 1H, H'_5), 9.82 (d, $J=7.38$ Hz, 1H, H'_4); ^{13}C NMR (DMSO): 56.4, 60.5, 60.8, 60.9, 71.0, 72.2–74.34, 82.0–82.7, 85.0, 102.6, 102.8, 103.0, 113.8, 114.8, 119.4, 123.4, 126.2, 129.3, 132.3, 146.5, 163.2, 184.5; *m/z* (%): 1511 (M+Na, 100), 1489 (M+H, 20); $C_{64}H_{85}N_3O_{37}\cdot 6H_2O$: Calcd C 48.15, H 6.12, N 2.63; found C 48.23, H 6.30, N, 2.82.

4.3.4. *N*-(6^{A}-Deoxy-β-cyclodextrin-6^{A}-yl)-1-amido-3-(4-chlorobenzoy-l)-7-pyridin-4-ylindolizine 2d. ^{1}H NMR (DMSO/TMS): 3.23–3.90 (m, 42H, *H*-2, *H*-4 *H*-3, *H*-5, *H*-6^{A,B}), 4.20–4.57 (m, 6H, –O*H*$_6$), 4.76–4.94 (m, 7H, *H*-1), 5.51–5.99 (m, 14H, –O*H*$_2$, *OH*$_3$), 7.64 (d, $J=8.5$ Hz, 2H, *H meta/CO*), 7.70 (dd, $J=2.4$, 7.4 Hz, 1H, H'_3), 7.81 (d, $J=8.5$ Hz, 2H, *H ortho/*CO), 7.83 (d, $J=6.1$ Hz, 2H, H'_2), 8.15 (s, 1H, H'_6), 8.26 (m, 1H, N*H*), 8.7 (d, $J=6.1$ Hz, 2H, H'_1), 8.94 (s, 1H, H'_5), 9.87 (d, $J=7.5$ Hz 1H, H'_4); ^{13}C NMR (DMSO): 60.4, 60.5, 60.8, 71.1, 72.76–74.04, 81.9, 82.0, 82.1, 82.5, 82.6, 82.9, 85.1, 102.7, 102.9, 103.1, 114.4, 117.9, 121.7, 127.1, 129.4, 129.5, 131.7, 151.5, 164.2, 184.2; *m/z* (%): 1516 (M+Na, 32), 1514 (M+Na−2); $C_{63}H_{82}ClN_3O_{36}\cdot 5H_2O$: Calcd C 47.81, H 5.86, N 2.65; found C 47.98, H 6.00, N 2.75.

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Characterization of PEDOT film functionalized with a series of automated synthesis ferrocenyl-containing oligonucleotides

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Abstract—In previous works we have described a fully automated synthesis of new ferrocene labelled oligonucleotides (Fc-ODNs) probes with one or more electroactive markers at different position in the chain. These Fc-ODNs have shown good properties to detect ODN target in solution. Here we describe the post-functionalization of a conducting co-polymer based on ethylenedioxythiophene (EDOT) derivatives by a series of Fc-ODNs. The grafting of the Fc-ODNs probes resulted in the appearance of the ferrocene redox couple which directly confirm the effectiveness of the ODN anchoring compared to traditional approach based on IR spectroscopy and X-ray fluorescence of the films. Moreover, the electrochemical response of the modified electrodes analysed in organic media before and after hybridization with ODN target confirm that properties obtain in solution for Fc-ODNs already exist in the film. The changes in the current intensity were found to be dependant on the structure of the grafted ODN that validate our strategy to synthesize an optimal Fc-ODNs.

1. Introduction

The development of efficient methods for real-time detection of specific DNA sequences is currently receiving a tremendous amount of interest for applications in clinical diagnostics[1] environmental protection,[2,3] food quality control,[4] and forensic science.[5] In this context electrochemical sensor devices have emerged as promising tools due to their high sensitivity, easy implementation, low production cost and ability to miniaturization.[6–8] Such systems are based on the covalent immobilization of probe oligonucleotides (ODNs) onto a surface, which allows the direct detection of the hybridization reaction with the target ODN.[9] In that connection, conjugated polymers as polythiophene or polypyrrole did appear as valuable conducting substrates for the grafting of the ODN probes. Indeed the change in either the intrinsic electroactivity of the conducting backbone or the electrochemical properties of a pending redox label can be used as a transduction mechanism to monitor the hybridization reaction with the target ODN.[9–18] However, IR spectroscopy and X-ray fluorescence of the films are generally necessary to confirm the grafting of ODNs[19] and no quantitative determination of the amount of ODN immobilized on the polymer film could be achieved. Moreover, the common functional feature pertaining to these systems is the intensity decrease of the electrochemical signal in response to hybridization, which is detrimental to the sensitivity performance of the sensor.

In this context, we have developed a new strategy based on the post-functionalization of a conducting polymers by ODN probes and ferrocene units at the same place and in a one-pot reaction. Indeed the ferrocene moiety displays a reversible and narrow redox behavior that is sensitive to electronic and steric factors. By this way the appearance of the ferrocene redox couple in cyclic voltammetry (CV) directly confirm the effectiveness of the ODN anchoring and the exact integration of the amount of charge exchanged by ferrocenyl groups allows to the electrode coverage.

In previous works we have prepared and demonstrated the good capacity to detect ODN target of a series of ODNs bearing different number of ferrocene unit directly incorporated into the base sequences during the automated solid phase (Chart 1).[20–22]

Keywords: Modified electrodes; Ethylenedioxythiophene; Electrochemical biosensing; Ferrocene.
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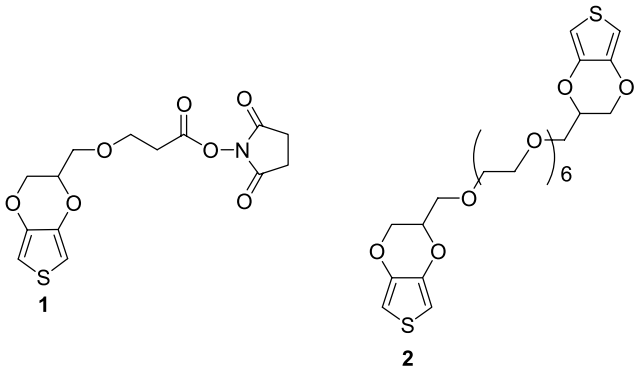
ODN 5.3	5' **Fe-**GTA TTC CTT GGA CTC ATA AGG T-**Fe-**C7-NH_2 3'
ODN 3.3	5' GTA TTC CTT GGA CTC ATA AGG T-**Fe-Fe-**C7-NH_2 3'
ODN 3.3.3	5' GTA TTC CTT GGA CTC ATA AGG T-**Fe-Fe-Fe-**C7-NH_2 3'

Chart 1. List of ferrocene Fc-ODNs used for film preparation.

In this paper, the post-functionalization of a poly(ethylenedioxythiophene) (PEDOT) film with the Fc-ODN systems was performed. So far the PEDOT backbone has not been investigated for the generation of DNA sensors although it represents a preferential conducting polymer for such application owing to its high chemical stability, compatibility with aqueous media, and conductivity.[23] According to our previous results on PEDOT-based modified electrodes,[24] we describe here the synthesis of a novel hydroxysuccinimidyl ester derivative of EDOT, **1**, and the electrochemical copolymerization of **1** and the bis-EDOT compound, **2** (Scheme 1).[25] It is shown that a redox signal corresponding to the ferrocene units appear upon covalent immobilization of ferrocene-ODN assemblies via amide bond formation, which directly confirm, the probes grafting.



Scheme 1. Precursors of copolymer.

2. Experimental

2.1. Reagents

Lithium hydride (LiH), 18-crown-6, ethyl-3-bromopropionate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, *N*-hydroxysuccinimide were purchased from Aldrich and used as received. THF (anhydrous) and DMF (anhydrous) were purchased from ACROS. Diethylether, absolute ethanol, ethyl acetate, cyclohexane were purchased from CarloErba, silica gel (240–400 mesh) from Merck and $MgSO_4$ from SDS. All aqueous solutions were made with MilliQ purified water (Maxima ELGA). Phosphate buffers (pH=6.8) were made with 0.25 M KH_2PO_4, 0.25 M Na_2HPO_4 and 0.75 M NaCl. 2,3-Dihydrothieno[3,4-*b*][1,4]dioxin-2-yl)methanol (hydoxymethyl-EDOT) and hexaethylene glycol Bis(2,3-dihydrothieno[3,4-*b*][1,4]-dioxin-2-ylmethyl)ether **2** were prepared as described in the literature.[23,25]

2.2. Physical and spectroscopic methods

Melting point are uncorrected and were measured on a Electrothermal 9100 apparatus. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer at 250 and 62.5 MHz, respectively. UV spectra were obtained on a Varian Cary 1E spectrophotometer. Mass spectrometry was performed with a JEOL FX 102 Mass spectrometer in the FAB mode (Laboratoire de Mesures Physiques, USTL, Montpellier, France). MALDI-TOF mass spectra of oligonucleotides were recorded at the IBCP, Lyon on a Voyager DE (Perseptive Biosystems, Framingham, MA, USA) mass spectrometer equipped with an N_2 Laser. The matrix used for oligonucleotide mass analyses was hydroxypicolinic acid (HPA). Calibration was carried out using internal data base reference.

2.3. Synthesis of functionalized EDOT

2.3.1. 3-(2,3-Dihydro-thieno[3,4-*b*][1,4]dioxin-2-yl-methoxy)-propionic acid ethyl ester 3. A mixture of NaH (110 mg, 2.73 mmol, 60% in mineral oil) and 18-crown-6 ether (13 mg, 0.05 mmol) in 2.8 mL of anhydrous THF was stirred under argon at −10 °C. 2,3-Dihydrothieno[3,4-*b*][1,4]dioxin-2-yl)methanol (Hydroxymethyl EDOT) (280 mg, 1.63 mmol) in 2.8 mL of anhydrous THF was added. The mixture was stirred at room temperature for 1 h and then cooled down to 0 °C. Ethyl-3-bromopropionate (500 mg, 2.76 mmol) in 2.8 mL of anhydrous THF was added drop by drop during 10 min. After 72 h under stirring at room temperature the mixture was diluted with 25 mL of 5% NH_4Cl aqueous solution. The mixture was extracted with diethylether (3×25 mL). The combined organic phases were washed with water, dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified on a silica gel column using cyclohexane–ethyl acetate (70:30 v/v) as eluent to afford **4** (93 mg, 21%) as a pale yellow oil. ^1H NMR (270 MHz, $CDCl_3$) δ: 1.12 (dd, $^3J=7.2$ Hz and $^3J=7.0$ Hz, 3H, CH_3), 2.44 (dd, $^3J=6.5$ Hz and $^3J=6.2$ Hz, 2H, CH_2–CO), 3.46–3.59 (m, 2H, CH_2O), 3.64 (t, $^3J=6.2$ Hz, 2H, OCH_2 CH_2CO), 3.84–4.19 (m, 5H, CH_3–CH_2O, CH, CH_2–CH), 6.17 (s, 2H, $H_{thiophene}$) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 14.2, 35.0, 60.6, 66.0, 67.2, 69.3, 74.5, 99.7, 141.5 (*C*H), 171.3 (C=O). MS (FAB): 273 (M^{+1}, 16), 272 ($M^{\cdot +}$, 12), 89 (16), 55 (11), 29 (2).

2.3.2. 3-(2,3-Dihydro-thieno[3,4-*b*][1,4]dioxin-2-yl-methoxy)-propionic acid 4. Compound **3** (37 mg, 0.14 mmol) in 2 mL of absolute ethanol and 2 mL of an aqueous solution of NaOH (22 mg, 0.54 mmol) were stirred at reflux during 6 h. After the reaction mixture was cooled to room temperature, the solvents were evaporated in vacuo. The crude product was dissolved in 40 mL of water and extracted with diethylether (2×30 mL). The aqueous phase was acidified with HCl 2 M until acidic pH and extracted again with diethylether (2×30 mL). The second combined organic layers were dried over $MgSO_4$, and evaporated in vacuum to afford 33 mg (0.14 mmol, quantitative yield) of a white powder corresponding to compound **4**: mp 76–78 °C; ^1H NMR (270 MHz, C_5D_5N) δ: 4.08 (dd, $^3J=6.0$ Hz and $^3J=6.6$ Hz, CH_2COOH), 4.93–5.07 (m, 2H, CHCH_2O),

5.19 (t, $^3J=6.3$ Hz, 2H, OCH_2CH$_2$COOH), 5.35–5.63 (m, 2H, CH_2CH), 5.64–5.66 (m, 1H, CH), 7.86 (s, 2H, $H_{thiophene}$), 10.0 (s, 1H, OH) ppm. ^{13}C NMR (62.5 MHz, C_5D_5N) δ: 37.8, 68.4, 70.0, 71.6, 75.2, 102.2 (CH), 175.9 (C=O) ppm. MS (FAB): 244 ($M^{\cdot+}$, 50); 89 (21). Anal. Calcd: C, 49.17; H, 4.95. Found: C, 49.33; H, 4.89.

2.3.3. 3-(2,3-Dihydro-thieno[3,4-*b*][1,4]dioxin-2-yl-methoxy)-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester 1. A mixture of **4** (110 mg, 0.45 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (121 mg, 0.63 mmol), *N*-hydroxysuccinimide (62 mg, 0.54 mmol) in 2 mL of anhydrous DMF was stirred under argon atmosphere at room temperature during 20 h. After addition of acetone (10 mL) and water (10 mL), the mixture was extracted (3×30 mL) with a mixture of diethylether and ethylacetate (2/1 v/v). The combined organic layers were washed with water, dried over $MgSO_4$, and evaporated in vacuum to afford 154 mg (0.45 mmol, quantitative yield) of **1** as a white solid: mp 84–85 °C; ^{1}H NMR ($CDCl_3$) δ: 2.63 (s, 4H, CH_2 (succi)), 2.70 (dd, $^3J=6.0$ Hz and $^3J=6.3$ Hz, 2H, CH_2CO), 3.52 (m, 2H, CH_2O), 3.69 (t, $^3J=6.0$ Hz, 2H, OCH_2CH$_2$CO), 3.84–4.08 (m, 2H, CH_2CH), 4.10–4.15 (m, 1H, CH), 6.13 (s, 2H, $CH_{thiophene}$) ppm. ^{13}C NMR ($CDCl_3$) δ: 26.4, 33.0, 66.8, 67.1, 70.3, 73.2, 100.4, 142.4, 167.4 (C=O), 169.8 (C=O) ppm. MS (FAB): 341 ($M^{\cdot+}$, 10). HRMS (FAB): calcd for $C_{14}H_{15}O_7NS$ 341.0569, found 341.0564. Anal Calcd: C, 49.26; H, 4.43; O, 32.81; N, 4.10; S, 9.39. Found: C, 50.08; H, 4.98; O, 29.20; N, 3.83; S, 8.08.

2.4. Ferrocenyl-labelled oligonucleotides

Ferrocenyl-labelled oligonucleotides **ODN 5.3** and **3.3** were synthesized as previously described.[20–22] The ODN probes have a terminal amino group at the 3′ position allowing covalent linking on the copolymer film (Chart 1). Oligonucleotide target, complementary to the oligonucleotide probes with 5′-ACC-TTA-TGA-GTC-CAA-GGA-ATA-C-3′ sequence was provided by the bioMerieux company. The noncomplementary oligonucleotide is T20: 3′-TTT-TTT-TTT-TTT-TTT-TTT-T-5′.

ODN 3.3.3 containing free ferrocenyl groups was synthesized using an Applied Biosystems 394 RNA/DNA synthesizer. 1-[3-*O*-dimethoxytritylpropyl]-1′-[3′-*O*-(2-cyanoethyl-*N*,*N*-diisopropyl phosphoramidityl) propyl]ferrocene[20] was dissolved in anhydrous acetonitrile (C= 0.09 M) and the solution was dried on 3 Å molecular sieves during 24 h. Solution was filtered on 0.22 μm PVDF filter before loading on DNA synthesizer. Standard 1 μmol coupling cycle was used for oligonucleotide elongation. The coupling reaction time was increased from 15 to 500 s for ferrocene synthons. After ODN synthesis (DMTr ON), controlled pore glass (CPG) support was treated in NH_4OH (30% aqueous) during 16 h at 55 °C, then supernatant was recovered and evaporated to dryness under vacuum. The pellet was dissolved in 500 μL of MilliQ water plus 500 μL of MOP buffer. ODN was purified on MOP column (CTGen, San Jose, CA) as followed: column was first washed with 2 mL of CH_3CN/H_2O (1:1) and 2 mL of TEAAc buffer 0.1 M (pH=7) successively before loading the ODN solution on column. Truncated sequences were eluted with 4 mL of TEAAc buffer 0.1 M (pH=7). ODN was eluted with 1 mL of CH_3CN/H_2O (1:1) and solvents were evaporated to dryness. Then, ODN was detritylated with 300 μL of 80% acetic acid/water during 30 min. Acetic acid was eliminated by evaporation and ODN was precipitated twice with 0.3 M AcONa (300 μL) and ethanol (900 μL) before lyophilization in water. Oligonucleotide was purified by HPLC on a RP-18e Lichrospher 100 (300×7.5, 10 μ, Merck) with linear gradient of acetonitrile (5–40%) in 0.05 M aqueous triethylammonium acetate (pH=7). HPLC analyses of ODN purities was run on a reverse-phase RP-18e Chromolith Performance column (100×4.6 mm, Merck) with the same eluents than above described. ODN 3.3.3 was characterized by MALDI-TOF mass spectral analyses. The result (*m*/*z* calcd 8039.05, found 8042,40.70) illustrate the successful incorporation of ferrocenyl moieties into the oligonucleotide. The difference between calculated and found masses is attributed to the calibration of the instrument with standards with a behavior similar to ferrocenyl-ODN. The same problem was observed in literature.[22,26]

2.5. Electrochemical materials

Cyclic voltammetry data were acquired using a computer-based Bioanalytical instrument (BAS 100) electrochemical workstation with a three-electrode setup. A 1.6 mm diameter gold working electrode was used and polished with 1–0.1 μm diamond paste and ultrasonically rinsed in absolute ethanol. Counter electrode in platinum and Ag/AgCl (with 3 M NaCl filling solution) reference electrode were used. All anhydrous solvent are of electronic grade purity.

2.6. Electrochemical polymerization

The copolymer was obtained from electropolymerization of precursor **1** and **2** in acetonitrile containing 10^{-1} M nBu$_4$NCF$_3$SO$_3$ as supporting electrolyte at a fixed potential of 1.3 V/Ag/AgCl. Therefore, their initial concentration were kept the same: 0.01 M. 5 mC cm^{-2} were deposited. Acetonitrile with 10^{-1} M nBu$_4$NCF$_3$SO$_3$ was used to analyse the co-polymers. Cyclic voltammograms were recorded without ohmic drop compensation and at a scan rate of 100 mV/s. All cyclic voltammetry experiments were carried out at 25 °C using a cell equipped with a jacket allowing circulation of water from the thermostat.

2.7. Covalent immobilization of the ferrocene-ODN probes onto PEDOT

Substitution of the succinimidyl ester groups of the copolymer using the amino Fc-ODN probes was carried out by simple immersion of the modified electrode during 3 h at 25 °C in acetonitrile/phosphate buffer pH 6.8 (80/20 v/v) solution of the Fc-ODN probe (6.25 μM). To remove any ungrafted Fc-ODN probes, the modified electrode was thoroughly washed with water. The grafted modified electrode was then analysed by cyclic voltammetry in acetonitrile solution containing 10^{-1} M nBu$_4$NCF$_3$SO$_3$ as supporting electrolyte.

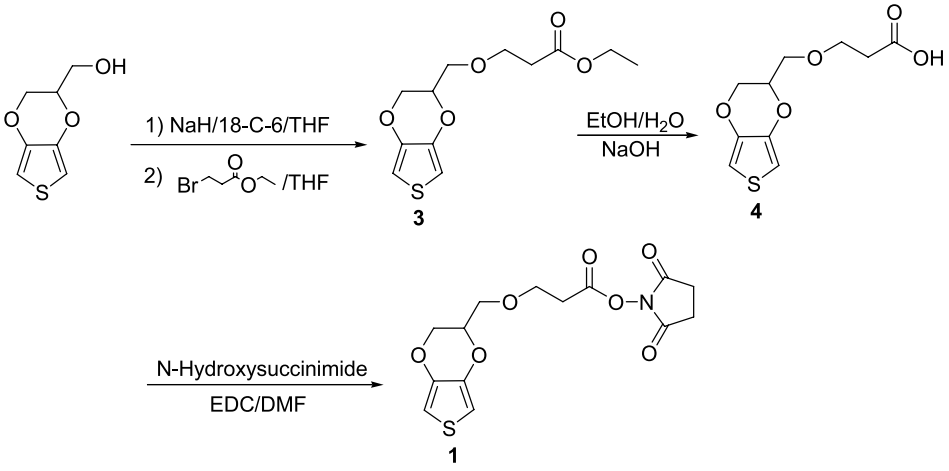
2.8. Hybridization of ODN target

PEDOT-ODN 5.3, **3.3** and **3.3.3** modified electrodes were incubated at 37 °C during 3 h in a phosphate buffer (pH 7.4) containing the ODN target (6.25 μM). After incubation, the modified electrodes were rinsed with the same buffer and electrochemically characterized in acetonitrile solution containing 10^{-1} M nBu$_4$NCF$_3$SO$_3$ as supporting electrolyte.

3. Results and discussion

3.1. Synthesis of the functionalized EDOT monomer 1

The synthetic route toward **1** is outlined in Scheme 2. The ester **3** was synthesized in 21% yield from hydroxymethyl EDOT by a Williamson reaction with ethyl-3-bromopropionate. The hydrolysis of ester group was performed in presence of NaOH to give quantitatively the carboxylic acid **4**. Reaction of **4** with *N*-hydroxysuccinimide in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride reagent lead quantitatively to the precursor **1**.



Scheme 2. Synthesis of precursor **1**.

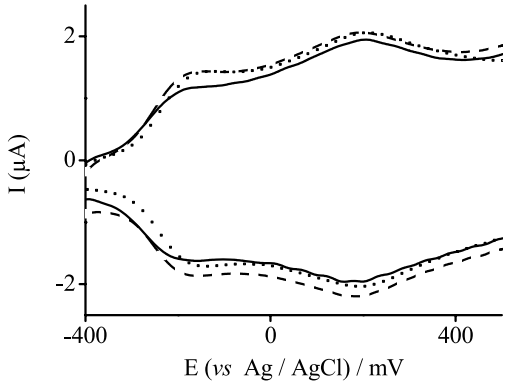


Figure 1. Cyclic voltammogram of copolymer in 0.1 M nBu$_4$NCF$_3$SO$_3$/CH$_3$CN, scan rate 100 mV s^{-1}. (Film grown under potentiostatic conditions, see text). Before immersion in solutions (dotted line); after immersion in grafting solution (dashed line); after immersion in grafting and hybridization solutions (solid line).

3.2. Co-electropolymerization of precursors

The precursor copolymer was formed easily on the gold electrode by electropolymerization of monomers **1** and **2** (10^{-2} M each) in an acetonitrile solution of nBu$_4$NCF$_3$SO$_3$ (10^{-1} M). Monomers **1** and **2** were shown to polymerize at the same oxidation potential.[24] The 5 mC cm^{-2} film was grown in potentiostatic conditions at 1.3 V/Ag/AgCl. The peak current of the electrochemical response of copolymer in acetonitrile was found to increase linearly with the scan rate, as expected for a confined surface electrochemical process with the formation of a stable adhesive film (Fig. 1). The cyclic voltammogram (CV) of the resulting co-polymer shows two anodic waves around −0.16 and +0.25 V characteristic of the PEDOT backbone. In order to test the influence of different solutions on the co-polymer, it was immersed 3 h at 25 °C in acetonitrile/phosphate buffer solution without ODN probes then washed and immersed 3 h at 37 °C in phosphate buffer without ODN target. The CV before and after immersion are similar. A little decrease of the current intensity is observed for the two redox systems of the PEDOT after the second immersion with a 40 mV negative shift for the first oxidation peak. This behavior reflects the change in solvation of the co-polymer when exposed to different solutions. Repetitive scans did not induce any change in the CV curves, which indicated a good stability of the PEDOT film.

3.3. Covalent immobilization of the ferrocene-ODN probes

After covalent grafting of the Fc-ODN probes, a small decrease of the current intensity of the first redox system of the copolymer was observed and attributed to the solution effects (Fig. 2 and Table 1). In contrast no decrease of the current intensity was observed for the second redox system of the copolymer except for **ODN 3.3.3**. In all cases a new redox system corresponding to the oxidation and subsequent reduction of ferrocenyl group was observed. The current intensity of the ferrocene redox system was observed to be depending on the nature of the ODN probe.

With **ODN 5.3** grafted onto co-polymer the anodic shoulder

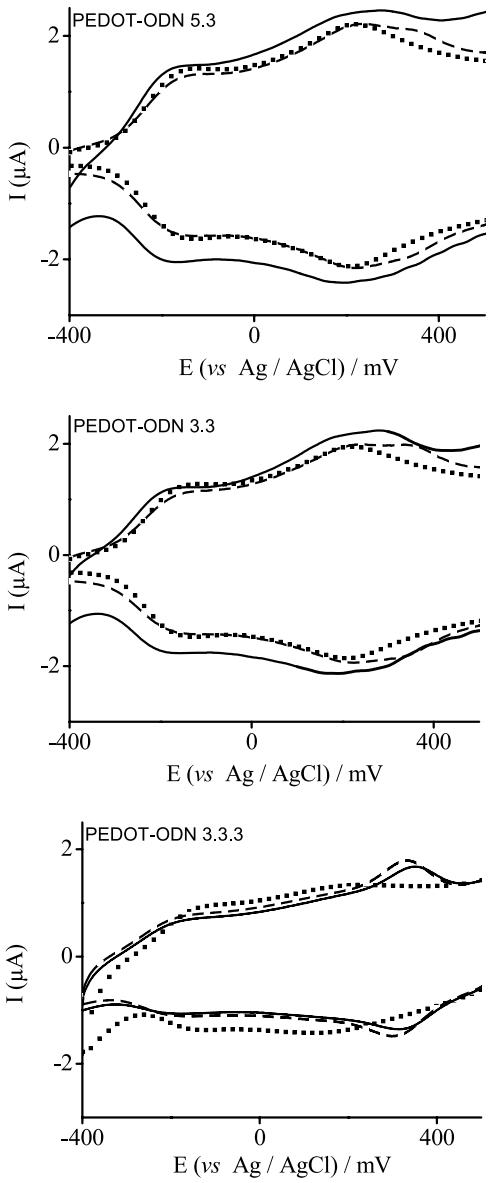


Figure 2. Cyclic voltammograms between −400 and 500 mV of functionalized copolymers in 0.1 M nBu$_4$NCF$_3$SO$_3$/CH$_3$CN, scan rate 100 mV s^{-1}. Before grafting (dotted line) and after grafting with a Fc-ODN (dashed line); after hybridization with target ODN (solid line).

associated with the ferrocene system was observed at ca. 0.3–0.4 V. The CV of co-polymers grafted with **ODN 3.3** show that the anodic shoulder associated with the ferrocene system become an anodic wave accompanied by the emergence of the subsequent cathodic shoulder. The most important effect is obtained with **PEDOT-ODN 3.3.3**. The CV curve of **PEDOT-ODN 3.3.3** exhibit the characteristic peaks of ferrocenyl groups with a quasi-ideal redox system, the oxidation and reduction peaks being respectively observed at 0.33 and 0.32 V.

The use of Fc-ODN probes allow direct assessment of the linkage of the ODN probes on the polymer film by visualization of the ferrocenyl electrochemical response that increases with the number of ferrocene units. Moreover, by exact integration of the areas under the ferrocene anodic peaks corrected from background current the efficiency of the post-functionalization of the co-polymer can be estimated. The exact integration of the amount of charge exchanged by ferrocenyl groups during the CV for **PEDOT-ODN 3.3.3** corrected from background current corresponded to an electrode coverage of 78 pmol cm^{-2}.

3.4. Incubation with non-complementary DNA strand

The PEDOT-Fc-ODN modified electrode were incubated at 37 °C during 3 h in a phosphate buffer (pH 7.4) containing the non-complementary ODN target (6.25 μM). After incubation, the modified electrode was rinsed with the same buffer solution and electrochemically characterized in acetonitrile. In all cases the electrochemical response of the modified electrodes before and after incubation with non-complementary ODN target were identical (Fig. 3).

3.5. Hybridization with ODN target

The hybridization of **PEDOT-ODN 5.3** and **3.3** with the complementary ODN target led to an increase of the current intensity and a 60 mV negative shift for all oxidation waves. The oxidation peaks of the ferrocenyl group shift from 0.35 to 0.29 and from 0.36 to 0.30 V for **PEDOT-ODN 5.3** and **3.3**, respectively. The negative shift of potentials can be attributed to a faster electron transfer through the copolymer after hybridization. Pharm et al. interpreted the current enhancement upon hybridization on the basis of changes in the conformation of the ODN strands. Indeed, single-stranded ODNs behave as random coils while after hybridization of a complementary sequence the double-stranded ODNs lead to a more organized surface, through which counter ions could diffuse more freely.[9] Additionally it is believed that the hydrophilic character of hybridization of DNA combined to the highly hydrophilic character of EDOT-based polymers containing oligooxyethylene chains can increase the permeability of the polymer films to doping anions. With **PEDOT-ODN 3.3.3** the hybridization induces a decrease in the current density together with a positive shift of the oxidation wave, as generally observed with conjugated polyheterocycles functionalized with ODN recognition centres. The decrease of the current intensity and a positive shift of oxidation potential peak were explained by a decrease of the permeability of the polymer

Table 1. Electrochemical values for the grafting of ODN-Fc and hybridization with complementary DNA target

ODN entry	Probe surface density corrected from background (pmol cm^{-2})	Variation of peak height of ferrocene oxidation wave after hybridization corrected from background grafting curve (μA)
ODN 5.3	32 (12)	0.37 (0.05)
ODN 3.3	46 (10)	0.27 (0.05)
ODN 3.3.3	78 (8)	−0.10 (0.03)

The values in parentheses represent the standard deviations from several electrode measurements ($n>4$) not the nonlinear curve fitting errors.

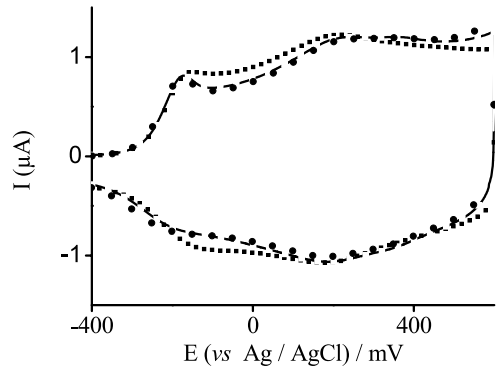


Figure 3. Cyclic voltammogram of **PEDOT-ODN 3.3.3** between −400 and 600 mV in 0.1 M nBu$_4$NCF$_3$SO$_3$/CH$_3$CN, scan rate 100 mV s^{-1}. Before grafting (dotted line), after grafting Fc-ODN (dashed line) and after incubation with non-complementary ODN target (circle dashed line).

films to doping anions and to the change of conformation of the conjugated backbone.[11–16]

These results are very interesting for the development of direct DNA hybridization electrochemical sensors as, to our knowledge, there is no reported example in the literature describing an increase of the current intensity after ODN probes linkage followed by a new enhancement of current intensity after hybridization of the ODN target. Moreover, this strategy allows the determination of the optimal position and the number of the ferrocenyl groups into the ODN probe sequences.

4. Conclusion

A succinimidyl ester derivative of EDOT has been synthesized and characterized. Its co-electropolymerization with oligo(oxyethylene)diEDOT in potentiostatic conditions in acetonitrile leads to a stable film. The use of this new copolymer film for the immobilization of ferrocene-modified ODN probes shows a sensitive and selective DNA sensor. Indeed hybridization of ODN target is observed to induce a positive shift of the oxidation waves and an increase of the current intensity. The latter increase is more important when three ferrocenyl groups are near the electrode surface. These results shows great promise for the development of direct DNA hybridization electrochemical sensors, as to the best of our knowledge, there are so far no examples reported in literature which describes an increase of the current intensity after ODN probes immobilization followed by a new enhancement of current intensity after hybridization of the ODN target. Moreover, this work also emphasizes the subtle balance between the number and position of the ferrocenyl groups in ODN probe sequence in order to achieve accurate electrochemical sensing of DNA hybridization.

Lastly this works validate ours simple strategy to prepare labelled ODN with one or more electroactive markers at different positions of the chain[22] because it is necessary to test different combination of Fc-ODNs to obtain the best DNA sensors. Work to prepare ODN probes with two and three ferrocenyl groups in 3′ position with one and more 5′ ferrocenyl groups is currently underway.

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Expanding the substitution pattern of 2(1*H*)-pyrazinones via Suzuki and Heck reactions

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Abstract—Various 3,5-dichloropyrazinones were substituted at the *C*-3 position with (hetero)aryl, alkyl and alkenyl groups by means of Suzuki and Heck reactions. The methodology could be extended to reactions on the far less reactive *C*-5 position by transhalogenation of the 5-Cl substituent to a 5-Br or a 5-I group prior to performing the cross-coupling.

1. Introduction

In the past few years, 2(1*H*)-pyrazinones started to emerge as valuable platforms in peptidomimetic chemistry. It has been shown that the diazine core is able to reduce the peptidyl features of peptide-like compounds, rendering them more interesting for pharmaceutical applications: a number of protease inhibitors have been designed around this template (Fig. 1). A pyrazinone was introduced at the P2–P3 (modified amino acid) positions of tryptase inhibitors (e.g., **1**),[1] thrombin inhibitors (e.g., **2**)[2–6] and caspase-3 inhibitors (e.g., **3**).[7] In all these cases, variation of the pyrazinone substituents representing the P1 and P4 residues led to potent compounds.

Another example is the application of a pyrazinone unit in somatostatin analogue **4** (Fig. 1) where it replaced a disulfide moiety, resulting in a compound with a high degree of antiproliferative activity.[8] The pyrazinone core also appears in an opioid-mimetic compound **5** (Fig. 1) which was shown to be able to cross epithelial tissue in the gastrointestinal tract and the blood–brain barrier, paving the way for new orally bioavailable synthetic opioid-mimetic substances.[9–11]

Considering the above mentioned applications of pyrazinone systems it is of interest to further explore the possibilities of functionalising this scaffold. Indeed, being able to modify the substitution pattern on the pyrazinone core can be advantageous if fine-tuning of pharmaceutically relevant compound properties like, e.g. lipophilicity and hydrogen bonding capacity is required.

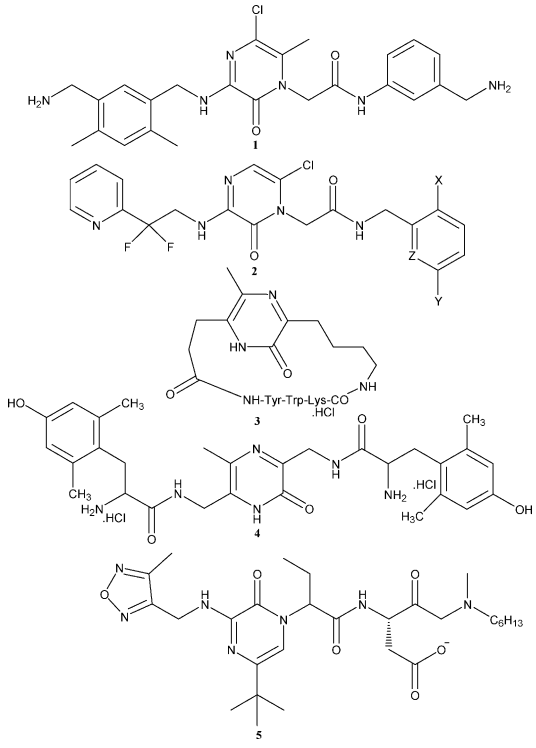

Figure 1. Pyrazinone containing compounds.

Keywords: 3- and 5-Substituted 2(1*H*)-pyrazinones; Heterocyclic compounds; Suzuki reaction; Heck reaction.
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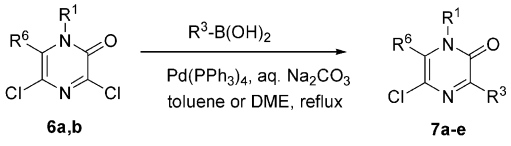
In this paper, in which we elaborate the results of a previous short communication,[12] we focus on the introduction of substituents like, e.g. alkenyl and (hetero)aryl groups at the reactive C-3 and the more challenging C-5 position of 3,5-dihalo-2(1*H*)-pyrazinones. In this respect, Suzuki and Heck cross coupling reactions using organoboron reagents or vinyl compounds appeared to be an attractive way of introducing the abovementioned functionalities. As far as the C-3 position is concerned, these methodologies are complementary to the methods described earlier.[13,14]

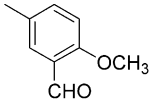
2. Results and discussion

2.1. Functionalisation of the *C*-3 position

2.1.1. Coupling with boron reagents. We first tried introducing (hetero)aryl- and alkenylboronic acids on 3,5-dichloro-2(1*H*)-pyrazinones. In agreement with earlier observations made in the Stille reaction, the initial oxidative addition occurs exclusively at the *C*-3 position of the pyrazinone. We used coupling conditions that were optimised previously for the Suzuki coupling of π-deficient heteroaryl chlorides.[15,16] The best results were obtained using tetrakis(triphenyl-phosphine)palladium(0) as a catalyst, aqueous Na_2CO_3 as the base and toluene as solvent. Thus reaction of pyrazinones **6a**[17] and **6b**[18] with 1.2 equiv of arylboronic acid and 3 mol % of tetrakis in toluene under reflux conditions produced 3-aryl-2(1*H*)-pyrazinones **7a** and **7b**,**c** in good yields (Scheme 1). After completion of the reaction and extractive workup, the mixture was subjected to column chromatography. A similar cross-coupling reaction of pyrazinones **6a** and **6b** with (*E*)-2-phenylethenylboronic acid produced the corresponding 3-(2-phenylethenyl)pyrazinones **7d** and **7e** in 87 and 98% yield, respectively. In the latter two reactions, the coupling succeeded in dimethoxyethane (DME) but not in toluene.

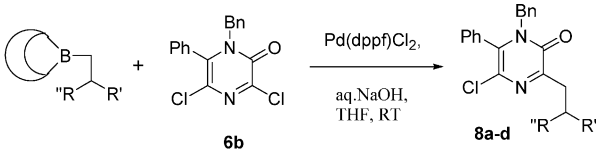


6a,b 7a-e

	R^1	R^3	R^6	Solvent	Yield%
7a	Ph	Ph	CH_3	Toluene	92
7b	Bn		Ph	Toluene	65
7c	Bn		Ph	Toluene	70
7d	Ph		CH_3	DME	87
7e	Bn		Ph	DME	98

Scheme 1. Suzuki-coupling of (hetero)aryl- and 1-alkenylboronic acid at C-3 of 2(1*H*)-pyrazinones **6a**,**b** to form 3-(hetero)aryl- and (*E*)-3-(2-phenylethenyl)-5-chloro-2(1*H*)-pyrazinones **7a–e**.

As a second class of boron containing reagents, alkyl-9-BBN derivatives were submitted to the coupling reaction with pyrazinones (Scheme 2).[19–21] The latter boron derivatives were prepared in situ by adding 9-BBN (solution in THF) to a THF solution of alkenes under argon atmosphere. The mixture was stirred for 6 h at room temperature before the 2(1*H*)-pyrazinone, $Pd(dppf)Cl_2$ and aqueous NaOH were added. The reaction was allowed to proceed at room temperature for 16 h after which complete conversion into 3-substituted products **8a–d** was observed. From the results displayed, it is apparent that primary alkyl-9-BBN reagents having either a single (phenyl, alkyl, trimethylsilyl) or double (cyclohexyl branching) substitution in β-position of the alkyl group attached to boron, all react well with 3,5-dichloro-2(1*H*)-pyrazinone **6b** to give the corresponding products **8a–d** in moderate to good yield. However, no coupling was observed in the reaction of **6b** with the secondary cyclopentyl-9-BBN reagent prepared from cyclopentene.

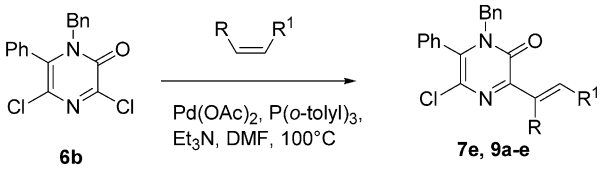


6b 8a-d

	R'	R"	Yield %
8a	H	Ph	60
8b	H	$(CH_2)_3CH_3$	30
8c		$-CH_2(CH_2)_3CH_2-$	80
8d	H	$CH_2Si(CH_3)_3$	40

Scheme 2. Pd-catalysed cross-coupling of alkyl-9-BBN derivatives at the C-3 position of 2(1*H*)-pyrazinone **6b** to form 3-alkyl-5-chloro-2(1*H*)-pyrazinones **8a–d**.

2.1.2. Heck reactions. Applying the Heck reaction to 3,5-dichloro-2(1*H*)-pyrazinones provides a direct method for preparing 3-alkenyl-5-chloro-2(1*H*)-pyrazinones. Thus reaction of pyrazinone **6b** with various alkenes afforded the corresponding 3-alkenyl substituted products **7e** and **9a–e** in good yield. The best conditions consisted of using 3 mol % of $Pd(OAc)_2$, 7 mol % of tri-*o*-tolylphosphine and 2 equiv of triethylamine in DMF at 100 °C. Less satisfactory results or no conversion at all were observed when replacing DMF with acetonitrile (Scheme 3). To avoid evaporation and/or oxidation of volatile vinylic starting materials, the reaction was carried out under argon in a capped heavy-walled glass tube heated in an oil bath. Styrene, methyl acrylate, and acrylonitrile reacted in the expected way to produce **7e**, **9a**, and **9b** in 80, 75, and 70% yield, respectively. A lower yield was observed in the reaction of **6b** with 1-hexene and cyclohexene. The reaction of **6b** with ethyl vinyl ether afforded the enol ether product **9c** that was isolated in 87% yield by flash chromatography. The (*E*)-configuration of the double bond was established by the magnitude of the coupling constant between the two vinylic protons in **7e**, and **9a**,**b**,**d** (16 Hz) and in the enol ether product **9c** (12 Hz).

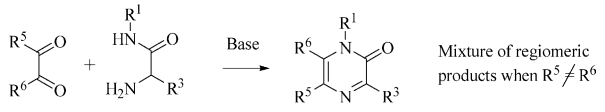


	R	R^1	AcCN Yield%	DMF Yield%
7e	H	Ph	60	80
9a	H	CO_2CH_3	50	75
9b	H	CN	-	70
9c	H	OC_2H_5	-	87
9d	H	C_4H_9	-	53
9e	$-CH_2(CH_2)_2CH_2-$		-	50

Scheme 3. Heck reaction at C-3 position of 2(1*H*)-pyrazinone **6b** to form 3-vinyl-5-chloro-2(1*H*)-pyrazinones **7e** and **9a–e.**

2.2. Functionalisation of the *C*-5 position

2.2.1. Attempts to functionalise the 5-chloro compounds. From previous research in our group, it is known that in contrast to the easy reaction of the 3-imidoyl chloride function, analogous substitution at the vinylic *C*-5-chloro position of 3,5-dichloro-2(1*H*)-pyrazinones via, e.g. Stille reaction is much more difficult. In fact, this has only been achieved by us in an indirect way via isomerisation of 6-alkyl- or 6-benzyl-5-chloro-3-methoxy-2(1*H*)-pyrazinones to form the tautomeric 6-alkylidene/benzylidene-5-chloro-3,6-dihydropyrazin-2(1*H*)-ones having a reactive 5-imidoyl chloride group: subsequent reaction with organotin reagents or amines then produced the corresponding 5-alkyl/aryl or 5-amino-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones, respectively.[22] Alternatively, 2(1*H*)-pyrazinones bearing a 5-alkyl substituent (and their 5-H analogues) can be obtained directly by base-catalyzed condensation of 1,2-dicarbonyl compounds with various α-amino *N*-substituted carboxamide derivatives (Scheme 4).[23] However, this reaction is only interesting in the case that R^5 and R^6 are the same, since otherwise a mixture of regiomeric pyrazinones is formed.



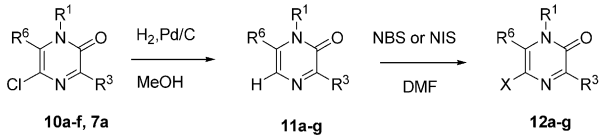
Scheme 4. Synthesis of 5-alkyl and 5-aryl-2(1*H*)-pyrazinones.

Thus exploring the possibilities for substitution at *C*-5 of the pyrazinone system via the methods described above for the *C*-3 position would be of great interest.

Similarly however as with our failure in effecting Stille couplings at the *C*-5 position, we were not successful in substituting the otherwise easily accessible 3-substituted 5-chloropyrazinones by means of a Suzuki-coupling methodology using $Pd(PPh_3)_4$ catalyst and aqueous Na_2CO_3 in either toluene or DME at reflux temperature. Not even a trace of the 5-aryl substituted compounds was formed. Other conditions involving the use of $Pd_2(dba)_3$, combined with P(*t*-Bu)$_3$ and CsF or KF in THF or dioxane, i.e. the conditions used for the synthesis of biaryl compounds starting from an aryl chloride,[24] were also unsuccessful.

A single-case solution to this reactivity issue has been reported by Kaval et al. who achieved a microwave enhanced Suzuki coupling reaction of phenylboronic acid with 1-benzyl-3,5-dichloro-2(1*H*)-pyrazinone to form the corresponding 3,5-diphenyl pyrazinone.[14] We followed a more general approach towards solving the problem by increasing the reactivity of the substrate: indeed, 5-bromo or 5-iodo-2(1*H*)-pyrazinones had to be better candidates as precursors for 5-aryl/alkenyl substituted compounds in this type of coupling reactions.

2.2.2. Synthesis of 5-Br and 5-I pyrazinones. To the best of our knowledge, the synthesis of 3-substituted 5-iodo-2(1*H*)-pyrazinones bearing various substituents at the *N*-1 position has not yet been described. However, 3,6-disubstituted 5-halo-2-pyrazinols have been prepared by halogenation at *C*-5 of the corresponding 2-pyrazinols.[25] Accordingly, we studied the analogous halogenation of 3-methoxy, 3-phenyl and 3-methyl-2(1*H*)-pyrazinones **11a–g** with *N*-bromo and *N*-iodosuccinimide (NBS, NIS) in DMF. The required 5-unsubstituted starting compounds **11a–g** were generated by hydrogenolysis of pyrazinones **10a–f** and **7a** using 10% Pd/C in methanol (Scheme 5).[26–28]



Start. Comp.	Prod.	R^1	R^3	R^6	X	Yield
11a (10a)	**12a**	Bn	OCH_3	CH_3	Br	75
11b (10b)	**12b**	Bn	OCH_3	H	Br	75
11b (10b)	**12b'**	Bn	OCH_3	H	I	75
11c (10c)	**12c**	Bn	OCH_3	Ph	Br	82
11d (10d)	**12d**	Ph	OCH_3	CH_3	Br	73
11d (10d)	**12d'**	Ph	OCH_3	CH_3	I	78
11e (10e)	**12e**	Bn	CH_3	Ph	Br	75
11f (10f)	**12f**	Bn	Ph	H	I	72
11g (7a)	**12g**	Ph	Ph	CH_3	I	66

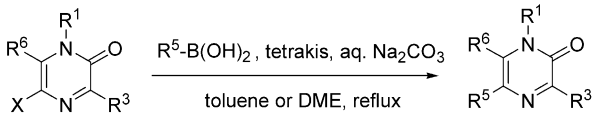
Scheme 5. 5-Bromination and 5-iodination of 2(1*H*)-pyrazinones.

In each of the reactions studied, bromine and iodine were introduced selectively at the *C*-5 position, even when R^6 = H. Halogenation of compounds **11a–d** (3-methoxy), **11e** (3-methyl), and **11f** and **11g** (3-phenyl) provided the corresponding products **12a–d**, **12e** and **12f,g**, respectively. Presumably electrophilic attack at *C*-5 is facilitated by delocalisation of the lone pair on *N*-1. Thus bromination of the 2(1*H*)-pyrazinones by NBS in DMF already proceeded at room temperature in the dark and was completed within 1 h. In contrast, iodination of **11b**, **11d**, **11f** and **11g** by NIS in DMF occurred only at higher temperature to produce the 5-iodo compounds in yields ranging from 66 to 78%. Consistent with a better electron donation of 3-OMe to the pyrazinone ring system, iodination of the 3-OMe compounds already was completed after 8 h at 50 °C whereas

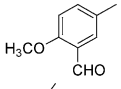
conversion of the less reactive 3-Ph-substituted pyrazinones required heating at 100 °C.

The position of the 5-halo substituent was verified by ^{1}H coupled ^{13}C NMR analysis of **12b′**, **12d**, **12d′** and **12f**, and confirmed by heteronuclear multiple bond correlation (HMBC) spectroscopy (^2J and ^3J) of **12d′**. In the ^{1}H coupled ^{13}C NMR spectrum of 6-H compound **12b′**, the methylene *C*-atom of the *N*-benzyl group appears as a triplet of quartets (tq) with $^1J=284.8$ Hz and $^3J=3.2$ Hz: these *J* values are due to coupling with the two attached protons (^1J) and to coupling with the two *ortho*-protons of the phenyl ring plus the 6-H atom on the 2(1*H*)-pyrazinone ring (^3J). For the carbonyl carbon atom *C*-2 a doublet of triplets (dt) coupling pattern was observed with $^3J=5$ and 3 Hz, which can be related to coupling of *C*-2 with H-6 and the methylene protons of the *N*-benzyl group. The carbon atom *C*-5 attached to the I-atom appears as a doublet (d, $^2J=$ 2.5 Hz) at δ 78.7 ppm, due to coupling with H-6. The *C*-6 atom in turn is detected as a doublet of triplets (dt) with $^1J=$ 189 Hz and $^3J=4.6$ Hz, due to coupling with H-6 and the methylene protons of the *N*-benzyl group.

In the ^{1}H coupled ^{13}C NMR spectrum of the *N*-Ph-6-Me compound **12d′**, *C*-2 is observed as a singlet at δ 151.4 ppm as expected. Owing to coupling with the OMe protons, *C*-3 appears as a multiplet. The quartet pattern with $^3J=7$ Hz observed for *C*-5 reveals coupling with the 6-Me group. Finally, *C*-6 appears as a quartet with $^2J=6$ Hz due to coupling with the protons of the methyl group. In the HMBC spectrum of **12d′**, protons of the 6-methyl group are correlated with *C*-5 and *C*-6 whereas those of the methoxy group are correlated with *C*-3.



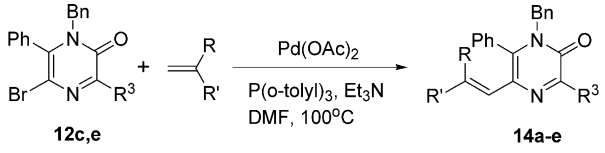
12a,b',d,d',e,f **13a-j**

Start. Comp.	Prod.	R^1	R^3	R^6	R^5	Yield %
12a	**13a**	Bn	OCH_3	CH_3	Ph	92
12a	**13b**	Bn	OCH_3	CH_3		90
12a	**13c**	Bn	OCH_3	CH_3		95
12a	**13d**	Bn	OCH_3	CH_3		80
12b'	**13e**	Bn	OCH_3	H	Ph	78
12d	**13f**	Ph	OCH_3	CH_3	Ph	94
12d'	**13f**	Ph	OCH_3	CH_3	Ph	85
12d	**13g**	Ph	OCH_3	CH_3		55
12d	**13h**	Ph	OCH_3	CH_3		95
12e	**13i**	Bn	CH_3	Ph	Ph	87
12f	**13j**	Bn	Ph	H	Ph	70

Scheme 6. Suzuki-coupling reaction of aryl- and 1-alkenylboronic acid and 5-bromo and 5-iodo-2(1*H*)-pyrazinones.

2.2.3. Functionalisation of the 5-Br and 5-I compounds. Cross-coupling of both 5-bromo- and 5-iodopyrazinones with aryl-, heteroaryl- and 1-alkenylboronic acids in all cases proceeded well to produce the corresponding 5-aryl- and 5-alkenyl-2(1*H*)-pyrazinones. The reactions involving arylboronic acids were carried out using aqueous Na_2CO_3 and $Pd(PPh_3)_4$ and went to completion after heating in toluene or DME at reflux temperature for 18 h. The resulting 5-arylpyrazinones were isolated in excellent yields. Similar cross-coupling of **12a** and **12d** with (*E*)-2-phenylethenylboronic acid in DME afforded compounds **13d** and **13h** in 80 and 95% yield (Scheme 6).

The Heck reaction of 5-bromo-2(1*H*)-pyrazinones **12c**,**e** with alkenes was carried out in a similar way as described above for 3-chloro-2(1*H*)-pyrazinones. Thus treatment of **12c**,**e** with 3 mol % of $Pd(OAc)_2$, 7 mol % of tri-*o*-tolylphosphine and 2 equiv of triethylamine in DMF at 100 °C was found to be most effective for conversion into the 5-substituted alkenyl-2(1*H*)-pyrazinones **14a–e** (Scheme 7).



12c,e **14a-e**

	R	R′	R^3	Yield%
14a	H	Ph	CH_3	71
14b	H	CO_2CH_3	CH_3	84
14c	H	Ph	OCH_3	71
14d	H	CO_2CH_3	OCH_3	66
14e	$-CH_2(CH_2)_3CH_2-$		OCH_3	60

Scheme 7. Heck-coupling of 5-bromopyrazinones with alkenes.

3. Conclusion

The reactive 3-Cl position of 3,5-dichloropyrazinones is easily substituted by means of palladium-catalysed Suzuki and Heck reactions providing easy access to 3-(hetero)aryl, 3-alkenyl and 3-alkyl derived pyrazinone compounds. The 5-Cl atom in these systems is inert towards these cross-coupling conditions and substitution at this position therefore requires prior transhalogenation proceeding via a reduction/bromination (or iodination) sequence. The resulting 5-Br and 5-I compounds smoothly undergo the expected cross-coupling reactions.

4. Experimental

Melting points were taken using an Electrothermal IA 9000 digital melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 Fouriertransform IR spectrometer. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10000. NMR spectra were recorded on a Bruker AMX 300 and 400. They were taken using $CDCl_3$ as

a solvent and the ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS.

The 2(1*H*)-pyrazinones **6a** and **6b** were prepared as described previously.[17,18]

4.1. Synthesis of 3-(hetero)aryl, 3-alkenyl-2(1*H*)-pyrazinones 7a–e via Suzuki-coupling reaction

General procedure. A mixture of pyrazinone **6a** and **6b** (1 mmol) and 28 mg of tetrakis $Pd(PPh_3)_4$ (2.5 mol %) in dry toluene or DME (for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) was stirred under nitrogen for 10 min. Following addition of (hetero)aryl boronic acid (1.5 mmol), the mixture was stirred further for 10 min whereupon 2 M aqueous sodium carbonate (3 mL) was added. The reaction mixture was then heated at reflux for 18 h (1.5 h for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) and cooled to RT. The mixture was distributed between 50 mL of water and CH_2Cl_2 (50 mL) and the aqueous phase further extracted with CH_2Cl_2 two times (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a pale residue, which was subjected to column chromatography (silica gel, 100% CH_2Cl_2).

4.1.1. 5-Chloro-6-methyl-1,3-diphenyl-2(1*H*)-pyrazinone 7a. Yield: 87%; solid, mp: 165 °C; IR (KBr) cm^{-1}: 1665 (s, CO), 1600 (s, C=N); ^{1}H NMR ($CDCl_3$, 300 MHz): 8.50–7.25 (m, 10H, ArH), 2.20 (s, 3H, CH_3); EIMS *m/z* (%): 296 (M^+, 95), 77 ($C_6H_5^+$, 100); HRMS: $C_{17}H_{13}ClN_2O$, calculated: 296.0716, found: 296.0722.

4.1.2. 5-(4-Benzyl-6-chloro-3-oxo-5-phenyl-3,4-dihydro-2-pyrazinyl)-2-methoxy-benzaldehyde 7b. Yield: 65%; solid, mp: 170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 10.48 (s, 1H, CHO), 8.99 (d, $J=2.2$ Hz, 1H, H6′), 8.79 (dd, $J=2.6$, 9.1 Hz, 1H, H4′), 7.49–6.85 (m, 11H, ArH), 5.14 (s, 2H, CH_2Ph), 4.00 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 189.8 (CHO), 163.4 (*C*-OCH_3), 155.3 (C3), 149.5 (C2), 137.7 (C5), 135.8, 131.3, 127.1 (ArC-*ipso*), 137.2, 131.2, 130.5, 129.8, 129.2, 128.9, 128.1, 127.6, 111.7 (ArCH), 128.3 (C6), 124.9 (*C*-CHO), 56.3 (OCH_3), 50.6 (CH_2Ph); EIMS *m/z* (%): 430 (M^+, 77), 91 ($C_7H_7^+$, 100); HRMS: $C_{25}H_{19}ClN_2O_3$, calculated: 430.1084, found: 430.1063.

4.1.3. 1-Benzyl-5-chloro-6-phenyl-3-(3-thienyl)-2(1*H*)-pyrazinone 7c. Yield: 70%; solid, mp: 164.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.94 (dd, $J=1.1$, 2.9 Hz, 1H, H2′), 8.00 (dd, $J=1.1$, 5.1 Hz, 1H, H4′), 7.50–6.83 (m, 11H, ArH), 5.14 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.9 (C2), 147.3 (C3), 137.4 (C6), 136.6, 135.9, 131.5 (ArC-*ipso*), 131.4, 130.4, 129.8, 129.2, 128.9, 128.3, 128.1, 127.4, 125.3 (ArCH), 126.9 (C6), 50.5 (CH_2Ph); EIMS *m/z* (%): 378 (M^+, 91), 91 ($C_7H_7^+$, 100); HRMS: $C_{21}H_{15}ClN_2OS$, calculated: 378.0593, found: 378.0589.

4.1.4. 5-Chloro-6-methyl-1-phenyl-3-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 7d. Yield: 87%; solid, mp: 178.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.15 (d, $J=16$ Hz, 1H, HC=), 7.45 (d, $J=16$ Hz, 1H, HC=), 7.63–7.21 (m, 10H, ArH), 2.14 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.0 (C2), 149.6 (C3), 137.9 (C6), 138.5 (HC=), 136.9, 133.7 (ArC-*ipso*), 130.6, 130.0, 129.5, 129.2, 128.1, 127.5 (ArCH), 126.9 (C5), 122.9 (HC=), 18.7 (CH_3); EIMS *m/z* (%): 322 (M^+, 100), 293 (–CO, 81); HRMS: $C_{19}H_{15}ClN_2O$, calculated: 322.0873, found: 322.0866.

4.1.5. 1-Benzyl-5-chloro-6-phenyl-3-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 7e. Yield: 98%; solid, mp: 182.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.12 (d, $J=16$ Hz, 1H, HC=), 7.66–6.84 (m, 16H, ArH), 5.10 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.7 (C2), 151.0 (C3), 137.8 (C6), 138.8 (HC=), 136.6, 135.8, 130.4 (ArC-*ipso*), 131.5, 129.9, 129.7, 129.23, 129.2, 128.9, 128.3, 128.1, 127.6 (ArCH), 127.5 (C5), 122.2 (HC=), 50.4 (CH_2Ph); EIMS *m/z* (%): 398 (M^+, 100), 307 (–C_7H_7, 79), 91 ($C_7H_7^+$, 90); HRMS: $C_{25}H_{19}ClN_2O$, calculated: 398.1186, found: 398.1179.

4.2. Synthesis of 3-alkyl-2(1*H*)-pyrazinones 8a–d using alkyl-9-BBN reagents

General procedure. A dry flask equipped with magnetic stirring bar, septum inlet, and condenser was flushed with nitrogen. To the flask was added an alkene (1.1 mmol) and 1 mL of dry THF and then 2.2 mL of a solution of 9-BBN (0.5 M solution in THF, 1.1 mmol) at 0 °C. The mixture was warmed up slowly to RT and then stirred for 4–6 h to give a solution of alkyl-9-BBN. To this solution were added 24 mg of $Pd(dppf)Cl_2$ (0.03 mmol, 3 mol %), 330 mg of pyrazinone **6b** (1 mmol), additional 5 mL of THF, 1 mL of aqueous NaOH (3 M solution) at RT. The mixture was stirred at RT for 14–16 h. After the reaction was completed, the reaction mixture was diluted with 50 mL of toluene and water. The mixture was extracted with toluene, washed with brine and dried over $MgSO_4$, followed by purification using column chromatography (silica gel, 50% heptane/CH_2Cl_2 → 20% heptane/CH_2Cl_2).

4.2.1. 1-Benzyl-5-chloro-3-phenethyl-6-phenyl-2(1*H*)-pyrazinone 8a. Yield: 60%; oil; IR (KBr) cm^{-1}: 1651 (s, CO), 1560 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz): 7.49–6.77 (m, 15H, ArH), 5.03 (s, 2H, CH_2Ph), 3.28–3.09 (m, 4H, $2CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.1 (C2), 155.9 (C3), 141.7 (C6), 136.7, 135.8, 130.4 (ArC-*ipso*), 131.3, 129.8, 129.2, 129.0, 128.9, 128.8, 128.1, 127.6, 126.4 (ArCH), 126.5 (C5), 50.2 (CH_2Ph), 35.7, 32.8 (CH_2); EIMS *m/z* (%): 400 (M^+, 33), 309 (–C_7H_7, 100), 91 ($C_7H_7^+$, 100); HRMS: $C_{25}H_{21}ClN_2O$, calculated: 400.1342, found: 400.1339.

4.2.2. 1-Benzyl-5-chloro-3-hexyl-6-phenyl-2(1*H*)-pyrazinone 8b. Yield: 30%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.45–6.83 (m, 10H, ArH), 5.10 (s, 2H, CH_2Ph), 2.90 (d, $J=$ 7.3 Hz, 2H, CH_2), 1.62–0.85 (m, 11H, $4CH_2+CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.9 (C2), 156.9 (C3), 136.3 (C6), 136.2, 130.5 (ArC-*ipso*), 130.4, 130.0, 129.5, 129.3, 128.7, 128.1 (ArCH), 126.9 (C5), 50.4 (CH_2Ph), 33.1, 29.5, 29.2, 28.5, 22.7 (CH_2), 14.0 (CH_3); EIMS *m/z* (%): 380 (M^+, 6), 287 (–C_7H_7, 15), 91 ($C_7H_7^+$, 100).

4.2.3. 1-Benzyl-5-chloro-3-cyclohexylmethyl-6-phenyl-2(1*H*)-pyrazinone 8c. Yield: 80%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.48–6.78 (m, 10H, ArH), 5.03 (s, 2H, CH_2Ph), 2.80 (d, $J=7.3$ Hz, 2H, CH_2), 2.05–1.05 (m, 11H, CH+

5CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.7 (C2), 156.1 (C3), 136.3 (C6), 136.0, 131.4 (ArC-*ipso*), 130.3, 129.8, 129.2, 128.8, 128.0, 127.6 (ArCH), 126.2 (C5), 50.1 (CH_2Ph), 41.5 (CH_2), 36.7 (CH), 33.7, 26.8, 26.6 (CH_2); EIMS *m/z* (%): 392 (M^+, 8), 310 (–C_6H_{10}, 37), 301 (–C_7H_7, 100), 91 ($C_7H_7^+$, 65); HRMS: $C_{24}H_{25}ClN_2O$, calculated: 392.1655, found: 392.1653.

4.2.4. 1-Benzyl-5-chloro-6-phenyl-3-[3-(trimethylsilyl)-propyl]-2(1*H*)-pyrazinone 8d. Yield: 40%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.45–6.77 (m, 10H, ArH), 5.02 (s, 2H, CH_2Ph), 2.91 (d, J=7.6 Hz, 2H, CH_2), 1.83–1.72 (m, 2H, CH_2), 0.66–0.60 (m, 2H, CH_2), 0.01 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 161.5 (C2), 157.2 (C3), 137.6 (C6), 137.2, 132.6 (ArC-*ipso*), 131.6, 131.1, 130.4, 130.1, 129.3, 128.9 (ArCH), 127.6 (C5), 51.3 (CH_2Ph), 39.2, 23.2, 18.5 (CH_2), 0.01 (Si(CH_3)$_3$); EIMS *m/z* (%): 410 (M^+, 8), 319 (–C_7H_7, 100), 91 ($C_7H_7^+$, 88); HRMS: $C_{23}H_{27}ClN_2OSi$, calculated: 410.1581, found: 410.1568.

4.3. Synthesis of 3-alkenyl-2(1*H*)-pyrazinones via Heck-coupling reaction

General procedure. A mixture of 330 mg of pyrazinone **6b** (1 mmol), 7 mg of $Pd(OAc)_2$ (3 mol %) and 26 mg of P(*o*-tolyl)$_3$ (7 mol %) was stirred at room temperature under argon for 10 min. Add 1.5 mmol of alkene, 300 mg of dry Et_3N (3 mmol) and 1 mL DMF. The reaction mixture was heated at 100 °C in a capped heavy-walled glass tube in an oil bath for 18 h. After the completion of the reaction, the mixture was poured in water and extracted with 50 mL of CH_2Cl_2 three times. The organic layer was collected and dried over $MgSO_4$. After filtration and evaporation of CH_2Cl_2, the mixture was subjected to column chromatography (silica gel, A: 30% heptane/CH_2Cl_2 or B: 100% CH_2Cl_2→5% EtOAc/CH_2Cl_2).

Compound **7e** was isolated in 80% yield (solvent system A) using the present method.

4.3.1. Methyl (2*E*)-3-(4-benzyl-6-chloro-3-oxo-5-phenyl-3,4-dihydro-2-pyrazinyl)-2-propenoate 9a. Yield: 75%; solvent system B; solid, mp: 93.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.93 (d, J=16 Hz, 1H, HC=), 7.34 (d, J=16 Hz, 1H, HC=), 7.50–6.81 (m, 10H, ArH), 5.10 (s, 2H, CH_2Ph), 3.81 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.7 (COO), 155.0 (C3), 147.8 (C2), 139.7 (C5), 137.4 (HC=), 135.0, 130.6 (ArC-*ipso*), 130.3, 129.0, 128.9, 128.5, 127.9, 127.2 (ArCH), 127.3 (C6), 126.6 (HC=), 51.9 (OCH_3), 50.2 (CH_2Ph); EIMS *m/z* (%): 380 (M^+, 25), 321 (–$COOCH_3$, 13), 91 ($C_7H_7^+$, 100); HRMS: $C_{21}H_{17}ClN_2O_3$, calculated: 380.0928, found: 380.0927.

4.3.2. (2*E*)-3-(4-benzyl-6-chloro-3-oxo-5-phenyl-3,4-dihydro-2-pyrazinyl)-2-propenenitrile 9b. Yield: 70%; solvent system B; solid, mp: 117.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.63 (d, J=16 Hz, 1H, HC=), 7.02 (d, J=16 Hz, 1H, HC=), 7.55–6.80 (m, 10H, ArH), 5.11 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.1 (C3), 146.1 (C2), 141.4 (C5), 143.9 (HC=), 135.0, 131.0 (ArC-*ipso*), 130.6, 129.4, 129.3, 129.0, 128.5, 127.6 (ArCH), 127.9 (C6), 118.1 (CN), 105.8 (HC=), 50.8 (CH_2Ph); EIMS *m/z* (%): 347 (M^+, 44), 91 ($C_7H_7^+$, 100); HRMS: $C_{20}H_{14}ClN_3O$, calculated: 347.0825, found: 347.0822.

4.3.3. 1-Benzyl-5-chloro-3-[(*E*)-2-ethoxyethenyl]-6-phenyl-2(1*H*)-pyrazinone 9c. Yield: 87%; solvent system B; oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.24 (d, J=12 Hz, 1H, HC=), 7.46–6.80 (m, 10H, ArH), 6.27 (d, J=12 Hz, 1H, HC=), 5.04 (s, 2H, CH_2Ph), 4.03 (q, J=6.9 Hz, 2H, CH_2), 1.36 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.2 (HC=), 155.0 (C2), 152.2 (C3), 136.0 (C6), 133.4, 131.7 (ArC-*ipso*), 130.2, 130.1, 129.1, 128.8, 127.9, 127.4 (ArCH), 127.2 (C5), 102.9 (HC=), 67.1 (CH_2CH_3), 50.2 (CH_2Ph), 15.1 (CH_2CH_3); EIMS *m/z* (%): 366 (M^+, 40), 338 (–C_2H_2, 50), 91 ($C_7H_7^+$, 100).

4.3.4. 1-Benzyl-5-chloro-3-(1-hexenyl)-6-phenyl-2(1*H*)-pyrazinone 9d. Yield: 53%; solvent system A; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.47–6.81 (m, 12H, ArH), 5.05 (s, 2H, CH_2Ph), 1.56–0.90 (m, 9H, $3CH_2+CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.4 (C2), 151.2 (C3), 144.1 (HC=), 136.1 (C6), 135.9, 130.3 (ArC-*ipso*), 131.5, 129.9, 129.1, 128.8, 128.0, 127.6 (ArCH), 127.3 (C5), 124.5 (HC=), 50.3 (CH_2Ph), 33.6, 31.2, 22.7 (CH_2), 14.3 (CH_3); EIMS *m/z* (%): 378 (M^+, 3), 287 (–C_7H_7, 10), 91 ($C_7H_7^+$, 100); HRMS: $C_{23}H_{23}ClN_2O$, calculated: 378.1499, found: 378.1486.

4.3.5. 1-Benzyl-5-chloro-3-(1-cyclohexenyl)-6-phenyl-2(1*H*)-pyrazinone 9e. Yield: 50%; solvent system B; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.86 (t, J=3.1 Hz, 1H, HC=), 7.44–6.81 (m, 10H, ArH), 5.06 (s, 2H, CH_2Ph), 2.57–2.54 (m, 2H, CH_2), 2.37–2.34 (m, 2H, CH_2), 1.78–1.75 (m, 2H, CH_2), 1.70–1.65 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.8 (C2), 151.6 (C3), 138.3 (HC=), 135.2 (C6), 135.8, 131.3 (ArC-*ipso*), 134.6 (*C*=CH), 129.8, 129.4, 128.7, 128.4, 127.5, 127.0 (ArCH), 126.1 (C5), 49.9 (CH_2Ph), 26.6, 25.8, 22.6, 21.7 (CH_2); EIMS *m/z* (%): 376 (M^+, 5), 91 ($C_7H_7^+$, 100); HRMS: $C_{23}H_{21}ClN_2O$, calculated: 376.1342, found: 376.1338.

4.4. Synthesis of 2(1*H*)-pyrazinones 10a–f

The 3-methoxy-2(1*H*)-pyrazinones **10a–d** were prepared as described previously[22,26] The 3-methyl- and 3-phenyl-2(1*H*)-pyrazinones **10e–f** were prepared via Pd-catalysed reaction according to procedures described previously.[17,27]

4.5. Dechlorination of *C*-5 position of 2(1*H*)-pyrazinones 10a–f and 7a

General procedure. A mixture of 2(1*H*)-pyrazinone **10a–f** or **7a** (2 mmol) in 10 mL of MeOH and 280 mg (2 mmol) of K_2CO_3 was hydrogenated for 0.5–8 h in the presence of catalyst (10% Pd/C; 50 mg) under H_2 at atmospheric pressure. After removal of the catalyst by filtration, the filtrate was evaporated and the residue was dissolved in dichloromethane. The solution was washed twice with 20 mL of water, dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel, 10% EtOAc/CH_2Cl_2—100%CH_2Cl_2) to give the corresponding dechlorinated compounds **11a–g**. Compounds **11a**,**d**,**e**,**g** have been described previously.[26–28]

4.5.1. 1-Benzyl-3-methoxy-2(1*H*)-pyrazinone 11b. Yield: 92%; solid, mp: 78.5–79.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.34–7.28 (m, 5H, ArH), 6.78 (d, J=4.6 Hz, 1H, H5/H6), 6.73 (d, J=4.6 Hz, 1H, H6/H5), 5.1 (s, 2H, CH_2Ph), 3.96 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 157.2 (C3), 151.9 (C2), 135.6 (ArC-*ipso*), 129.3, 128.8, 128.7 (ArCH), 122.0 (C6), 119.7 (C5), 54.9 (OCH_3), 51.8 (CH_2Ph); EIMS *m/z* (%): 216 (M^+, 70), 91 ($C_7H_7^+$, 100); HRMS: $C_{12}H_{12}N_2O_2$, calculated: 216.0899, found: 216.0896.

4.5.2. 1-Benzyl-3-methoxy-6-phenyl-2(1*H*)-pyrazinone 11c. Yield: 30%; solid, mp: 116.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.42–6.85 (m, 10H, ArH), 6.73 (s, 1H, H5), 5.14 (s, 2H, CH_2Ph), 4.02 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.2 (C3), 152.3 (C2), 136.4 (C6), 135.2, 132.3 (ArC-*ipso*), 130.2, 129.7, 128.8, 128.7, 127.86, 127.82 (ArCH), 119.9 (C5), 54.8 (OCH_3), 48.8 (CH_2Ph); EIMS *m/z* (%): 292 (M^+, 90), 91 ($C_7H_7^+$, 100); HRMS: $C_{18}H_{16}N_2O_2$, calculated: 292.1212, found: 292.1203.

4.5.3. 1-Benzyl-3-phenyl-2(1*H*)-pyrazinone 11f. Yield: 84%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.32–8.28 (m, 2H, ArH), 7.44–7.37 (m, 9H, ArH), 7.08 (d, J=4.3 Hz, 1H, H5/H6), 5.17 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.9 (C2), 154.2 (C3), 136.3, 135.3 (ArC-*ipso*), 130.4, 129.5, 129.4, 128.97, 128.95, 128.4 (ArCH), 127.8 (C6), 123.8 (C5), 52.8 (CH_2Ph); EIMS *m/z* (%): 262 (M^+, 80), 91 ($C_7H_7^+$, 100); HRMS: $C_{17}H_{14}N_2O$, calculated: 262.1106, found: 262.1103.

4.6. Synthesis of 5-bromo and 5-iodo-2(1*H*)-pyrazinones 12a–g

General procedure. To a solution of pyrazinone **11a–g** (2 mmol) in DMF (2 mL) was added NBS or NIS (2.2 mmol). The reaction mixture was stirred in the dark under nitrogen atmosphere at RT for 1–2 h (NBS) or at 50–100 °C for 8–12 h (NIS). The mixture was poured into 50 mL of ice-water and extracted three times with CH_2Cl_2. After the usual work up, the residue was purified by column chromatography (silica gel, 100% CH_2Cl_2→5%EtOAc/CH_2Cl_2).

4.6.1. 1-Benzyl-5-bromo-3-methoxy-6-methyl-2(1*H*)-pyrazinone 12a. Yield: 90%; solid, mp: 85.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.35–7.15 (m, 5H, ArH), 5.34 (s, 2H, CH_2Ph), 4.01 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.5 (C3), 152.0 (C2), 135.3 (ArC-*ipso*), 129.2 (C6), 129.3, 128.3, 127.1 (ArCH), 112.1 (C5), 55.4 (OCH_3), 49.2 (CH_2Ph), 18.6 (CH_3); EIMS *m/z* (%): 308 (M^+, 100), 229 (–Br, 57); HRMS: $C_{13}H_{13}BrN_2O_2$, calculated: 308.0160, found: 308.0149.

4.6.2. 1-Benzyl-5-bromo-3-methoxy-2(1*H*)-pyrazinone 12b. Yield: 75%; solid, mp: 75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.37–7.23 (m, 5H, ArH), 7.04 (s, 1H, H6), 5.04 (s, 2H, CH_2Ph), 3.92 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.2 (C3), 151.0 (C2), 135.0 (ArC-*ipso*), 129.2, 128.4, 128.1 (ArCH), 125.3 (C6), 115.2 (C5), 55.3 (OCH_3), 51.5 (CH_2Ph); EIMS *m/z* (%): 294 (M^+, 60), 215 (–Br, 20), 91 ($C_7H_7^+$, 100); HRMS: $C_{12}H_{11}BrN_2O_2$, calculated: 294.0004, found: 294.0001.

4.6.3. 1-Benzyl-5-iodo-3-methoxy-2(1*H*)-pyrazinone 12b′. Yield: 75%; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.36–7.29 (m, 5H, ArH), 7.01 (s, 1H, H6), 5.02 (s, 2H, CH_2Ph), 3.95 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.5 (C3), 151.4 (C2), 134.7 (ArC-*ipso*), 129.0, 128.6, 128.4 (ArCH), 127.2 (C6), 78.6 (C5), 55.2 (OCH_3), 51.5 (CH_2Ph); EIMS *m/z* (%): 341 (M^+, 40), 215 (–I, 8), 91 ($C_7H_7^+$, 100); HRMS: $C_{12}H_{11}IN_2O_2$, calculated: 341.9865, found: 341.9860.

4.6.4. 1-Benzyl-5-bromo-3-methoxy-6-phenyl-2(1*H*)-pyrazinone 12c. Yield: 82%; solid, mp: 138.4–139.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.45–6.77 (m, 10H, ArH), 5.04 (s, 2H, CH_2Ph), 4.06 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.8 (C3), 151.6 (C2), 133.0 (C6), 135.9, 132.9 (ArC-*ipso*), 130.5, 130.1, 129.0, 128.7, 128.0, 127.8 (ArCH), 112.7 (C5), 55.6 (OCH_3), 50.3 (CH_2Ph); EIMS *m/z* (%): 370 (M^+, 40), 91 ($C_7H_7^+$, 100); HRMS: $C_{18}H_{15}BrN_2O_2$, calculated: 370.0317, found: 370.0300.

4.6.5. 5-Bromo-3-methoxy-6-methyl-1-phenyl-2(1*H*)-pyrazinone 12d. Yield: 73%; solid, mp: 141.1–141.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.57–7.15 (m, 5H, ArH), 4.00 (s, 3H, OCH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.2 (C3), 151.3 (C2), 135.9 (ArC-*ipso*), 129.8 (C6), 130.5, 129.8, 127.8 (ArCH), 115.6 (C5), 55.6 (OCH_3), 22.8 (CH_3); EIMS *m/z* (%): 294 (M^+, 100), 264 (–CO, 31), 77 ($C_6H_5^+$, 79); HRMS: $C_{12}H_{11}BrN_2O_2$, calculated: 294.0003, found: 293.9982.

4.6.6. 5-Iodo-3-methoxy-6-methyl-1-phenyl-2(1*H*)-pyrazinone 12d′. Yield: 78%; solid, mp: 128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.53–7.13 (m, 5H, ArH), 3.97 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.3 (C3), 151.4 (C2), 138.0 (ArC-*ipso*),131.9 (C6), 130.0, 129.5, 127.3 (ArCH), 83.3 (C5), 54.9 (OCH_3), 23.2 (CH_3); EIMS *m/z* (%): 341 (M^+, 100), 312 (–CO, 12); HRMS: $C_{12}H_{11}IN_2O_2$, calculated: 341.9865, found: 341.9861.

4.6.7. 1-Benzyl-5-bromo-3-methyl-6-phenyl-2(1*H*)-pyrazinone 12e. Yield: 75%; solid, mp: 136.2–136.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.49–6.79 (m, 10H, ArH), 5.03 (s, 2H, CH_2Ph), 2.57 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 157.6 (C2), 156.3 (C3), 138.6 (C6), 135.8, 132.7 (ArC-*ipso*), 130.4, 129.8, 129.2, 128.8, 128.1, 127.7 (ArCH), 115.9 (C5), 50.5 (CH_2Ph), 21.4 (CH_3); EIMS *m/z* (%): 354 (M^+, 60), 275 (–Br, 6), 91 ($C_7H_7^+$, 100); HRMS: $C_{18}H_{15}BrN_2O$, calculated: 354.0368, found: 354.0362.

4.6.8. 1-Benzyl-5-iodo-3-phenyl-2(1*H*)-pyrazinone 12f. Yield: 72%; solid, mp: 140.3–141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.34–8.31 (m, 2H, ArH), 7.42–7.33 (m, 8H, ArH), 5.09 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.4 (C2), 154.1 (C3), 134.9, 134.5 (ArC-*ipso*), 133.2 (C6), 130.5, 129.2, 129.1, 128.7, 128.6, 128.0 (ArCH), 83.2 (C5), 52.4 (CH_2Ph); EIMS *m/z* (%): 388 (M^+, 30), 91 ($C_7H_7^+$, 100); HRMS: $C_{17}H_{13}IN_2O$, calculated: 388.0073, found: 388.0069.

4.6.9. 5-Iodo-1,3-diphenyl-6-methyl-2(1*H*)-pyrazinone 12g. Yield: 66%; solid, mp: 184.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.38–8.34 (m, 2H, ArH), 7.60–7.18 (m, 8H, ArH), 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.8

(C2), 150.9 (C3), 139.5 (C6), 138.7, 135.3 (ArC-*ipso*), 130.6, 130.5, 129.9, 129.3, 128.4, 127.4 (ArCH), 89.7 (C5), 24.6 (CH_3); EIMS *m/z* (%): 388 (M^+, 100), 360 (–CO, 36), 77 ($C_6H_5^+$, 50); HRMS: $C_{17}H_{13}IN_2O$, calculated: 388.0073, found: 388.0051.

4.7. Synthesis of 5-(hetero)aryl and 5-alkenyl-2(1*H*)-pyrazinones 13a–j by Suzuki coupling of 5-bromo or 5-iodo-2(1*H*)-pyrazinones

General procedure. A mixture of pyrazinone **12a**,**b′**,**d**, **d′**, **e** and **f** (1 mmol) and 28 mg of tetrakis $Pd(PPh_3)_4$ (2.5 mol %) in dry toluene or DME (for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) was stirred under nitrogen for 10 min. Following addition of (hetero)aryl boronic acid (1.5 mmol), the mixture was stirred further for 10 min whereupon 2 M aqueous sodium carbonate (3 mL) was added. The reaction mixture was then heated at reflux for 18 h (1.5 h for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) and cooled to RT. The mixture was distributed between 50 mL of water and CH_2Cl_2 (50 mL) and the aqueous phase further extracted with CH_2Cl_2 two times (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a pale residue, which was subjected to column chromatography (silica gel, 100% CH_2Cl_2).

4.7.1. 1-Benzyl-3-methoxy-6-methyl-5-phenyl-2(1*H*)-pyrazinone 13a. Yield: 92%; solid, mp: 115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.44–7.20 (m, 10H, ArH), 5.39 (s, 2H, CH_2Ph), 4.00 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.8 (C3), 152.2 (C2), 138.8, 136.0 (ArC-*ipso*), 129.4 (C6/C5), 127.8 (C5/C6), 129.9, 129.2, 128.5, 128.0, 127.9, 127.1 (ArCH), 54.7 (OCH_3), 48.3 (CH_2Ph), 16.9 (CH_3); EIMS *m/z* (%): 306 (M^+, 100), 215 (–C_7H_7, 65), 91 ($C_7H_7^+$, 90); HRMS: $C_{19}H_{18}N_2O$, calculated: 306.1368, found: 306.1366.

4.7.2. 5-(4-Benzyl-6-methoxy-3-methyl-5-oxo-4,5-dihydro-2-pyrazinyl)-2-methoxy-benzaldehyde 13b. Yield: 90%; solid, mp: 68 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 10.48 (s, 1H, CHO), 7.85 (d, J=2.5 Hz, 1H, H6′), 7.67 (dd, J=2.6,8.8 Hz, 1H, H4′), 7.33–7.19 (m, 5H, ArH), 7.05 (d, J=8.8 Hz, 1H, H3′), 5.39 (s, 2H, CH_2Ph), 3.99 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 189.9 (CHO), 161.6 (*C*–OCH_3), 153.9 (C6), 152.1 (C5), 135.8, 131.4 (ArC-*ipso*), 137.4, 129.5, 129.3, 128.1, 127.1, 112.1 (ArCH), 128.1 (C2/C3), 127.8 (C3/C2), 124.9 (*C*–CHO), 56.2 (ArO*C*H_3), 54.7 (OCH_3), 48.3 (CH_2Ph), 16.9 (CH_3); EIMS *m/z* (%): 364 (M^+, 100), 273 (–C_7H_7, 37), 41 (–C_7H_7 + (–CO), 37), 91 ($C_7H_7^+$, 79); HRMS: $C_{21}H_{20}N_2O_4$, calculated: 364.1423, found: 364.1420.

4.7.3. 1-Benzyl-3-methoxy-6-methyl-5-(3-thienyl)-2(1*H*)-pyrazinone 13c. Yield: 95%; solid, mp: 112–112.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.34–7.18 (m, 8H, ArH), 5.38 (s, 2H, CH_2Ph), 4.00 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.6 (C3), 152.1 (C2), 139.7, 135.9 (ArC-*ipso*), 127.7 (C5/C6), 125.1 (C6/C5), 129.3, 129.1, 128.0, 127.1, 125.5, 124.2 (ArCH), 54.6 (OCH_3), 48.3 (CH_2Ph), 16.8 (CH_3); EIMS *m/z* (%): 312 (M^+, 100), 221 (–C_7H_7, 60), 91 ($C_7H_7^+$, 95); HRMS: $C_{17}H_{16}N_2O_2S$, calculated: 312.0933, found: 312.0930.

4.7.4. 1-Benzyl-3-methoxy-6-methyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 13d. Yield: 80%; solid, mp: 194.4–195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.48–7.14 (m, 11H, ArH), 7.01 (d, J=15 Hz, 1H, HC=), 5.34 (s, 2H, CH_2Ph), 4.09 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.0 (C3), 151.8 (C2), 137.4, 135.4 (ArC-*ipso*), 129.8 (HC=), 128.8, 128.5, 127.6, 127.4, 126.5, 126.4 (ArCH), 127.2 (C5/C6), 125.4 (C6/C5), 122.2 (HC=), 54.8 (OCH_3), 50.4 (CH_2Ph), 14.2 (CH_3); EIMS *m/z* (%): 332 (M^+, 28), 241 (–C_7H_7, 16), 91 ($C_7H_7^+$, 100); HRMS: $C_{21}H_{20}N_2O_2$, calculated: 332.1525, found: 332.1522.

4.7.5. 1-Benzyl-3-methoxy-5-phenyl-2(1*H*)-pyrazinone 13e. Yield: 78%, oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.05–7.32 (m, 11H, ArH), 5.05 (s, 2H, CH_2Ph); EIMS *m/z* (%): 292 (M^+, 100), 91 ($C_7H_7^+$, 60).

4.7.6. 3-Methoxy-6-methyl-1,5-diphenyl-2(1*H*)-pyrazinone 13f. Yield: 94%; solid, mp: 160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.58–7.24 (m, 10H, ArH), 4.02 (s, 2H, CH_2Ph), 1.93 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.3 (C3), 151.9 (C2), 138.7, 138.1 (ArC-*ipso*), 128.8 (C6/C5), 127.9 (C5/C6), 130.3, 129.8, 129.6, 128.5, 128.1, 127.6 (ArCH), 54.7 (OCH_3), 18.5 (CH_3); EIMS *m/z* (%): 306 (M^+, 100), 215 (–C_7H_7, 65), 91 ($C_7H_7^+$, 90); HRMS: $C_{19}H_{18}N_2O$, calculated: 306.1368, found: 306.1366.

The same compound **13f** was isolated in 85% yield when applying Suzuki coupling of 5-iodo compound **12d′** with phenylboronic acid.

4.7.7. 3-Methoxy-6-methyl-1-phenyl-5-(3-thienyl)-2(1*H*)-pyrazinone 13g. Yield: 55%; solid, mp: 165.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.57–7.21 (m, 8H, ArH), 4.02 (s, 3H, OCH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.1 (C3), 151.8 (C2), 139.7, 138.0 (ArC-*ipso*), 127.5 (C5/C6), 124.6 (C6/C5), 130.3, 129.6, 129.0, 128.0, 125.5, 124.0 (ArCH), 54.6 (OCH_3), 18.4 (CH_3); EIMS *m/z* (%): 298 (M^+, 100); HRMS: $C_{16}H_{14}N_2O_2S$, calculated: 298.0776, found: 298.0770.

4.7.8. 3-Methoxy-6-methyl-1-phenyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 13h. Yield: 95%; solid, mp: 186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.58–7.17 (m, 11H, ArH), 7.05 (d, J=15 Hz, 1H, HC=), 4.11 (s, 3H, OCH_3), 2.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.9 (C3), 152.0 (C2), 137.9 2x(ArC-*ipso*), 129.7 (HC=), 130.4, 130.1, 129.1, 128.0, 127.9, 127.9 (ArCH), 127.6 (C5/C6), 125.4 (C5/C6), 122.7 (HC=), 54.6 (OCH_3), 16.1 (CH_3); EIMS *m/z* (%): 318 (M^+, 100); HRMS: $C_{20}H_{18}N_2O_2$, calculated: 318.1368, found: 318.1368.

4.7.9. 1-Benzyl-3-methyl-5,6-diphenyl-2(1*H*)-pyrazinone 13i. Yield: 87%; solid, mp: 123.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.34–6.87 (m, 15H, ArH), 5.13 (s, 2H, CH_2Ph), 2.64 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.6 (C2), 156.2 (C3), 138.2 (C6), 136.8, 136.6, 132.4 (ArC-*ipso*), 133.1 (C5), 131.1, 129.7, 129.6, 128.8, 128.8, 128.1, 127.8,

127.6, 127.3 (ArCH), 49.3 (CH_2Ph), 21.7 (CH_3); EIMS *m/z* (%): 352 (M^+, 100), 91 ($C_7H_7^+$, 64); HRMS: $C_{24}H_{20}N_2O$, calculated: 352.1576, found: 352.1573.

4.7.10. 1-Benzyl-3,5-diphenyl-2(1*H*)-pyrazinone 13j. Yield: 70%, oil; ^1H NMR ($CDCl_3$, 300 MHz): 8.49–8.46 (m, 2H, ArH), 7.79–7.29 (m, 14H, ArH), 5.17 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.1 (C2), 152.3 (C3), 136.6, 136.3, 135.6 (ArC-*ipso*), 133.2 (C5), 130.4 (C6), 129.7, 129.5, 129.2, 128.9, 128.8, 128.4, 128.3, 125.4, 124.0 (ArCH), 53.3 (CH_2Ph); EIMS *m/z* (%): 338 (M^+, 100), 91 ($C_7H_7^+$, 40).

4.8. Synthesis of 5-alkenyl-2(1*H*)-pyrazinones 14a–e via Heck-coupling reaction of 5-bromo-2(1*H*)-pyrazinones

General procedure. A mixture of pyrazinone **12c** or **12e** (1 mmol), 7 mg of $Pd(OAc)_2$ (3 mol %) and 26 mg of P(*o*-tolyl)$_3$ (7 mol %) was stirred at room temperature under argon for 10 min. Add 1.5 mmol of alkene, 300 mg of dry Et_3N (3 mmol) and 1 mL DMF. The reaction mixture was heated at 100 °C in a capped heavy-walled glass tube in an oil bath for 18 h. After the completion of the reaction, the mixture was poured in water and extracted with 50 mL of CH_2Cl_2 three times. The organic layer was collected and dried over $MgSO_4$. After filtration and evaporation of CH_2Cl_2, the mixture was subjected to column chromatography (silica gel, A: 30% heptane/CH_2Cl_2 or B: 100% $CH_2Cl_2 \rightarrow$ 5% EtOAc/CH_2Cl_2).

4.8.1. 1-Benzyl-3-methyl-6-phenyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 14a. Yield: 71%; oil; ^1H NMR ($CDCl_3$, 300 MHz): 7.50–6.81 (m, 16H, ArH), 6.35 (d, J= 16 Hz, 1H, HC=), 5.03 (s, 2H, CH_2Ph), 2.65 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 157.0 (C2), 156.3 (C3), 137.7, 136.4, 131.4 (ArC-*ipso*), 130.1 (C6), 129.6 (HC=), 130.6, 129.6, 129.1, 128.9, 128.8, 127.9, 12.8, 127.5, 126.9 (ArCH), 127.8 (C5), 123.6 (HC=), 49.3(CH_2Ph), 21.9 (CH_3); EIMS *m/z* (%): 378 (M^+, 100), 287 (–C_7H_7, 38), 91 ($C_7H_7^+$, 50); HRMS: $C_{26}H_{22}N_2O$, calculated: 378.1732, found: 378.1729.

4.8.2. Methyl (2*E*)-3-(4-benzyl-6-methyl-5-oxo-3-phenyl-4,5-dihydro-2-pyrazinyl)-2-propenoate 14b. Yield: 84%; solid, mp: 141.5–142.2 °C; ^1H NMR ($CDCl_3$, 300 MHz): 6.96 (d, J=15 Hz, 1H, HC=), 7.51–7.02 (m, 8H, ArH), 6.81–6.78 (m, 2H, ArH), 6.76 (d, J=15 Hz, 1H, HC=), 5.00 (s, 2H, CH_2Ph), 3.66 (s, 3H, OCH_3), 2.59 (CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 168.0 (*C*OO), 157.3 (C5), 156.4 (C6), 140.7 (C3), 139.7, 136.0 (ArC-*ipso*), 130.5 (HC=), 130.3, 130.2, 129.3, 128.8, 128.0, 127.5 (ArCH), 127.6 (C2), 118.6 (HC=), 51.8 (COO*C*H$_3$), 49.4 (CH_2Ph), 21.7 (CH_3); EIMS *m/z* (%): 360 (M^+, 65), 301 (–$COOCH_3$, 16), 91 ($C_7H_7^+$, 100); HRMS: $C_{22}H_{20}N_2O_3$, calculated: 360.1474, found: 360.1464.

4.8.3. 1-Benzyl-3-methoxy-6-phenyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 14c. Yield: 71%; solid, mp: 148 °C; ^1H NMR ($CDCl_3$, 300 MHz): 7.46–6.80 (m, 16H, ArH), 6.34 (d, J=15 Hz, 1H, HC=), 5.05 (s, 2H, CH_2Ph), 4.16 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.9 (C3), 151.9 (C2), 137.6, 136.3, 131.6 (ArC-*ipso*), 132.0 (C6), 129.6 (HC=), 131.2, 129.9, 129.0, 128.9, 128.7, 127.8, 127.7, 127.6, 126.9 (ArCH), 127.0 (C5), 123.7 (HC=), 54.8 (OCH_3), 49.3 (CH_2Ph); EIMS *m/z* (%): 394 (M^+, 100), 303 (–C_7H_7, 36), 91 ($C_7H_7^+$, 80); HRMS: $C_{26}H_{22}N_2O_2$, calculated: 394.1681, found: 394.1674.

4.8.4. Methyl (2*E*)-3-(4-benzyl-6-methoxy-5-oxo-3-phenyl-4,5-dihydro-2-pyrazinyl)-2-propenoate 14d. Yield: 66%; solid, mp: 173.7 °C; ^1H NMR ($CDCl_3$, 300 MHz): 6.94 (d, J=15 Hz, 1H, HC=), 7.50–7.02 (m, 8H, ArH), 6.80–6.77 (m, 2H, ArH), 6.66 (d, J=15 Hz, 1H, HC=), 5.03 (s, 2H, CH_2Ph), 4.09 (s, 3H, OCH_3), 3.67 (s, 3H, COO*C*H$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 167.9 (*C*OO), 154.8 (C6), 152.1 (C5), 136.6 (C3), 139.8, 135.9 (ArC-*ipso*), 130.4 (HC=), 130.8, 130.5, 129.1, 128.7, 128.0, 127.7 (ArCH), 124.9 (C2), 118.5 (HC=), 55.0 (OCH_3), 51.8 (COO*C*H$_3$), 49.4 (CH_2Ph); EIMS *m/z* (%): 376 (M^+, 61), 317 (–$COOCH_3$, 11), 91 ($C_7H_7^+$, 100); HRMS: $C_{22}H_{20}N_2O_4$, calculated: 376.1423, found: 376.1422.

4.8.5. 1-Benzyl-5-cyclohexylidenemethyl-3-methoxy-6-phenyl-2(1*H*)-pyrazinone 14e. Yield: 60%; oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.38–6.79 (m, 10H, ArH), 5.33 (s, 1H, *H*C=), 5.03 (s, 2H, CH_2Ph), 2.74 (t, J=6.1 Hz, 2H, CH_2), 1.94 (t, J=6.1 Hz, 2H, CH_2), 1.58–1.47 (m, 6H, $3CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.8 (C2), 150.8 (C3), 145.5 (*C*=CH), 136.1, 131.2 (ArC-*ipso*), 131.5 (C6), 130.6, 129.0, 128.4, 128.1, 127.3, 127.2 (ArCH), 127.6 (C5), 116.4 (*C*H=), 54.3 (OCH_3), 48.7 (CH_2Ph), 38.4 (C2′), 29.9 (C6′), 28.8, 27.7, 26.5 (CH_2); EIMS *m/z* (%): 386 (M^+, 55), 295 (–C_7H_7, 50), 91 ($C_7H_7^+$, 100); HRMS: $C_{25}H_{26}N_2O_2$, calculated: 386.1994, found: 386.1993.

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Reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of 2,4-dihydro-3*H*-pyrazol-3-ones. One-pot synthesis of highly functionalized 7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazoles

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Abstract—The reactive 1:1 intermediate produced in the reaction between isocyanides and dialkyl acetylenedicarboxylates was trapped by 2,4-dihydro-3*H*-pyrazol-3-ones to yield highly functionalized 7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazoles in fairly good yields.

1. Introduction

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.[1] Whilst the naturally occurring fused bicyclic compounds with two ring junction nitrogen atoms and no extra heteroatoms are very rare,[2] the interest in the 5–5 systems stems from the appearance of saturated and partially saturated pyrazolo[1,2-*a*]pyrazole ring systems in biologically active compounds, some of which are active bronchodilators,[3] dopamine receptor antagonists active as gastric prokinetic agents,[4] highly active angiotensin-converting enzyme inhibitors and highly potent antihypertensives in vivo,[2] and some are also broad spectra carbapenem active against aerobic and anaerobic bacteria that could yield significant candidates for evaluation in human medicine.[5]

By far the most common synthetic methods for the preparation of pyrazolo[1,2-*a*]pyrazole ring systems involve: ring synthesis from nonheterocyclic precursors, by formation of one bond (α or β to the ring junction atom), by formation of two bonds {[3+2] atom fragments, one bond (or the both) adjacent to the ring junction nitrogen atom(s)}, and also by transformation of an existing heterocycle.[2,6–8] Up to now, we know of no published report concerning the synthesis of pyrazolo[1,2-*a*]pyrazole ring systems by formation of three bonds. As part of our current studies on the development of new routes in heterocyclic synthesis,[9–12] in this paper, we wish to report a facile synthesis of highly functionalized pyrazolo[1,2-*a*]pyrazoles by formation of three bonds, [2+2+1] atom fragments.

2. Results and discussion

Isocyanides **1** and dialkyl acetylenedicarboxylates **2** in the presence of 2,4-dihydro-3*H*-pyrazol-3-ones **3** undergo a smooth 1:1:1 addition reaction in acetone at ambient temperature, to produce highly functionalized 7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole derivatives **4** in 69–81% yields (Scheme 1).

The structures of compounds **4a**–**h** were deduced from their elemental analyses, their IR, and high-field ^{1}H and ^{13}C NMR spectra. The mass spectrum of **4a** displayed the molecular ion (M^{+}) peak at 349 *m*/*z*, which is consistent with the 1:1:1 adduct of 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one, dimethyl acetylenedicarboxylate, and cyclohexyl

Keywords: Isocyanides; Acetylenic esters; 2,4-Dihydro-3*H*-pyrazol-3-ones; Three-component reactions; 7-Oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazoles.
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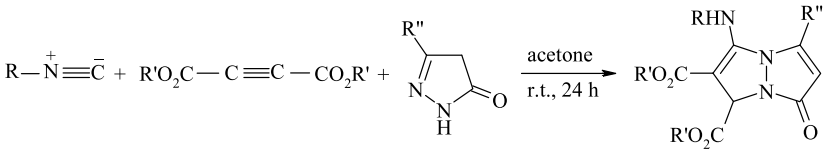


1 2 3 4

1	R
a	Cyclohexyl
b	^{t}Bu

2	R′
a	Me
b	Et

3	R″
a	Me
b	Ph

4	R	R′	R″	% Yield
a	Cyclohexyl	Me	Me	79
b	Cyclohexyl	Et	Me	75
c	Cyclohexyl	Me	Ph	77
d	Cyclohexyl	Et	Ph	70
e	^{t}Bu	Me	Me	81
f	^{t}Bu	Et	Me	78
g	^{t}Bu	Me	Ph	70
h	^{t}Bu	Et	Ph	69

Scheme 1.

isocyanide. The ^{1}H NMR spectrum of **4a** exhibited five sharp singlets readily recognized as arising from methyl ($\delta=2.03$ ppm), methoxy ($\delta=3.62$ and 3.68 ppm), methine and vinylic ($\delta=5.17$ and 5.18 ppm) protons. A broad signal ($\delta=7.33$ ppm) is observed for the NH group, along with the characteristic multiplets for the 11 protons of the cyclohexyl moiety. The proton decoupled ^{13}C NMR spectrum of **4a** showed 17 distinct resonances in agreement with the proposed structure. Partial assignment of these resonances is given in the Section 4.

The ^{1}H and ^{13}C NMR spectra of compounds **4b–h** are similar to those of **4a**, except for the 5-substituents, the alkylamino moieties, and the ester groups, which exhibit characteristic signals with appropriate chemical shifts and coupling constants (see Section 4).

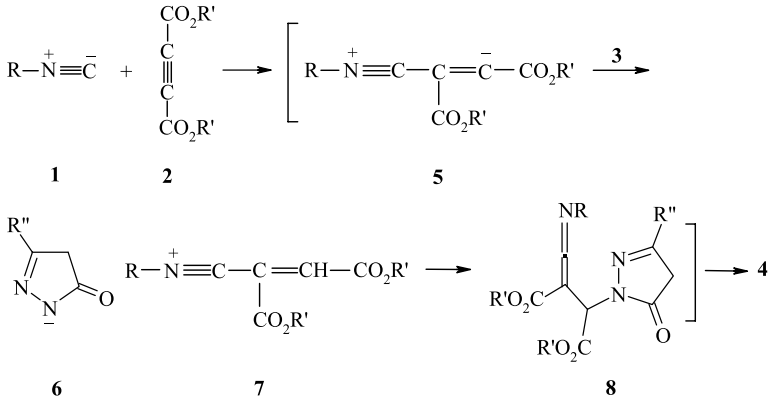
Although we have not established the mechanism of the reaction between the isocyanides and the acetylenic esters in the presence of the pyrazole derivatives **3** in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,[13–17] it is reasonable to assume that the functionalized pyrazolo[1,2-*a*]pyrazoles **4** apparently result from initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct **5** by compound **3**, followed by attack of the anion of the NH-acid **6** on the positively charged ion **7** to form ketenimine **8**. The ketenimine intermediate **8** can isomerize under the reaction condition employed to produce the fused heterocyclic system **4**.

3. Conclusion

In summary, the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of 2,4-dihydro-3*H*-pyrazol-3-ones provides a simple one-pot entry into the synthesis of polyfunctional pyrazolo[1,2-*a*]pyrazole derivatives of potential synthetic and pharmaceutical interest. The present method carries the advantage of being performed under the neutral conditions and requiring no activation or modification of the educts.

4. Experimental

Dimethyl- and diethyl acetylenedicarboxylates, *tert*-butyl- and cyclohexyl isocyanides were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. 2,4-Dihydro-3*H*-pyrazol-3-ones **3** were prepared according to the literature procedure.[18] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a



1 2 5

6 7 8

Scheme 2.

Heraeus CHN–O– Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 60 mesh.

4.1. General procedure

To a magnetically stirred solution of the appropriate 2,4-dihydro-3*H*-pyrazol-3-one, **3** (1 mmol) and the appropriate acetylenic ester (1 mmol) in acetone (6 mL) was added dropwise a mixture of the appropriate isocyanide (1 mmol) in acetone (2 mL) at −5 °C for 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 h. The solvent was removed and the product was purified by column chromatography using hexane–ethyl acetate (3:1) as eluent. The solvent was removed under the reduced pressure and the product was crystallized from 1:1 hexane–ethyl acetate.

4.1.1. Dimethyl 3-(cyclohexylamino)-5-methyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4a. Colorless crystals, mp 69–71 °C, yield 0.27 g, 79%. IR (KBr) (υ_{max}/cm^{-1}): 3285 (NH), 1747, 1704, and 1657 (C·O), 1612, 1450, 1420, 1379, 1346, 1232, 1121, 1013, 918, 781, 731. MS, *m*/*z* (%): 349 (M^+, 3), 305 (2), 247 (2), 208 (5), 176 (5), 139 (3), 98 (9), 83 (11), 67 (100), 59 (19), 55 (74), 40 (56). Anal. Calcd for $C_{17}H_{23}N_3O_5$ (349.39): C, 58.44; H, 6.64; N, 12.03. Found: C, 58.6; H, 6.7; N, 11.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.19–2.01 [10H, m, CH(CH_2)$_5$], 2.03 (3H, s, CH_3), 3.62 and 3.68 (6H, 2s, 2 OCH_3), 4.37 (1H, m, NHC*H*), 5.17 and 5.18 (2H, 2s, NCH and NC·CH), 7.33 (1H, br, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.10 (CH_3), 24.21, 24.26, 25.28, 33.83, and 33.94 (5 CH_2), 50.57 and 52.69 (2 OCH_3), 55.06 (NHCH), 61.24 (NCH), 79.53 (N_2C·*C*), 98.60 (NC·*C*H), 149.95 and 153.36 (N*C*·CH and N_2*C*·C), 162.41, 165.11, and 168.77 (3 C·O).

4.1.2. Diethyl 3-(cyclohexylamino)-5-methyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4b. Colorless crystals, mp 80–82 °C, yield 0.28 g, 75%. IR (KBr) (υ_{max}/cm^{-1}): 3277 (NH), 1749, 1700 and 1645 (C·O), 1610, 1555, 1465, 1445, 1375, 1323, 1258, 1223, 1115, 1028, 966, 910, 783, 733. MS, *m*/*z* (%): 377 (M^+, 9), 223 (10), 180 (21), 133 (24), 105 (30), 83 (14), 70 (25), 55 (36), 40 (75), 28 (100). Anal. Calcd for $C_{19}H_{27}N_3O_5$ (377.44): C, 60.46; H, 7.21; N, 11.13. Found: C, 60.5; H, 7.1; N, 11.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.23 and 1.24 (6H, 2t, J=7.1 Hz, 2 OCH_2CH_3), 1.20–2.04 [10H, m, CH(CH_2)$_5$], 2.08 (3H, s, CH_3), 4.10 and 4.16 (2H, 2dq, *AB*X$_3$ system, ^2J=11.5 and ^3J=7.1 Hz, $OCH_AH_BCH_3$), 4.19 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.43 (1H, m, NHC*H*), 5.20 and 5.21 (2H, 2s, NCH and NC·CH), 7.37 (1H, br., NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.21 (CH_3), 14.03 and 14.43 (2 OCH_2CH_3), 24.23, 24.28, 25.35, 33.85 and 33.97 (5 CH_2), 55.01 (NHCH), 59.22 (OCH_2CH_3), 61.51 (NCH), 61.87 (OCH_2CH_3), 79.94 (N_2C·*C*), 98.61 (NC·*C*H), 150.00 and 153.28 (N*C*·CH and N_2*C*·C), 162.47, 164.86 and 168.39 (3 C·O).

4.1.3. Dimethyl 3-(cyclohexylamino)-5-phenyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4c. Colorless crystals, mp 113–115 °C, yield 0.31 g, 77%. IR (KBr) (υ_{max}/cm^{-1}): 3288 (NH), 1747, 1701 and 1664 (C·O), 1612, 1460, 1391, 1340, 1265, 1215, 1136, 1074, 760, 692. MS, *m*/*z* (%): 411 (M^+, 25), 401 (20), 292 (5), 212 (9), 152 (10), 126 (5), 106 (10), 83 (5), 77 (10), 59 (15), 40 (55), 28 (100). Anal. Calcd for $C_{22}H_{25}N_3O_5$ (411.46): C, 64.22; H, 6.12; N, 10.21. Found: C, 64.0; H, 6.2; N, 10.3%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.20–2.19 [10H, m, CH(CH_2)$_5$], 3.37 and 3.69 (6H, 2s, 2 OCH_3), 4.41 (1H, m, NHC*H*), 5.40 and 5.69 (2H, 2s, NCH and NC·CH), 7.39 (1H, br., NH), 7.42–7.52 (5H, m, 5 $CH_{aromatic}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 24.37, 24.50, 25.45, 33.79 and 34.25 (5 CH_2), 50.80 and 52.27 (2 OCH_3), 55.61 (NHCH), 63.34 (NCH), 79.68 (N_2C·*C*), 99.48 (NC·*C*H), 127.17 (CH_{meta}), 127.77 (C_{ipso}), 129.27 (CH_{ortho}), 131.32 (CH_{para}), 150.66 and 158.30 (N*C*·CH and N_2*C*·C), 163.06, 165.55, and 168.67 (3 C·O).

4.1.4. Diethyl 3-(cyclohexylamino)-5-phenyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4d. Colorless crystals, mp 116–118 °C, yield 0.30 g, 70%. IR (KBr) (υ_{max}/cm^{-1}): 3271 (NH), 1742, 1703, and 1651 (C·O), 1609, 1474, 1448, 1301, 1325, 1246, 1211, 1140, 1109, 1026, 808, 760. MS, *m*/*z* (%): 440 (M^++1, 8), 285 (4), 243 (2), 198 (5), 170 (4), 158 (2), 129 (7), 115 (4), 103 (3), 83 (10), 77 (8), 70 (20), 55 (35), 43 (55), 40 (59), 28 (100). Anal. Calcd for $C_{24}H_{29}N_3O_5$ (439.51): C, 65.59; H, 6.65; N, 9.56. Found: C, 65.8; H, 6.7; N, 9.7%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.93 and 1.24 (6H, 2t, J=7.1 Hz, 2 OCH_2CH_3), 1.20–2.17 [10H, m, CH(CH_2)$_5$], 3.80 and 3.84 (2H, 2dq, *AB*X$_3$ system, ^2J=10.8 and ^3J=7.1 Hz, $OCH_AH_BCH_3$), 4.13 and 4.19 (2H, 2dq, *AB*X$_3$ system, ^2J=10.7 and ^3J=7.1 Hz, $OCH_AH_BCH_3$), 4.42 (1H, m, NHC*H*), 5.38 and 5.69 (2H, 2s, NCH and NC·CH), 7.38 (1H, br, NH), 7.42–7.50 (3H, m, 2 CH_{meta} and CH_{para}), 7.52 (2H, d, J=7.7 Hz, 2 CH_{ortho}). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.78 and 14.54 (2 OCH_2CH_3), 24.35, 24.49, 25.48, 33.79 and 34.23 (5 CH_2), 55.47 (NHCH), 59.37 and 61.46 (2 OCH_2CH_3), 63.43 (NCH), 80.09 (N_2C·*C*), 99.40 (NC·*C*H), 127.25 (CH_{meta}), 127.93 (C_{ipso}), 129.23 (CH_{ortho}), 131.18 (CH_{para}), 150.35 and 157.99 (N*C*·CH and N_2*C*·C), 163.01, 165.12 and 168.39 (3 C·O).

4.1.5. Dimethyl 3-(*tert*-butylamino)-5-methyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4e. Colorless crystals, mp 83–85 °C, yield 0.26 g, 81%. IR (KBr) (υ_{max}/cm^{-1}): 3275 (NH), 1749, 1695 and 1657 (C·O), 1610, 1582, 1458, 1406, 1344, 1238, 1190, 1117, 1005, 781, 714. MS, *m*/*z* (%): 323 (M^+, 3), 208 (16), 176 (22), 149 (13), 131 (7), 110 (12), 98 (42), 84 (23), 67 (100), 59 (55), 57 (98), 40 (85). Anal. Calcd for $C_{15}H_{21}N_3O_5$ (323.35): C, 55.72; H, 6.55; N, 13.00. Found: C, 55.5; H, 6.7; N, 12.9%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.50 [9H, s, C(CH_3)$_3$], 2.08 (3H, s, CH_3), 3.68 and 3.74 (6H, 2s, 2 OCH_3), 5.20 and 5.25 (2H, 2s, NCH and NC·CH), 7.38 (1H, br, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.35 (CH_3), 30.16 [C(*C*H$_3$)$_3$], 50.73 and 52.77 (2 OCH_3), 57.00 [*C*(CH$_3$)$_3$], 61.89 (NCH), 83.32 (N_2C·*C*), 99.73 (NC·*C*H), 149.63 and 154.51 (N*C*·CH and N_2*C*·C), 163.53, 165.11, and 168.83 (3 C·O).

4.1.6. Diethyl 3-(*tert*-butylamino)-5-methyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4f. Colorless crystals, mp 73–75 °C, yield 0.27 g, 78%. IR (KBr) (υ_{max}/cm^{-1}): 3281 (NH), 1744, 1705, and 1660 (C=·O), 1612, 1466, 1439, 1367, 1335, 1229, 1192, 1112, 1026, 916, 781, 733. MS, *m/z* (%): 351 (M^+, 3), 297 (1), 222 (2), 176 (8), 126 (5), 98 (8), 82 (9), 67 (52), 57 (100), 40 (75). Anal. Calcd for $C_{17}H_{25}N_3O_5$ (351.40): C, 58.11; H, 7.17; N, 11.96. Found: C, 58.2; H, 7.2; N, 12.0%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.25 and 1.26 (6H, 2t, $J=7.2$ Hz, 2 OCH_2CH_3), 1.51 [9H, s, $C(CH_3)_3$], 2.10 (3H, s, CH_3), 4.12 and 4.18 (2H, 2dq, *AB*X$_3$ system, $^2J=10.8$ Hz and $^3J=7.2$ Hz, $OCH_AH_BCH_3$), 4.21 (2H, q, $J=7.2$ Hz, OCH_2CH_3), 5.20 and 5.25 (2H, 2s, NCH and NC·CH), 7.35 (1H, br, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.42 (CH_3), 14.06 and 14.40 (2 OCH_2CH_3), 30.19 [$C(CH_3)_3$], 56.99 [$C(CH_3)_3$], 59.39 and 61.87 (2 OCH_2CH_3), 62.10 (NCH), 84.02 ($N_2C·C$), 99.65 (NC·CH), 149.65 and 154.49 (NC·CH and $N_2C·C$), 163.60, 164.80, and 168.37 (3 C·O).

4.1.7. Dimethyl 3-(*tert*-butylamino)-5-phenyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4g. Colorless crystals, mp 152–155 °C, yield 0.27 g, 70%. IR (KBr) (υ_{max}/cm^{-1}): 3258 (NH), 1744, 1707, and 1645 (C·O), 1618, 1454, 1373, 1344, 1242, 1211, 1128, 1012, 810, 766. MS, *m/z* (%): 385 (M^+, 5), 333 (6), 316 (4), 270 (3), 238 (4), 168 (2), 129 (8), 77 (10), 57 (100), 41 (65). Anal. Calcd for $C_{20}H_{23}N_3O_5$ (385.42): C, 62.33; H, 6.01; N, 10.90. Found: C, 62.3; H, 5.9; N, 11.0%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.55 [9H, s, $C(CH_3)_3$], 3.36 and 3.69 (6H, 2s, 2 OCH_3), 5.36 and 5.71 (2H, 2s, NCH and NC·CH), 7.32 (1H, br, NH), 7.43–7.52 (5H, m, 5 $CH_{aromatic}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 30.20 [$C(CH_3)_3$], 50.78 and 52.14 (2 OCH_3), 57.45 [$C(CH_3)_3$], 63.64 (NCH), 83.40 ($N_2C·C$), 100.15 (NC·CH), 127.12 (CH_{meta}), 127.78 (C_{ipso}), 129.20 (CH_{ortho}), 131.30 (CH_{para}), 149.97 and 158.95 (NC·CH and $N_2C·C$), 163.75, 165.34, and 168.46 (3 C·O).

4.1.8. Diethyl 3-(*tert*-butylamino)-5-phenyl-7-oxo-1*H*,7*H*-pyrazolo[1,2-*a*]pyrazole-1,2-dicarboxylate 4h. Colorless crystals, mp 122–124 °C, yield 0.28 g, 69%. IR (KBr) (υ_{max}/cm^{-1}): 3260 (NH), 1747, 1701, and 1643 (C·O), 1610, 1558, 1468, 1443, 1383, 1333, 1222, 1144, 1113, 1026, 949, 814, 771. MS, *m/z* (%): 413 (M^+, 14), 284 (5), 215 (5), 154 (4), 129 (25), 105 (9), 77 (15), 68 (10), 57 (100), 41 (32), 28 (85). Anal. Calcd for $C_{22}H_{27}N_3O_5$ (413.47): C, 63.91; H, 6.58; N, 10.16. Found: C, 63.8; H, 6.6; N, 10.2%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.94 and 1.24 (6H, 2t, $J=7.1$ Hz, 2 OCH_2CH_3), 1.55 [9H, s, $C(CH_3)_3$], 3.80 and 3.84 (2H, 2dq, *AB*X$_3$ system, $^2J=10.7$ and $^3J=7.1$ Hz, $OCH_AH_BCH_3$), 4.12 and 4.19 (2H, 2dq, *AB*X$_3$ system, $^2J=10.7$ and $^3J=7.1$ Hz, $OCH_AH_BCH_3$), 5.35 and 5.71 (2H, 2s, NCH and NC·CH), 7.29 (1H, br, NH), 7.40·7.49 (3H, m, 2 CH_{meta} and CH_{para}), 7.53 (2H, d, $J=7.6$ Hz, 2 CH_{ortho}). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.79 and 14.48 (2 OCH_2CH_3), 30.28 [$C(CH_3)_3$], 57.43 [$C(CH_3)_3$], 59.47 and 61.40 (2 OCH_2CH_3), 63.77 (NCH), 84.16 ($N_2C·C$), 100.14 (NC·CH), 127.26 (CH_{meta}), 127.99 (C_{ipso}), 129.20 (CH_{ortho}), 131.21 (CH_{para}), 149.99 and 158.84 (NC·CH and $N_2C·C$), 163.81, 165.07, and 168.26 (3 C·O).

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Ab initio and density functional study of substituent effects in halogenated cations of alkenes

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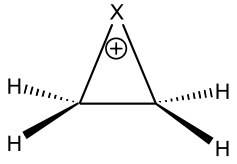
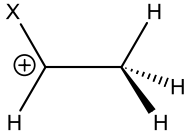
Abstract—A theoretical study of the halogenated cations of mono-, di-, tri- and tetramethyl-substituted ethylenes, $C_3H_6X^+$, $C_4H_8X^+$, $C_5H_{10}X^+$ and $C_6H_{12}X^+$, X=F, Cl, Br, have been studied at the ab initio MP2 and density functional B3LYP levels of theory implementing 6-311++G(d,p) basis set. The potential energy surfaces of all molecules under investigation have been scanned and the ^{13}C and ^1H NMR chemical shifts for all the bridged halonium ions studied have been calculated using the GIAO method at the B3LYP level. The calculated halogen binding energies in the halonium ions have been correlated with the experimental rates of chlorination and bromination of the corresponding alkenes. The computed hydride affinities and the NICS values for the bridged cations show that the bromo cations are more stable than the analogous chloro and fluoro cations.

1. Introduction

Organic halogen cations, since their first identification in the case of some remarkably stable diaryliodonium compounds, have played vital roles as intermediates in organic chemistry.[1] As a consequence, the structure and energetics of halogenated cations of acyclic[2–15] and cyclic alkenes[12–15] have generated widespread interest. In the case of the parent halogenated cation of ethene, $C_2H_4X^+$ (X=F, Cl, Br), almost all of the ab initio calculations of various quality have found two classes of minima (Scheme 1), the non-classical halonium ion (**1a**,**b**,**c**), where the halogen is bridged and the classical methylhalocarbenium ion (**2a**,**b**,**c**), where the halogen is directly bound to the cationic center.[3–14] For the fluorine and chlorine substituted cations the classical α-haloethyl isomer (**2a**,**b**) is most stable, whereas the bridged cation (**1c**) is the minimum on the potential energy surface when the halogen is bromine. Gas phase[16,17] and solution studies,[1] and matrix isolation studies[18] for $C_2H_4Cl^+$ and $C_2H_4Br^+$ confirm the theoretical findings. In the halonium ions of all alkenes studied so far, the larger and less electronegative bromine atom stabilizes more effectively the bridged halonium ions followed by chlorine and fluorine.



1a,b,c



2a,b,c

a, X = F
b, X =Cl
c, X = Br

There has been a great deal of experimental work on the effect of methyl substitution for hydrogen in the parent cations giving secondary or tertiary carbocations.[1] Although theoretical studies on these structures could be proved useful, because of their possible role in the charge conduction mechanism of doped polyacetylene,[19–22] there has not been a systematic theoretical study, except an elegant qualitative discussion of Shaefer and co-workers,[8] a study of the halogenated cations of the 2-butyl system[9] and some sporadic low level ab initio works on methyl substituted halonium ions of ethene.[2,6]

Continuing our theoretical study on the halogenated cations of various alkenes,[14,15] we present in this work a detailed study of the conformational space of the halogenated cations of mono-, bi-, tri- and tetramethyl substituted ethene, $C_2Me_nH_{4-n}X^+$, where X=F, Cl and Br, at the

Keywords: Ab initio; Halonium ions; DFT; MP2; NICS; Hydride affinity.
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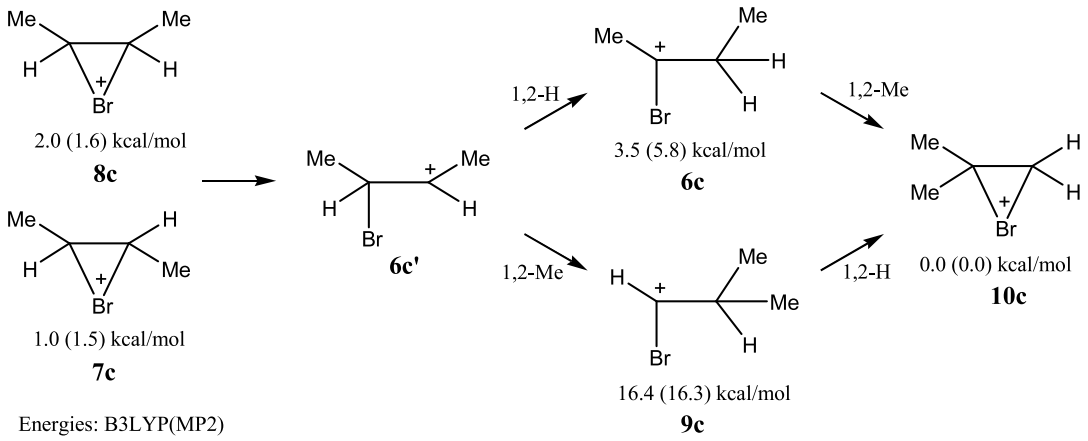


Scheme 1.

B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) level of theory. The relative energies, the equilibrium geometries and the calculated proton and carbon NMR chemical shifts are discussed in relation to existing experimental and theoretical data. The relative stabilities of the fluoro-, chloro- and bromo-analogous species are also discussed in terms of their hydride affinities. In the case of the 1,2-bridged cations, the nuclear independent chemical shifts (NICS) calculated in the center of the three-membered ring have been used as a measure of their relative stability. Furthermore, the correlation between the experimental bromination rates and calculated halogen cation–alkene binding energies has been also explored.

2. Results and discussion

The assessment of the computational level and basis set necessary to achieve reasonable energy comparisons for the halogenated cations under investigation was made in our

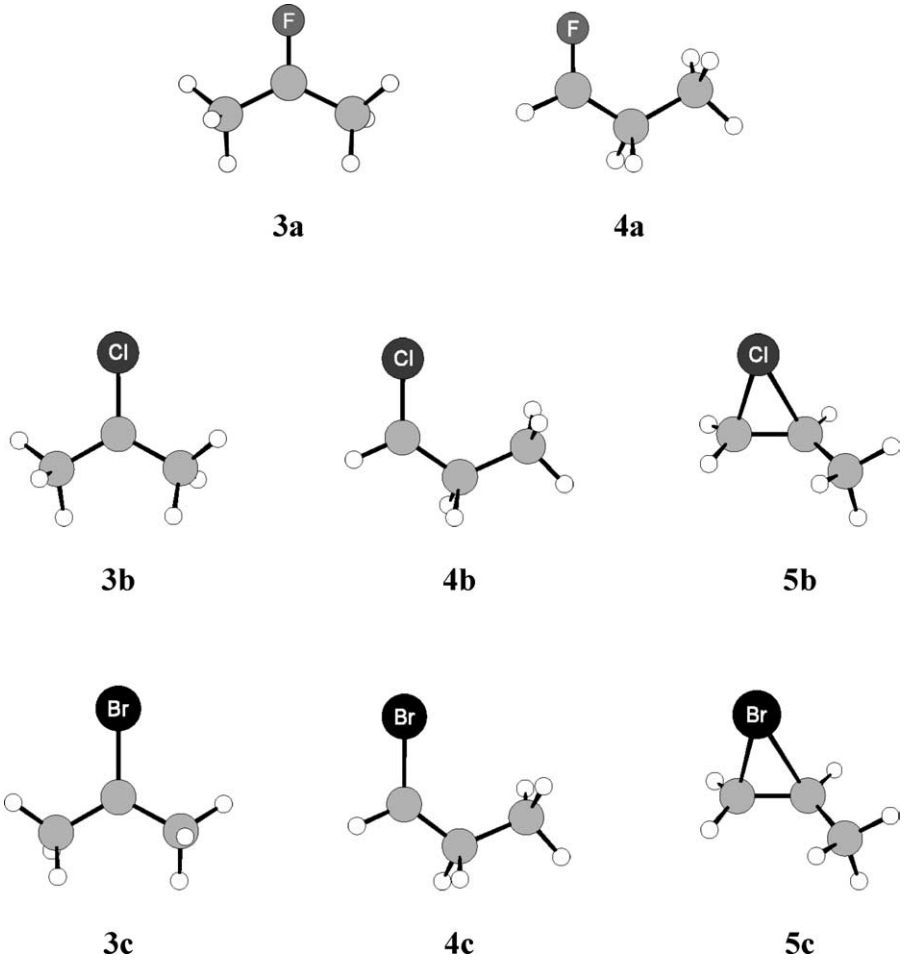


Figure 1. Structures of halogenated cations of propene, $C_3H_6X^+$, optimized at the B3LYP level.

Table 1. Calculated geometric parameters (Å, °), relative energies, (kcal/mol), zero point energies (kcal/mol), hydride affinities (kcal/mol) and NICS values (ppm) of halogenated cations of propene, $C_3H_6X^+$

X		Method	C–C′[a]	C–X	C′–X	X–C–C′	ΔE	ZPE	HA	NICS
F	**3a**	B3LYP	1.451	1.280		116.3	0.0	51.3	248.1	
		MP2	1.454	1.270		116.7	0.0		260.1	
	4a	B3LYP	1.426	1.263		121.7	19.2	51.6	263.1	
		MP2	1.432	1.255		121.8	18.0		260.2	
Cl	**3b**	B3LYP	1.463	1.665		118.8	0.0	50.5	248.4	
		MP2	1.468	1.638		119.4	0.0		260.2	
	4b	B3LYP	1.441	1.640		125.1	14.4	50.8	260.4	
		MP2	1.448	1.617		124.5	13.8		270.7	
	5b	B3LYP	1.459	1.864	2.037	74.5	12.1	51.8	260.5	−44.2
		MP2	1.462	1.844	1.909	69.4	8.5		268.8	
Br	**3c**	B3LYP	1.464	1.824		119.1	0.0	50.2	248.4	
		MP2	1.470	1.793		119.8	0.0		261.3	
	4c	B3LYP	1.443	1.796		125.8	13.2	50.5	259.6	
		MP2	1.451	1.769		125.3	12.6		271.1	
	5c	B3LYP	1.453	2.024	2.180	75.7	4.8	51.5	253.2	−46.3
		MP2	1.458	2.004	2.072	71.6	1.5		262.8	

[a] C′ is C1 in **3**, C2 in **4** and the second bridged carbon in **5** (Fig. 1).

previous works[14,15] by comparing the results of density functional and MP2 calculations with previous ab initio works on the $C_2H_4X^+$ system and experimental data for cyclopentyl, $C_5H_8X^+$, and cyclohexyl, $C_6H_{10}X^+$, halonium ions (X=Cl, Br). It has been found that the energy differences depend more on the quality of the basis set used than on the method describing the correlation effects. In the present study, we have used both density functional and MP2 calculations with the same basis set (6-311++G(d,p)).

2.1. Halogenated cations of propene, $C_3H_6X^+$

The optimized structures of the isomers found at B3LYP/6-311++G(d,p) level, are shown in Figure 1, whereas the relative energies, zero point energies at the B3LYP level

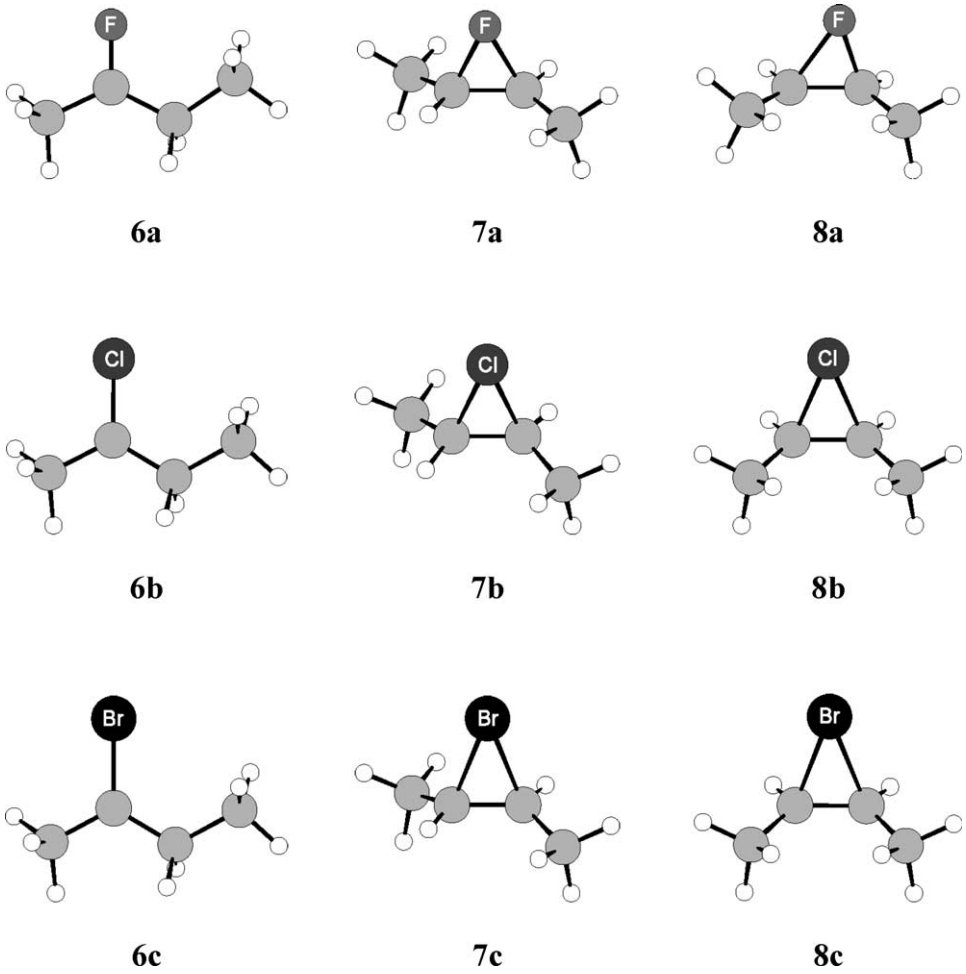


Figure 2. Structures of halogenated cations of 2-butene, $C_4H_8X^+$, optimized at the B3LYP level.

Table 2. Calculated geometric parameters (Å, °), relative energies, (kcal/mol), zero point energies (kcal/mol), hydride affinities (kcal/mol) and NICS values (ppm) of halogenated cations of 2-butene, $C_4H_8X^+$

X		Method	C–C′[a]	C–X	C′-X	X–C–C′	ΔE	ZPE	HA	NICS
F	**6a**	B3LYP	1.452	1.282		117.2	0.0	69.0	244.4	
		MP2	1.453	1.273		117.3	0.0		257.1	
	7a	B3LYP	1.469	1.597	1.597	64.8	24.9	69.1	269.3	−35.4
		MP2	1.464	1.586	1.586	62.5	25.1		282.1	
	8a	B3LYP	1.478	1.521	1.521	72.3	26.2	69.2	270.6	−33.5
		MP2	1.469	1.586	1.586	62.4	26.3		283.4	
Cl	**6b**	B3LYP	1.464	1.668		120.0	0.0	68.2	245.2	
		MP2	1.467	1.640		120.1	0.0		257.5	
	7b	B3LYP	1.463	1.960	1.960	68.1	4.2	69.2	249.4	−44.3
		MP2	1.463	1.892	1.892	67.2	1.0		258.5	
	8b	B3LYP	1.467	1.962	1.962	68.0	5.4	69.3	250.6	−43.7
		MP2	1.468	1.894	1.894	67.2	2.3		259.8	
Br	**6c**	B3LYP	1.466	1.828		120.5	2.5	67.9	245.4	
		MP2	1.469	1.797		120.7	4.3		258.7	
	7c	B3LYP	1.458	2.118	2.118	69.9	0.0	68.9	242.9	−46.1
		MP2	1.460	2.055	2.055	69.2	0.0		253.3	
	8c	B3LYP	1.461	2.121	2.121	69.9	1.0	69.0	243.9	−45.6
		MP2	1.463	2.057	2.057	69.2	0.1		254.5	

[a] C′ is C3 in **6** and the second bridged carbon in **7** and **8** (Fig. 2).

and selected optimized geometrical parameters, at the B3LYP and MP2 level, are given in Table 1. In the case of the fluoronium ion, no bridged structure has been located in the potential energy surface of the molecule. Instead, the dimethylfluorocarbenium ion, **3a**, is the more stable isomer with the ethylfluorocarbenium ion, **4a**, being 18–19 kcal/mol higher in energy. No similar species have been identified or obtained experimentally.

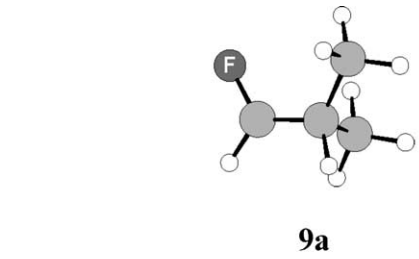
In the case of the less electronegative and larger chlorine and bromine atoms the dimethylhalocarbenium ion, **3b**,**c**, was the more stable isomer but the bridged halonium ions, **5b**,**c**, are stabilized and have been also located. The stabilization is larger at the MP2 level and the energy of the propylenebromonium ion, **5c**, is very close to the global minimum, **3c**. The results are in agreement with the experimental findings. Thus, while **5c** has been obtained experimentally from ionization of a 2-fluoro-1-bromopropane in SbF_5–SO_2 solution at −60 °C, the corresponding propylenechloromium ion could not be obtained and was only tentatively identified in equilibrium with ethylchlorocarbenium ion, **3b**.[23,24] Both chloro- and bromo-bridged cations, **5b**,**c**, are asymmetric with the halogen atom bent away from the methyl substituted carbon. Thus, the X–C–C′ angle is nearly 75° instead of 67–69°, found in the parent ethylenehalonium ions, **1b**,**c**, at the B3LYP level.[14] The calculated values of X–C′ and X–C–C′ are systematically smaller at the MP2 level, showing a smaller distortion at this level of calculation, and this is the case in all the asymmetric halonium ions studied in this work. Yamade and co-workers[6] have located structures close to β-haloalkenium ions, with angles equal to 87 and 97.5° for **5b** and **5c**, respectively, at the HF level. They characterized the structures as open cations, as no X–C′ bonding interaction exists. No such structures have been located at our levels of calculation.

2.2. Halogenated cations of 2-butene, $C_4H_8X^+$

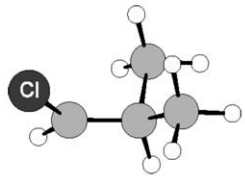
The methylethylhalocarbenium ions, **6a**,**b**,**c**, and the *trans*- and *cis*-1,2-dimethylethylenehalonium ions, **7a**,**b**,**c**–**8a**,**b**,**c**, have been located in the potential energy surface for all halogens. Their optimized structures calculated at B3LYP/6-311++G(d,p) level, are shown in Figure 2, whereas the relative energies, zero point energies at the B3LYP level and selected optimized geometric parameters, at the B3LYP and MP2 level, are given in Table 2. In the case of the fluoro- and chloro-ions, the methylethylhalocarbenium ions, **6a**,**b**, are the global minima with the halonium ions, **7a**,**b**–**8a**,**b**, been in higher energies. Indeed, it has been experimentally found that fluorine and chlorine show no ability to form bridged ions, existing solely as open-chain halocarbenium ions.[1] In the case of bromine, the symmetrical *cis*- and *trans*-1,2-dimethylethylenebromonium ions, **7c**–**8c**, are strongly stabilized, being lower in energy than the carbenium ion, **6c**. The *trans*-bridged cations are 1–1.3 kcal/mol lower in energy than the corresponding *cis*-structures independently from the halogen and the level of calculation, in agreement with the 70/30% **7c/8c** ratio found experimentally. A similar energy pattern has been calculated for **6a**–**7a**–**8a** at the HF level by Reynolds.[9] The lengthening of the C–C′ bond in going from the parent ethylene halonium ions (**1a**: 1.458 Å, **1b**: 1.456 Å, **1c**:1.450 Å at the B3LYP level) to the symmetric dimethyl substituted compounds studied here, is indicative for a stronger halogen binding in the later, as it has been shown that the halogen binding involves electron withdrawing from π and electron donation to π* molecular orbitals of the alkene.[14]

2.3. Halogenated cations of 2-methyl-propene, $C_4H_8X^+$

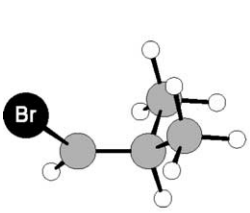
The ionic species derived from 2-methyl-propene are structural isomers with those derived from 2-butene discussed previously. The optimized structures of the minima found at B3LYP/6-311++G(d,p) level, are shown in Figure 3, whereas the relative energies, zero point energies at the B3LYP level and selected optimized geometric parameters, at the B3LYP and MP2 level, are given in Table 3. Only the *i*-propylfluorocarbenium ion, **9a**, has been located as a stable minimum. It lies 17.8 kcal/mol higher in energy at B3LYP (14.8 kcal/mol at MP2) than **6a** and has not been experimentally observed. In the case of chlorine and bromine the 1,1-dimethylethylenehalonium



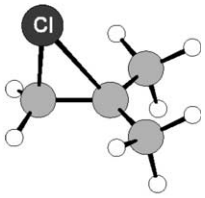
9a



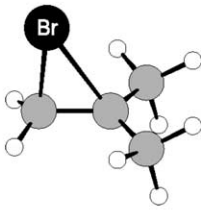
9b



9c

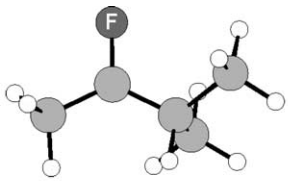


10b

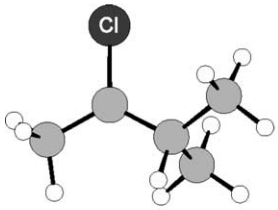


10c

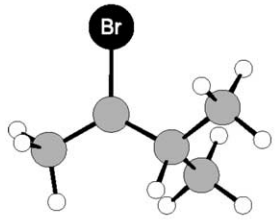
Figure 3. Structures of halogenated cations of 2-methyl-propene, $C_4H_8X^+$, optimized at the B3LYP level.



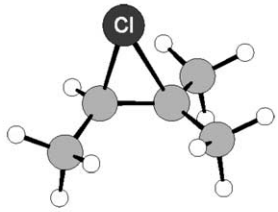
11a



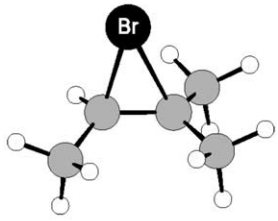
11b



11c



12b



12c

Figure 4. Structures of halogenated cations of 2-methyl-2-butene, $C_5H_{10}X^+$, optimized at the B3LYP level.

ions, **10b**–**10c**, are the global minima, being lower in energy than the carbenium ions, **9b**–**9c** and having a highly asymmetrical structure. The C–X bonds to the primary carbon are relatively short, whereas those to the tertiary carbon are significantly longer. The optimized Br–C–C′ angle for **10c** is equal to 85.3°, whereas Yamabe *et al.*[25] have calculated at the PM3 level a value equal to 100.5° being indicative of an almost open structure.

It is interesting to note that the bridged ions **10b**,**c** have lower energies than their structural isomers **7b**,**c** and **8b**,**c** and a conversion path from the former to the latter should exist. Indeed, the 1,1-dimethylethylenebromonium ion, **10c**, has been experimentally obtained by warming the isomeric *cis*- and *trans*-1,2-dimethylethylenebromonium ions, **7c**–**8c**, to −40 °C. A possible mechanism for this transformation involving the breaking of a carbon–bromine bond in **7c**–**8c**, to give intermediate **6c**′ followed by subsequent 1,2-hydrogen and 1,2-methyl shifts (a) or 1,2-methyl and 1,2-hydrogen shifts (b) to give **10c**. From the energy profile of the two mechanisms shown in Scheme 1, it is concluded that mechanism (a) going through intermediate **6c** is more

Table 3. Calculated geometric parameters (Å, °), relative energies, (kcal/mol), zero point energies (kcal/mol), hydride affinities (kcal/mol) and NICS values (ppm) of halogenated cations of 2-methyl-propene, $C_4H_8X^+$

X		Method	C–C′[a]	C–X	C′–X	X–C–C′	ΔE	ZPE	HA	NICS
F	**9a**	B3LYP	1.412	1.276		121.5	—	70.0	258.5	
		MP2	1.405	1.277		121.4	—		268.7	
Cl	**9b**	B3LYP	1.435	1.649		125.2	11.4	69.0	257.4	
		MP2	1.464	1.629		126.6	10.9		267.6	
	10b	B3LYP	1.474	1.832	2.296	87.3	0.0	68.6	249.4	−38.4
		MP2	1.464	1.835	1.987	73.1	0.0		262.3	
Br	**9c**	B3LYP	1.438	1.804		127.0	16.4	68.5	256.9	
		MP2	1.431	1.780		126.2	16.3		268.2	
	10c	B3LYP	1.464	2.002	2.382	85.3	0.0	68.5	243.3	−42.3
		MP2	1.460	1.997	2.150	75.2	0.0		256.6	

[a] C′ is C2 in **9** and the second bridged carbon in **10** (Fig. 3).

Table 4. Calculated geometric parameters (Å, °), relative energies, (kcal/mol), zero point energies (kcal/mol), hydride affinities (kcal/mol) and NICS values (ppm) of halogenated cations of 2-methyl-2-butene, $C_5H_{10}X^+$

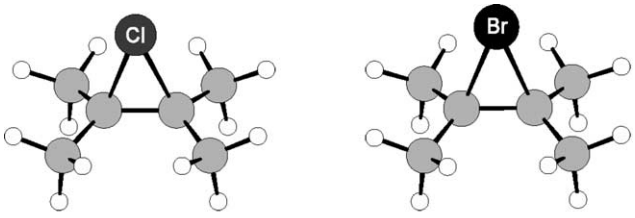
X		Method	C–C′[a]	C–X	C′–X	X–C–C′	ΔE	ZPE	HA	NICS
F	**11a**	B3LYP	1.447	1.288		117.1		87.2	240.5	
		MP2	1.442	1.280		117.2			253.1	
Cl	**11b**	B3LYP	1.462	1.674		119.9	2.2	86.3	242.0	
		MP2	1.457	1.648		119.7	3.1		254.0	
	12b	B3LYP	1.477	1.889	2.169	79.2	0.0	86.3	241.1	−40.6
		MP2	1.470	1.879	1.956	70.3	0.0		253.5	
Br	**11c**	B3LYP	1.464	1.835		120.5	8.1	85.9	242.3	
		MP2	1.459	1.806		120.4	9.0		256.2	
	12c	B3LYP	1.470	2.065	2.279	78.3	0.0	86.0	235.3	−43.4
		MP2	1.466	2.042	2.121	72.3	0.0		248.4	

[a] C′ is C2 in **11** and the second bridged carbon in **12** (Fig. 4).

energetically favorable than mechanism (b) involving the high energy intermediate **9c**. This mechanism has also been claimed by Olah and co-workers.[26] The intermediate **6c′** has not been observed either experimentally or theoretically.

2.4. Halogenated cations of 2-methyl-2-butene, $C_5H_{10}X^+$

The *i*-propylmethylhalocarbenium ions, **11a**,**b**,**c**, have been located on the potential energy surface for all halogens, whereas the 1,1,2-trimethylethylenehalonium ions, **12b**,**c**, only for chlorine and bromine. Their optimized structures calculated at B3LYP/6-311++G(d,p) level, are shown in Figure 4, whereas the relative energies, zero point energies at the B3LYP level and selected optimized geometrical parameters, at the B3LYP and MP2 level, are given in Table 4. The chloronium and bromonium ions, **12a**,**b**, are the global minima and both have been obtained experimentally.[26] Their extent of asymmetry imposed by substitution, as described by the calculated X–C–C′ angles, is between that found for the corresponding methylethylenehalonium ions, **5b**,**c**, and 1,1-dimethylethylenehalonium ions, **10b**,**c**.

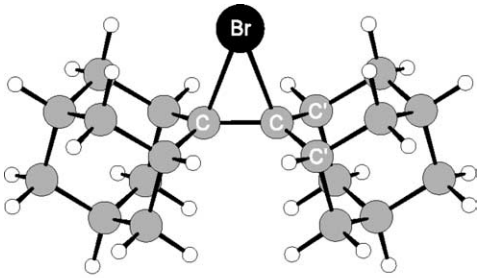


13b **13c**

Figure 5. Structures of halogenated cations of 2,3-dimethyl-2-butene, $C_6H_{12}X^+$, optimized at the B3LYP level.

2.5. Halogenated cations of 2,3-dimethyl-2-butene, $C_6H_{12}X^+$

The only minima found for this family of ions are the 1,1,2,2-tetramethylethylene-chloronium and bromonium ions, **13b**,**c**, the optimized structures of which calculated at B3LYP/6-311++G(d,p) level, are shown in Figure 5, whereas zero point energies at the B3LYP level and selected optimized geometrical parameters, at the B3LYP and MP2 level, are given in Table 5. Both structures have been experimentally observed.[26] In the case of fluorine, the only structure found was the *t*-butylmethyl-fluorocarbenium ion not further discussed herein. The chloronium and bromonium ions, are symmetric. The central C–C bond distances are the longest among the other bridged species compared



	Calc.	Exp.
C-C	1.496	1.497
C-Br	2.205	2.155
C-Br-C	39.7	40.6
Br-C-C	70.2	69.7
C'-C-C'	111.8	112.9

14c

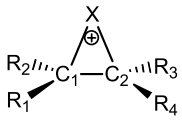
Figure 6. Optimized structure and selected calculated at the B3LYP level and experimental geometric parameters for the bromonium ion of adamantylideneadamantane.

Table 5. Calculated geometric parameters (Å, °), zero point energies (kcal/mol), hydride affinities (kcal/mol) and NICS values (ppm) of halogenated cations of 2,3-dimethyl-2-butene, $C_6H_{12}X^+$

X		Method	C–C′[a]	C–X	C′–X	X–C–C′	ZPE	HA	NICS
Cl	**13b**	B3LYP	1.487	2.017	2.017	68.4	103.7	234.5	−41.3
		MP2	1.480	1.932	1.932	67.5		246.8	
Br	**13c**	B3LYP	1.482	2.176	2.176	70.1	103.5	229.1	−43.3
		MP2	1.476	2.096	2.096	69.4		242.2	

[a] C′ is the second bridged carbon (Fig. 5).

Table 6. Calculated ^{13}C (ppm from CS_2) and ^{1}H NMR (ppm from TMS) chemical shifts of halonium ions of the studied alkenes along with experimental values in parentheses[a]



	R_1	R_2	R_3	R_4	X	^{13}C NMR				^{1}H NMR			
						δC_1	δC_2	$\delta CH_3(C_1)$	$\delta CH_3(C_2)$	$\delta H(R_1)$	$\delta H(R_2)$	$\delta H(R_3)$	$\delta H(R_4)$
1b	H	H	H	H	Cl	124.9 (119.7)	124.9 (119.7)			5.8 (5.9)	5.8 (5.9)	5.8 (5.9)	5.8 (5.9)
1c	H	H	H	H	Br	125.6 (120.8)	125.6 (120.8)			5.7 (5.5)	5.7 (5.5)	5.7 (5.5)	5.7 (5.5)
5b	Me	H	H	H	Cl					2.9 (3.0)	7.6 (7.2)	5.2 (6.2)	5.4 (6.2)
5c	Me	H	H	H	Br	64.0 (71.6)	135.6 (121.1)	181.2 (168.4)		2.9 (3.0)	7.5 (7.8)	5.3 (5.9)	5.3 (5.9)
7c	Me	H	Me	H	Br	85.8 (82.9)	85.7 (82.9)	184.7 (171.4)	184.7 (171.4)	2.5 (2.6)	6.8 (6.7)	2.6 (2.6)	6.8 (6.7)
8c	H	Me	Me	H	Br	87.5 (85.0)	87.4 (85.0)	189.5 (176.4)	189.5 (176.4)	2.5 (2.6)	6.5 (6.7)	6.5 (6.7)	2.5 (2.6)
10c	Me	Me	H	H	Br	−21.7 (−17.6)	145.0 (133.3)	170.3 (158.4)		2.9 (3.3)	3.2 (3.5)	4.9 (5.5)	4.9 (5.5)
12b	Me	Me	Me	H	Cl					2.9 (3.4)	3.0 (3.4)	2.2 (2.5)	5.8 (6.3)
12c	Me	Me	Me	H	Br	12.5 (21.0)	109.2 (101.1)	175.8 (163.3)	190.2 (175.6)	2.8 (3.1)	2.9 (3.1)	2.3 (2.6)	6.0 (6.6)
								174.9 (163.3)				2.3 (2.6)	
13b	Me	Me	Me	Me	Cl	54.5 (42.1)	54.5 (42.1)	181.1 (165.8)	181.1 (165.8)	2.6 (2.7)	2.6 (2.7)	2.6 (2.7)	2.6 (2.7)
13c	Me	Me	Me	Me	Br	54.0 (54.1)	54.0 (54.1)	179.7 (167.1)	179.7 (167.1)	2.6 (2.9)	2.6 (2.9)	2.6 (2.9)	2.6 (2.8)

[a] Exp. values from Ref. 23,24,26,28.

so far and the parent ethylenehalonium ions,[14] indicating that these species are better described as halonium ions rather than as π-complexes.[27] The calculated geometry of **13c** may be compared with those calculated at the B3LYP level for the bromonium ion of adamantylideneadamantane, **14c**, shown in Figure 6 along with the experimental data for comparison.[29]

2.6. Calculation of ^{13}C and ^{1}H NMR chemical shifts

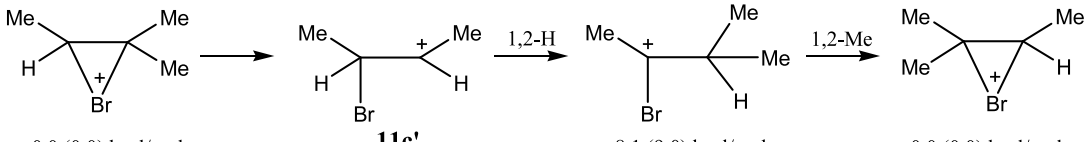
The ^{13}C and ^{1}H NMR chemical shifts for all the bridged halonium ions studied have been calculated using the GIAO method at the B3LYP level. The results along with the experimental values[23,24,26,28] are given in Table 6. There is an overall agreement between calculated and experimental values. The larger deviations concern the chemical shifts of the methyl substituents. Thus, the correlation coefficient between all the calculated and experimental ^{13}C chemical shifts is equal to 0.99, whereas this concerning the chemical shifts of the methyl carbons falls to 0.97.

Another source of discrepancy is due to the equivalence of the geminal methyl groups in the experimental ^{1}H and ^{13}C spectra of trimethylethylenebromonium ion, **12c**, as well as in the ^{13}C spectrum of trimethylethylenechloronium ion, **12b**,[26,27] obviously not shown in the calculated values. It has been claimed that this could be attributed to a equilibration between the asymmetric bridged halonium ion and an open ion form, **11c′** (Scheme 2), or by an accidental equivalence of both the geminal methyl carbon and proton shielding in the bridged ions.[26] Although the open ion form, **11c′**, is not a stable point in the potential energy surface of the molecule, a possible mechanism for this transformation could involve the breaking of a carbon-halogen bond and a 1,2-hydrogen shift in **12b**,**c**, to give intermediate **11c** followed by an 1,2-methyl shift to give **12b**,**c**. The energy profile for the bromonium ion (Scheme 2) shows that such a mechanism is possible. However, the accidental equivalence should not be excluded as the calculated chemical shifts for both methyls are very close.

In the ^{13}C spectra of *cis*- and *trans*-1,2-dimethylethylene-bromonium ions, **7c**, **8c**, there is a 5 ppm up field shift in the methyl carbon shielding of the *cis* isomer compared to the *trans* isomer resulting from the enhanced steric interaction between the methyl groups.

2.7. Binding energies, hydride affinities, nuclear independent chemical shifts and relative stabilities

The most common mechanism of liquid-phase chlorination or bromination of alkenes occurs heterolytically with the formation of the bridged halonium ions as the first step. The rates of chlorination and bromination of various alkenes studied herein have been experimentally determined.[30–32] There is a fairly good linear correlation between $\log(k)$ of halogen addition to alkenes and the binding energies (BE) of halogen cation to the corresponding halonium ions calculated at the B3LYP level, shown in Figure 7. The correlation coefficients are equal to 0.957 and 0.990 for chlorination



Energies: B3LYP(MP2)

Scheme 2.

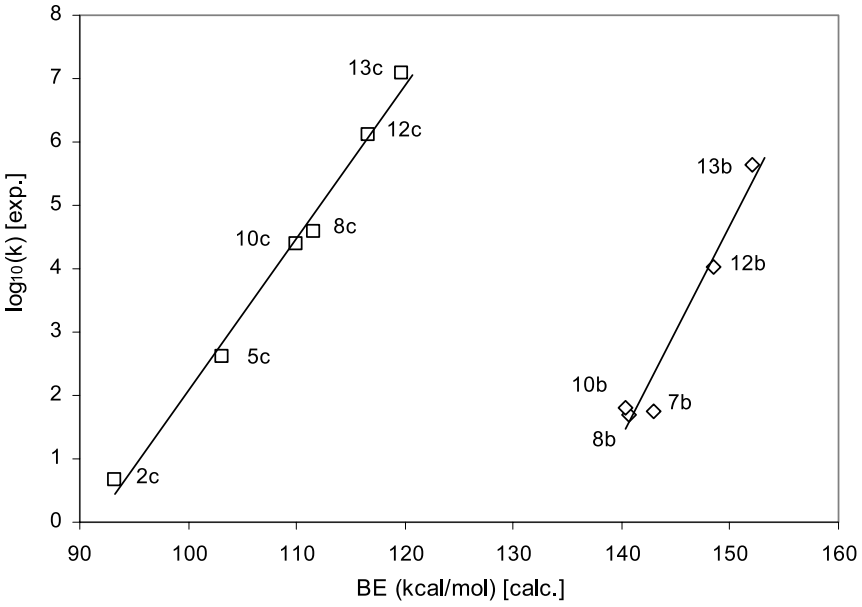


Figure 7. Experimental rates of chlorination (◇) and bromination (□) of substituted ethylenes versus the calculated halocation binding energies (BE).

and bromination, respectively. Also, the binding energies show a straightforward correlation to the number of the methyl substituents on the double bond, revealing that the substitution stabilizes the halonium ions and enhances the halogenation rate for the alkene.

The hydride affinities have been used for the comparison of, not only the energetic differences between halocations, but also of the relative abilities of halogens to stabilize the halonium ions, an important question with respect to many practical applications including photo-resists and conducting polymers.[10,14,15] A cation with enhanced stability should have a small hydride affinity. The calculated values for all the isomers studied are shown in Tables 1–5. Concerning the bridged halonium ions the general trend is the obvious stabilization of the bromo- relative to the chloro- and fluoro-cations and there is a systematic stabilization the upon increasing the number of methyl substituents on the ethylenic double bond **13b**,**c**> **12b**,**c**≥**7b**,**c**≥**10b**,**c**≥**8b**,**c**>**5b**,**c**. The differences between the dimethyl derivatives, **7b**,**c**, **10b**,**c**, **8b**,**c** are very close to each other with the *trans*-1,2-dimethyl-ethylenehalonium ions, **7b**,**c**, being more stable. The hydride affinities of the open carbenium ions depend strongly on the substituents and not on the halogen. Thus, disubstituted carbenes, **3a**,**b**,**c** and **6a**,**b**,**c** are much more stable than their monosubstituted isomers, **4a**,**b**,**c** and **9a**,**b**,**c**, respectively.

In order to further compare the relative stability of the 1,2-bridged halonium ions, we have also used the nuclear independent chemical shifts (NICSs) defined as the negative of the absolute magnetic shielding, computed at ring centers (non-weighted mean of the heavy atom coordinates).[33] Negative NICS values imply delocalization and a diatropic ring current, while positive NICS values imply a paratropic ring current. NICSs have been extensively used for the study of two or three-dimensional aromaticity and the relative stability of ring heterocycles,[33,34] cage molecular systems[35]

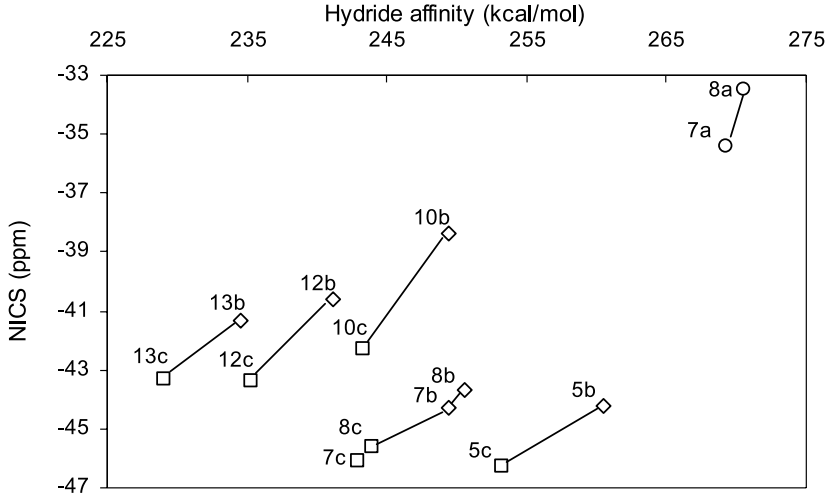


Figure 8. Correlation of calculated hydride affinities and NICS values for the studied bridged fluoro- (○), cloro- (◇) and bromonium (□) ions.

and halonium ions.[14,15] The NICS values calculated at the B3LYP level for all the bridged halonium ions found as real minima in the potential energy surfaces of the studied molecules are shown in Tables 1–5. As has been stated previously a cation of enhanced stability shows small hydride affinities and more negative NICS values.[14,15] According to NICS values the bromo cations are more stable than the chloro and fluoro analogues. The dependence of the NICS values on the number of the methyl substituents on the ethylenic double bond does not parallel the stability trend predicted by the hydride affinities. This could be explained by the structural differences of these species and by the fact that thermodynamic stability is influenced by strain and many other effects besides delocalization or aromaticity. However, as shown in the correlation diagram of Figure 8, where the cations are grouped by their structural resemblance, there is quite good overall agreement between the stability predictions based on hydride affinities and NICS values, with an isomer of enhanced stability showing small hydride affinities and more negative NICS values.

3. Computational details

The electronic structure and geometry of the halonium cations studied were computed within density functional theory, using gradient corrected functionals, at the B3LYP computational level.[36] The basis set used was 6-311++G(d,p).[37,38] Full geometry optimizations were carried out without symmetry constraints. Frequency calculations after each geometry optimization ensured that all the calculated structures are real minima and not transition states in the potential energy surface of the molecules. The optimized structures from the B3LYP level were reoptimized with the frozen core Møller–Plesset perturbation theory, MP2(fc), computational level.[39,40] The basis set used was the 6-311++G(d,p). The hydride affinities have been calculated using a total energy of H^- equal to 335 kcal/mol at B3LYP level and 317 kcal/mol at MP2 level, respectively. These values are in good agreement with the value of 331 kcal/mol, which has been estimated from the experimental ionization potential and electron affinity of hydrogen.[41] All isomers and conformations of the hydride addition product have been considered in each case and the values reported have been calculated on the basis of the energy of the most stable isomer or conformer. The NICS and the ^{13}C and ^{1}H NMR shielding constants of the B3LYP/6-311++G(d,p) optimized structures were calculated with the gauge-independent atomic orbital (GIAO) method[42] at the B3LYP/6-311++G(2d,p) level. The atom shielding constants were converted to chemical shifts by calculating at the same level of theory the ^{13}C and ^{1}H shieldings of TMS or CS_2. All calculations were performed using the Gaussian98 package.[43]

4. Conclusions

The potential energy surfaces of the halonium cations of mono-, di-, tri- and tetramethyl substituted ethylenes, $C_3H_6X^+$, $C_4H_8X^+$, $C_5H_{10}X^+$ and $C_6H_{12}X^+$, X=F, Cl and Br, were computed at the B3LYP/6-311++G(d,p) and MP2/6-311++G(d,p) levels of theory. The potential energy surfaces of all molecules under investigation have been scanned. The ^{13}C and ^{1}H NMR chemical shifts for all the bridged halonium ions studied, calculated using the GIAO method at the B3LYP level, agree quite well with the experimental values. A linear correlation has been found between the calculated halogen binding energies in the halonium ions and the experimental rates of chlorination and bromination of the corresponding alkenes. The computed hydride affinities show that the stability of the cations is systematically stabilized upon increasing the number of methyl substituents, whereas both the hydride affinities and the NICS values for the bridged cations show that the bromo cations are more stable than the analogous chloro and fluoro cations.

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Stereocontrol in cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines

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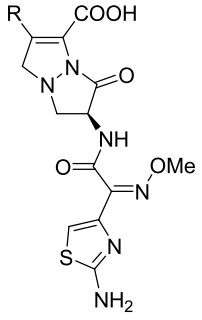
Dedicated to Professor José Elguero, Madrid, Spain, on the occasion of his 70th anniversary

Abstract—Cycloadditions of (1*Z*,4*R**,5*R**)-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines to olefinic dipolarophiles were studied. Stereochemistry of cycloadditions to azomethine imines **3** was found to be controlled by stereodirecting phenyl group at position 3, as well as by the *ortho*-substituents at the aromatic ring at position 1′. The structures of dipoles and products were confirmed by NMR and X-ray diffraction.

1. Introduction

1,3-Dipolar cycloaddition reactions are useful methods for the preparation of five-membered heterocycles, since they enable access to polyfunctional compounds with multiple asymmetric centres, usually with excellent stereocontrol.[1–3] Although asymmetric cycloadditions are well elaborated in chiral nitrone, nitrile oxide, and azomethine ylide series,[4] much less examples of asymmetric cycloadditions to chiral azomethine imines have been reported.[5–13]

The importance of pyrazolidin-3-ones significantly rose in the last two decades, since several pyrazolidin-3-one derivatives exhibit biological activities and applicability in industrial processes.[14–16] Important fused analogs of pyrazolidinones are 2-acylamino-1-oxo-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-7-carboxylates, useful scaffolds for the preparation of conformationally constrained peptidomimetics.[17] Such examples of bicyclic pyrazolidinone peptidomimetics are Eli-Lilly's γ-lactam antibiotics LY 186826, LY 193239, and LY 255262 (Fig. 1).[17–22]



LY 186826 (R = COMe)
LY 193239 (R = SO_2Me)
LY 255262 (R = CN)

Figure 1.

Since the first reports of Dorn[23–25] and Oppolzer,[26,27] 1,3-dipolar cycloaddition of pyrazolidin-3-one derived azomethine imines to acetylenic and olefinic dipolarophiles represent a simple and efficient method for the preparation of substituted 1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-ones. However, most of these studies were performed on achiral dipoles and on poorly substituted chiral azomethine imines.[14,15,17,28,29]

In the course of our studies in the field of 3-pyrazolidinone chemistry,[9,30–35] we have previously reported regio- and stereoselective 1,3-dipolar cycloadditions to polysubstituted racemic (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines **3a–c**,**f** leading to polysubstituted 1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-ones.[9] Similarly, Chuang and Sharpless in racemic pyrazolidin-3-on-1-azomethine imine series,[12] as well as

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Husson, Bonin, Micouin, and co-workers in related nonracemic 1,3,4-oxadiazin-1-azomethine imine series,[11,13] reported high facial selectivity of these 1,3-dipolar cycloadditions.

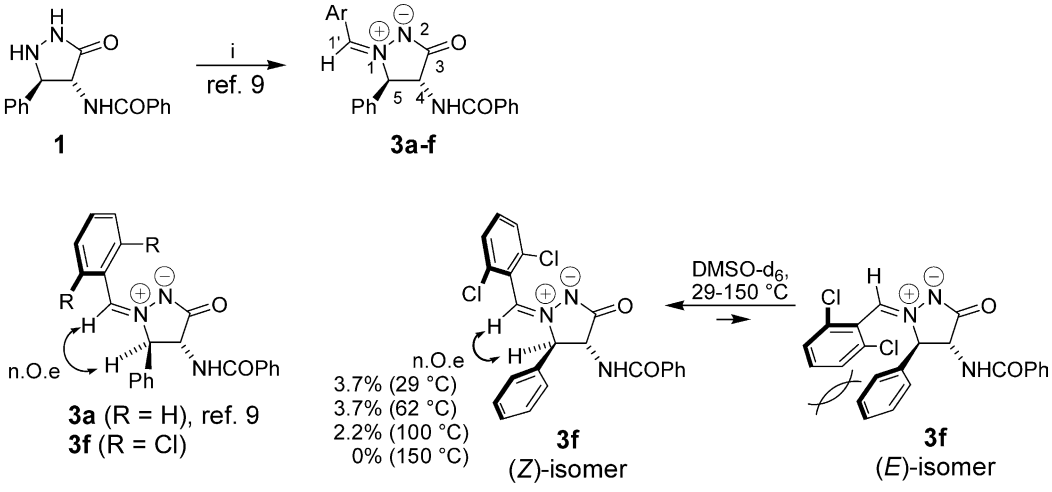
On the other hand, our previous study on the cycloaddition reactions of achiral 1-arylmethylidene-5,5-dimethylpyrazolidin-3-on-1-azomethine imines to methyl propiolate showed that the regioselectivity was strongly dependent on the *ortho*-substituents at the aromatic ring.[34] These results prompted us to investigate also the influence of *ortho*-substituents in chiral racemic (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-one-1-azomethine imines **3a–f** on the stereoselectivity and regioselectivity associated with the 1,3-dipolar cycloaddition process.

In connection with this work, we now report the results of a study, which indicate a strong dependence of diastereoselectivity on the *ortho*-substituents at the aryl residue attached to the C(1′)=N(1) exocyclic double bond in azomethine imines **3a–f**. Generally, cycloadditions of azomethine imines **3a–d**, without *ortho*-substituents at the aryl residue (*ortho*-unsubstituted dipoles), and cycloadditions of azomethine imines **3e**,**f** with two *ortho*-substituents at the aryl residue (*ortho*-disubstituted dipoles), furnished two diastereomerically different types of cycloadducts.

2. Results and discussion

Stable azomethine imines **3a–f** were prepared in 76–93% yields from (4*R**,5*R**)-4-benzoylamino-5-phenyl-3-pyrazolidinone (**1**) and substituted benzaldehydes **2a–f** according to a literature procedure (Scheme 1).[9]

Cycloadditions of azomethine imines **3a–f** were carried out with dimethyl maleate (**4**), dimethyl fumarate (**5**), and methyl acrylate (**6**) as the model dipolarophiles. Cycloadditions of *ortho*-unsubstituted dipoles **3a–d** to dimethyl maleate (**4**) were stereoselective and afforded the cycloadducts **7a–d** with (2*R**,3*R**,5*R**,6*S**,7*R**)-configuration as the single isomers in 49–68% yields. Similarly, reactions of

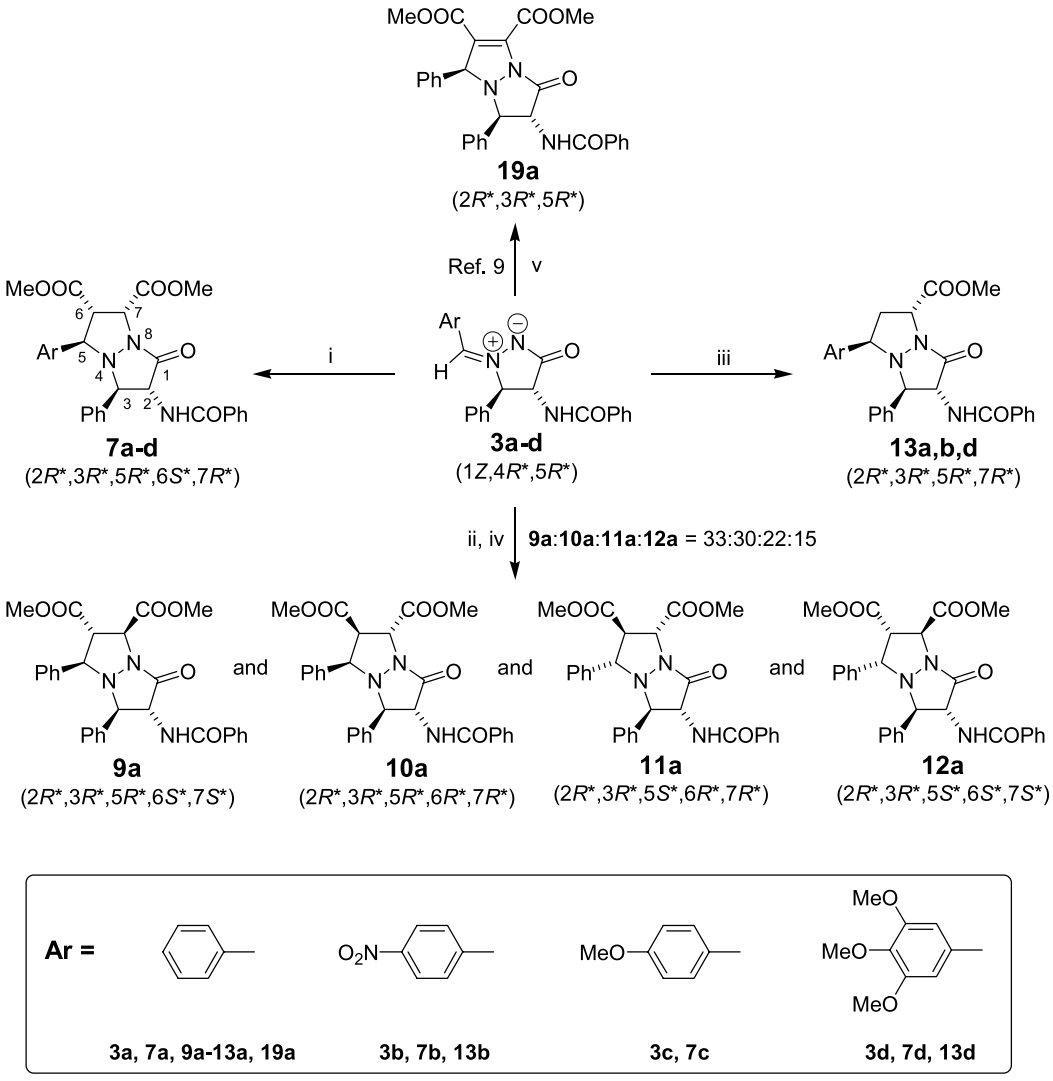


Compound	Ar	Yield (%)	δ (ppm)			J_{H-H} (Hz)	Ref.
			4–H	5–H	1'–H	4–5	
2a, **3a**	phenyl	89	4.65	5.80	7.40	5.2	9
2b, **3b**	4-nitrophenyl	76	4.67	5.90	~7.5[a]	5.6	9
2c, **3c**	4-methoxyphenyl	78	4.64	5.71	7.30	4.9	9
2d, **3d**	3,4,5-trimethoxyphenyl	92	4.61	5.75	7.32	5.1	b
2e, **3e**	2,4,6-trimethylphenyl	93	4.68	5.79	~7.5[a]	5.6	b
2f, **3f**	2,6-dichlorophenyl	88	4.80	5.86	7.41	6.3	9

[a]) Overlapped by signals for aromatic protons.

[b]) This paper.

Scheme 1. Reaction conditions: (i) Ar-CHO (**2a–f**), EtOH, CF_3COOH (cat.), reflux.



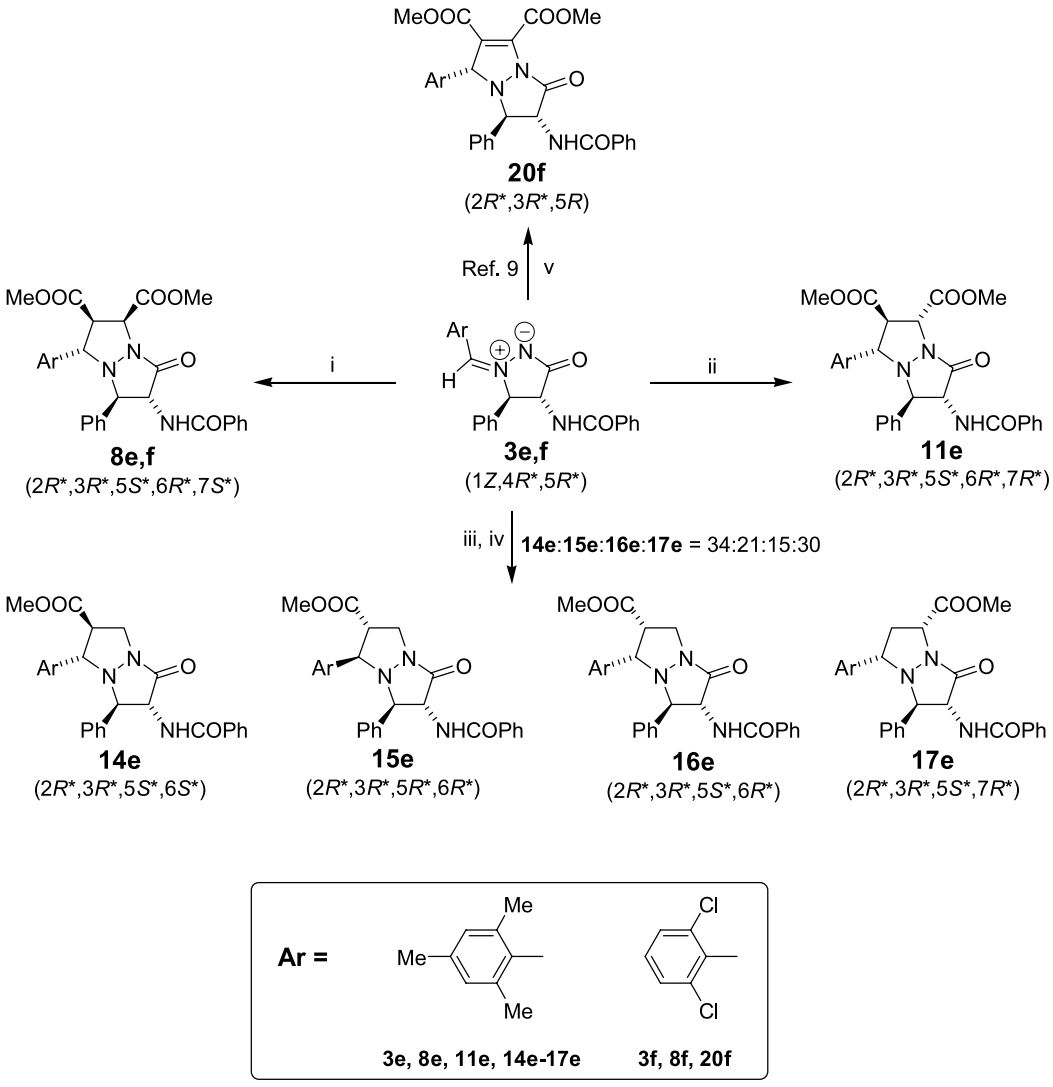
Scheme 2. Reaction conditions: (i) dimethyl maleate (**4**), anisole, reflux; (ii) dimethyl fumarate (**5**), anisole, reflux; (iii) methyl acrylate (**6**), anisole, reflux; (iv) chromatographic separation (CC followed by MPLC); (v) dimethyl acetylenedicarboxylate (**18**), anisole, reflux.

Table 1. Cycloadducts **7**–**17**, **19**, **20**

Compound	Ar	Yield (%)[a]	Configuration
7a	Phenyl	49	2*R**,3*R**,5*R**,6*S**,7*R**
7b	4-Nitrophenyl	55	2*R**,3*R**,5*R**,6*S**,7*R**
7c	4-Methoxyphenyl	49	2*R**,3*R**,5*R**,6*S**,7*R**
7d	3,4,5-Trimethoxyphenyl	68	2*R**,3*R**,5*R**,6*S**,7*R**
8e	2,4,6-Trimethylphenyl	73	2*R**,3*R**,5*S**,6*R**,7*S**
8f	2,6-Dichlorophenyl	81	2*R**,3*R**,5*S**,6*R**,7*S**
9a	Phenyl	22	2*R**,3*R**,5*R**,6*S**,7*S**
10a	Phenyl	22[a]	2*R**,3*R**,5*R**,6*R**,7*R**
11a	Phenyl	18	2*R**,3*R**,5*S**,6*R**,7*R**
11e	2,4,6-Trimethylphenyl	26	2*R**,3*R**,5*S**,6*R**,7*R**
12a	Phenyl	10[a]	2*R**,3*R**,5*S**,6*S**,7*S**
13a	Phenyl	88	2*R**,3*R**,5*R**,7*R**
13b	4-Nitrophenyl	72	2*R**,3*R**,5*R**,7*R**
13d	3,4,5-Trimethoxyphenyl	68	2*R**,3*R**,5*R**,7*R**
14e	2,4,6-Trimethylphenyl	18	2*R**,3*R**,5*S**,6*S**
15e	2,4,6-Trimethylphenyl	15	2*R**,3*R**,5*R**,6*R**
16e	2,4,6-Trimethylphenyl	10	2*R**,3*R**,5*S**,6*R**
17e	2,4,6-Trimethylphenyl	2	2*R**,3*R**,5*S**,7*R**
19a	Phenyl	86[9]	2*R**,3*R**,5*R**[b]
20f	2,6-Dichlorophenyl	77[9]	2*R**,3*R**,5*R**[b]

[a] Isolated as a mixture of **10a** and **12a** in a ratio of 69:31, respectively.

[b] Configurations at C(5) in compounds **19a** and **20f** are formally the same, due to chlorine atoms at the *ortho*-positions, which change the order of priority in compound **20f**. Essentially, the configuration at C(5) in compounds **19a** and **20f** are of the opposite sense.



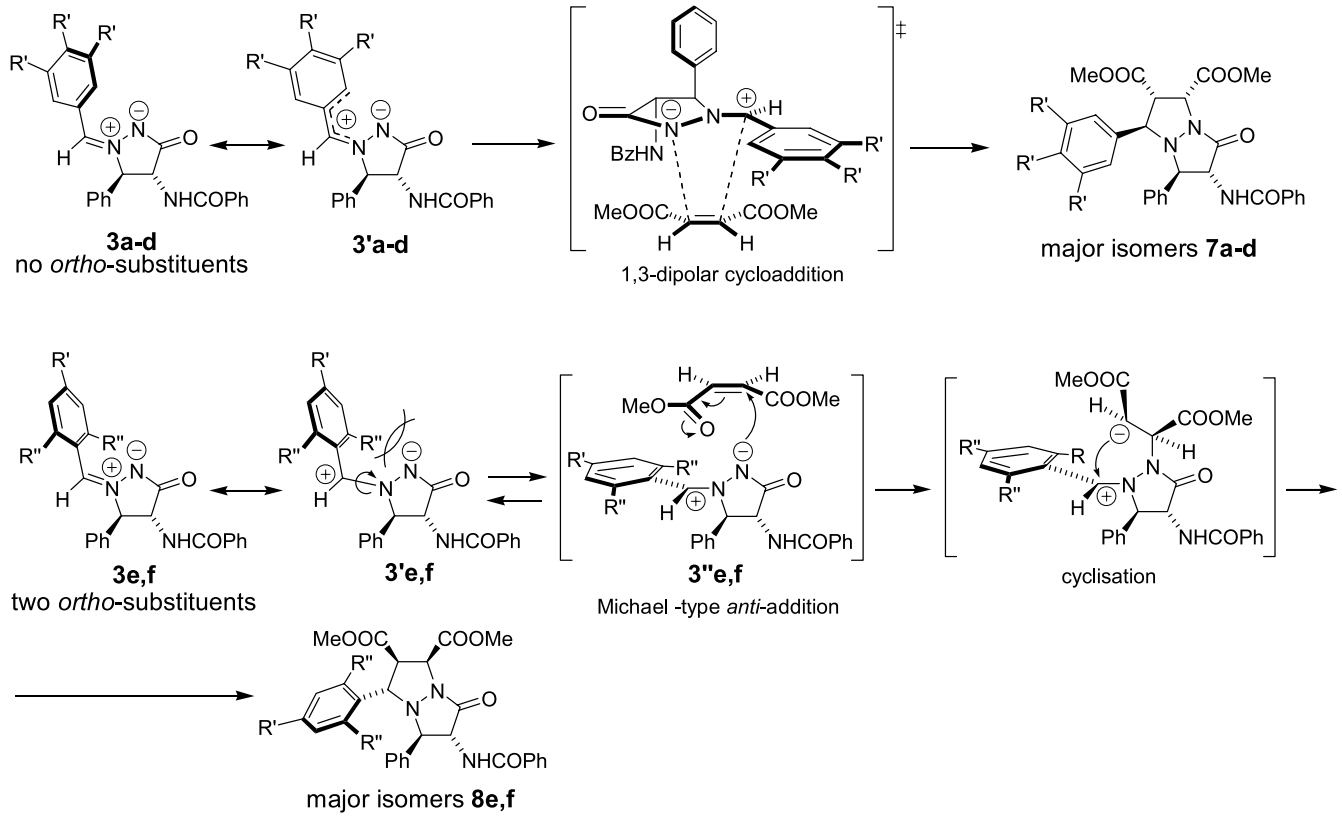
Scheme 3. Reaction conditions: (i) dimethyl maleate (**4**), anisole, reflux; (ii) dimethyl fumarate (**5**), anisole, reflux; (iii) methyl acrylate (**6**), anisole, reflux; (iv) chromatographic separation (CC followed by MPLC); (v) dimethyl acetylenedicarboxylate (**18**), anisole, reflux.

3a,**b**,**d** with methyl acrylate (**6**) proceeded selectively to give the (2*R**,3*R**,5*R**,7*R**)-isomers **13a**,**b**,**d** in 68–88% yields. In contrast, cycloaddition of **3a** to dimethyl fumarate (**5**) was not stereoselective and a mixture of four isomeric cycloadducts **9a**, **10a**, **11a**, and **12a** in a ratio of 33:30:22:15, respectively, was obtained. Isomeric products **9a**–**12a** were separated by column chromatography (CC) followed by medium pressure liquid chromatography (MPLC), to give isomerically pure (2*R**,3*R**,5*R**,6*S**,7*S**)-isomer **9a** in 22% yield, isomerically pure (2*R**,3*R**,5*S**,6*R**,7*R**)-isomer **11a** in 18% yield, and a mixture of isomers **10a** and **12a** in a ratio of 69:31, respectively, in 32% yield. Crystallisation of isomerically enriched compound **10a** from a mixture of ethyl acetate and petroleum ether afforded a few crystals of pure **10a**, which were used for X-ray structure determination (Scheme 2, Table 1).

Reactions of *ortho*-disubstituted azomethine imines **3e**,**f** with dimethyl maleate (**4**) gave, stereoselectively, the (2*R**,3*R**,5*S**,6*R**,7*S**)-isomers **8e** and **8f** in 73 and 81% yield, respectively. Similarly, reaction of **3e** with dimethyl fumarate (**5**) afforded the major (2*R**,3*R**,5*S**,6*R**,7*R**)-isomer **11e** in 26% yield. On the other hand, cycloaddition of **3e** to methyl acrylate (**6**) was not selective and furnished a mixture of four isomeric products **14e**, **15e**, **16e**, and **17e** in a ratio of 34:21:15:30, respectively. The major (2*R**,3*R**,5*S**,6*S**)-isomer **14e** and the minor isomers **15e**–**17e** were separated by chromatography (CC followed by MPLC) to give isomerically pure compounds **14e**–**17e** in 2–18% yields (Scheme 3, Table 1).

In all cases, the ^{1}H NMR spectra of crude reaction mixtures were taken in order to establish stereo- and regioselectivity of cycloadditions. In this manner, ratios of isomers **9a**:**10a**:**11a**:**12a** and **14e**:**15e**:**16e**:**17e** were determined. In ^{1}H NMR spectra of the crude products **7a**–**d**, **8e**–**f**, **11e**, and **13a**,**b**,**d**, no sets of signals corresponding to the minor isomers, could be found. However, this observation does not confirm high stereoselectivity of these reactions, since the possible low-intensity signals of the minor isomers could be overlapped by the signals of impurities, such as unreacted reactants, decomposition products etc.

Concerning the mechanism, we do not have, so far, a firm



Scheme 4.

explanation for stereoselectivity of these cycloaddition reactions. Stereochemical outcome of these reactions was dependent on the aryl residue, *Ar*-C(1′), in dipoles **3a–f**, as well as on the type of the dipolarophile **4–6**. Generally, cycloadditions to dipoles **3a–d** with free *ortho*-positions afforded the major isomers **7**, **9**, and **13** with *syn*-oriented *H*–C(3) and *H*–C(5) and *trans*-oriented *H*–C(5) and *H*–C(6) (cf. Scheme 2), while cycloadditions to dipoles **3e**,**f** with two *ortho*-substituents afforded the major isomers **8**, **11**, and **14** with *anti*-oriented *H*–C(3) and *H*–C(5) and *trans*-oriented *H*–C(5) and *H*–C(6) (cf. Scheme 3). A possible explanation for different stereoselectivity might be exemplified at best by stereoselective cycloadditions of dipoles **3a–f** to dimethyl maleate (**6**). Dipoles **3a–d** with free *ortho*-positions in the aromatic ring can adopt the planar conformation **3′** allowing transition state for the concerted 1,3-dipolar cycloaddition. Consequently, the formation of (2*R**,3*R**,5*R**,6*S**,7*R**)-isomers **7a–d** could be explained by preferential *endo*-approach of **6** from the less hindered face of the (1*Z*,4*R**,5*R**)-dipoles **3a–d** (Scheme 4).[36,37] According to the concerted 1,3-dipolar cycloaddition mechanism, stereoselective formation of (2*R**,3*R**,5*S**,6*R**,7*S**)-isomers **8e**,**f** would be in agreement with the *exo*-approach of the dipolarophile **4** from the less hindered face of the (1*E*,4*R**,5*R**)-dipoles **3e**,**f**. This explanation for formation of isomers **8e**,**f** does not seem suitable for at least two major reasons: (a) both, (*Z*)- and (*E*)-planar conformation of dipoles **3′e**,**f** would be sterically unfavourable due to *ortho*-substituents and (b) the *Z*/*E*-isomerisation of dipole **3f** at 150 °C was not unambiguously established by NMR experiments (cf. Scheme 1, see also 3. Structure determination). Alternatively, stereoselective formation of **8e**,**f** might be explained by a two-step 1,4-addition–cyclization mechanism. In the mesomeric structures **3′e**,**f**, rotation around the N(1)–C(1′) single bond gives the rotamers **3″e**,**f** with the bulky aryl group twisted away from the phenyl ring at position 3. Conformers **3″e**,**f** undergo Michael-type *anti*-addition to the dipolarophile to form the intermediate zwitterions (or biradicals[36,37]), which cyclise into the final products **8e**,**f** (Scheme 4).

Accordingly, cycloadditions of methyl acrylate (**6**) to *ortho*-unsubstituted dipoles **3a**,**b**,**d** might be explained by concerted mechanism, whilst cycloaddition of dimethyl fumarate (**5**) to *ortho*-disubstituted dipole **3e** might be explained by a two-step mechanism. On the other hand, both mechanisms might be involved in the non-selective cycloadditions leading to mixture of isomers **9a–12a** and **14e–17e** (Schemes 2–4).

3. Structure determination

The structures of novel compounds **3d**,**e**, **7b–d**, **8e**,**f**, **9a**,**e**, **10a–12a**, **13a**,**b**,**d**, and **14e–17e** were determined by spectroscopic methods (IR, ^{1}H and ^{13}C NMR, 2D NMR, NOESY spectroscopy, HMBC spectroscopy, MS) and by elemental analyses for C, H, and N. Compounds **3d**, **11e**, **14e**, **16e**, and **17e** were not isolated in analytically pure form. The identities of **3d**, **11e**, **14e**, **16e**, and **17e** were confirmed by ^{13}C NMR and EI-HRMS. ^{13}C NMR characterization of **17e** failed, due to a very small amount of the sample. Compounds **10a** and **12a** were not obtained in

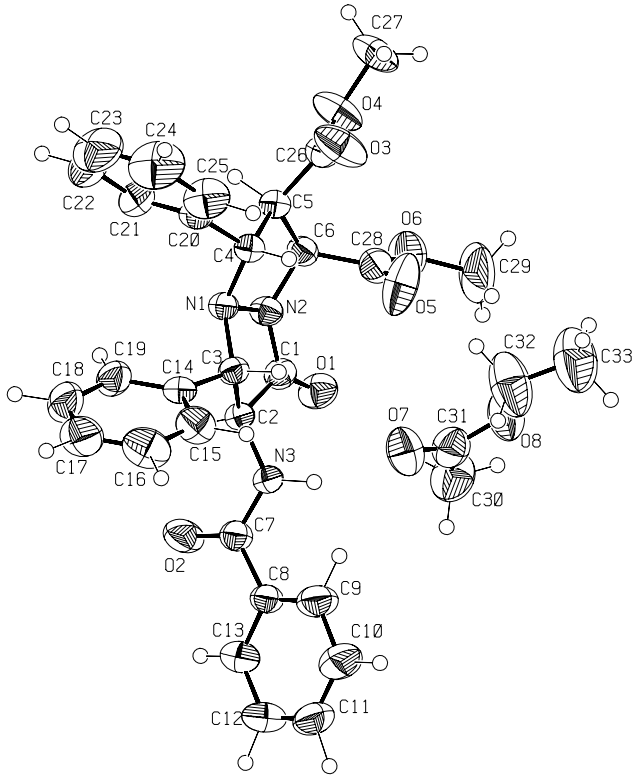


Figure 2. ORTEP view of the molecule of compound **7a** with labelling of nonhydrogen atoms (ellipsoids are drawn at 50% probability level).

isomerically pure form and were characterized only by ^{1}H NMR and NOESY spectroscopy.

The structures of compounds **7a**, **8f**, **10a**, and **11a** were determined by X-ray diffraction (Figs. 2–5).

The (*Z*)-configuration around the exocyclic C(1′)=N(1) double bond for dipoles **3a**[9] and **3f** was determined by

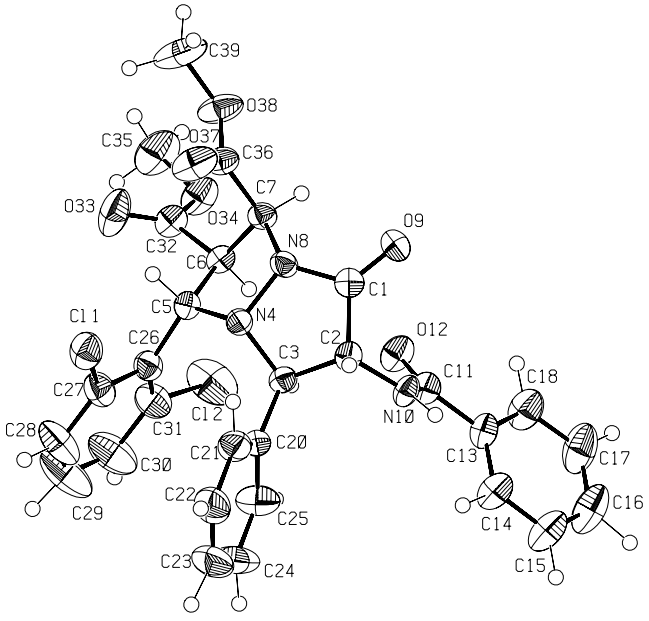


Figure 3. ORTEP view of the molecule of compound **8f** with labelling of nonhydrogen atoms (ellipsoids are drawn at 50% probability level).

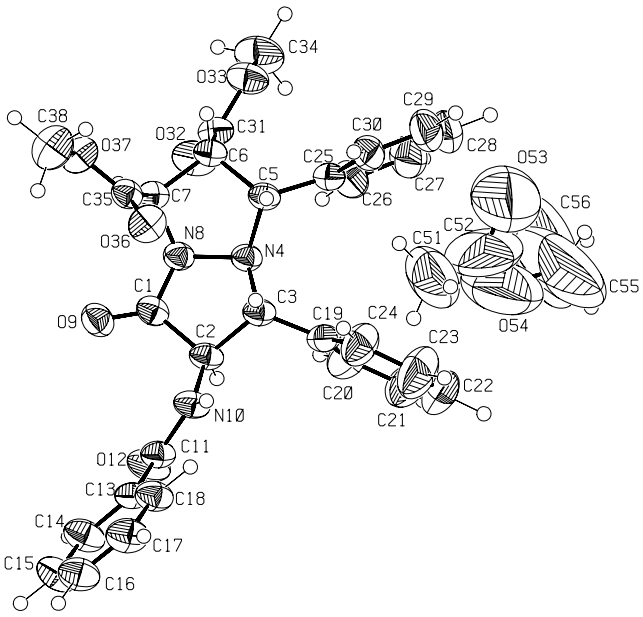


Figure 4. ORTEP view of the molecule of compound **10a** with labelling of nonhydrogen atoms (ellipsoids are drawn at 50% probability level).

NOESY spectroscopy, while the (*Z*)-configuration of other azomethine imines **3b**–**e** was determined by correlation of ^{1}H NMR spectra. In order to establish the *Z*/*E*-isomerisation at elevated temperatures, the ^{1}H NMR and NOESY spectra of **3f** were taken in DMSO-d_6 at 29, 62, 100, and 150 °C. In all four ^{1}H NMR spectra, even at 150 °C, a single set of signals supported retention of the (*Z*)-configuration. On the other hand, decreasing intensity of NOE between *H*–C(1′) and *H*–C(5): from 3.7% (29 and 62 °C) to 2.2% (100 °C), and 0% (150 °C) indicated, that *Z*/*E*-isomerisation might be possible at temperatures above 100 °C. Lower stability of the (*E*)-isomer could be explained by steric repulsion between the two bulky *syn*-oriented aryl groups, while, in the (*Z*)-isomer, these two groups are *anti*-oriented (Scheme 1).

Regiochemistry of cycloadducts **13**–**17** was established by ^{1}H NMR on the basis of chemical shifts for COOMe and

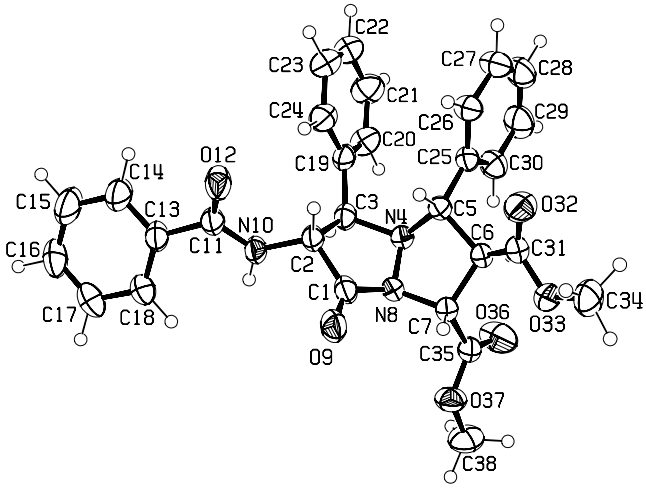


Figure 5. ORTEP view of the molecule of compound **11a** with labelling of nonhydrogen atoms (ellipsoids are drawn at 50% probability level).

Table 2. Characteristic ^{1}H NMR and NOESY data for dimethyl 1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylates **7–20**

	δH [ppm]						*J*$_{H-H}$ [Hz]			NOE (%)[a]	
	2	3	5	6	7	6,7-COOMe	2–3	5–6	6–7	3···5	5···6
7a	5.57	4.37	4.38	3.86	4.82	3.59, 3.85	12.0	11.0	8.8		
7b	5.60	4.45	4.55	~3.8[b]	4.86	3.61, 3.85	12.1	10.9	8.7	6.4	0
7c	5.54	4.32	4.34	3.81	4.81	3.65, 3.85	12.1	10.9	8.7		
7d	5.62	4.37	4.33	~3.8[b]	4.81	3.66, 3.93	11.9	11.0	9.0		
8e	4.92	4.39	4.99	4.30	5.01	3.58, 3.83	5.6	10.2	9.4	0	0
8f	5.16	4.33	5.28	4.77	5.80	3.68, 3.85	9.8	9.0	8.7	0	0
9a	4.81	4.44	4.33	3.73	5.25	3.73, 3.87	8.7	9.0	6.2	5.0	0
10a	5.56	4.20	4.44	3.62	4.85	3.28, 3.92	11.7	7.2	2.3	8.6	8.1
11a	5.78	4.87	3.99	3.70	5.07	3.67, 3.90	9.8	7.9	5.3	0	0
11e	5.67	4.80	4.29	3.85	5.12	3.63, 3.88	7.9	9.0	5.3	0	0
12a	5.18	3.73	4.62	4.32	5.43	3.36, 3.89	9.4	7.5	7.5	0	6.7
19a[9]	5.27	4.67	5.51				11.5			6.9	—
20f[9]	5.39	4.29	6.48				10.9			0	—

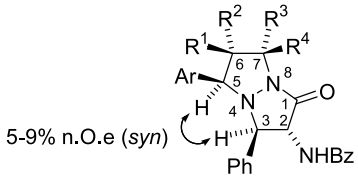
	δH [ppm]							*J*$_{H-H}$ [Hz]				NOE (%)[a]	
	2	3	5	6a	6b	7	COO-Me	2–3	5–6a	5–6b	6a–7	6b–7	3···5	5···MeO
13a	5.51	4.28	4.08	2.59	2.81	4.58	3.88	12.4	5.3	11.3	1.1	9.2	5.4	9.1
13b	5.58	4.31	4.23	2.65	2.76	4.60	3.90	12.1	5.9	11.1	1.8	8.7		
13d	5.53	4.26	4.05	2.59	2.76	4.56	3.89	12.1	5.3	11.3	1.1	9.2		
17e	5.56	4.74	4.00	2.52	2.81	4.72	3.84	6.4	10.6	7.5	6.4	10.4	0	0

	δH [ppm]							*J*$_{H-H}$ [Hz]				NOE (%)[a]	
	2	3	5	6	7a	7b	COO-Me	2–3	5–6	6–7a	6–7b		3···5	5···6
14e	5.58	4.78	4.54	3.60	3.86	4.19	3.65	9.4	7.9	9.4	5.2		0	0
15e	4.89	4.33	4.80	3.76	3.88	4.35	3.71	7.2	8.5	10.0	4.9		7.4	0
16e	5.54	4.73	4.35	3.60	4.10	4.13	3.21	6.8	10.5	7.0	9.0		0	5.4

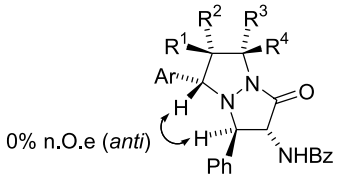
[a] Relative intensity with respect to −100% intensity of the irradiated proton.
[b] Overlapped by signal for 7-COOMe.

CH_2 protons with typical *δ* values 3.2–3.7 ppm (6-COOMe), 3.8–3.9 ppm (7-COOMe), 2.5–2.8 ppm (6-CH_2, 2×ddd), and 3.8–4.2 ppm (7-CH_2, 2×dd). Accordingly, in compounds **14–16** the COOMe is attached at position 6, while in compounds **13** and **17** the COOMe group is attached at position 7 (Table 2).

The configuration at the newly formed stereocenters at positions 5–7 was essential for structure determination of compounds **7–17**. First, the configuration at position 5 in the representative compounds **7b**, **8e**,**f**, **9a**, **10a**, **11a**,**e**, **13a**, and **14e–17e** was established on the basis of NOE between *H*–C(3) and *H*–C(5). In compounds **7b**, **9a**, **10a**, **13a**, and

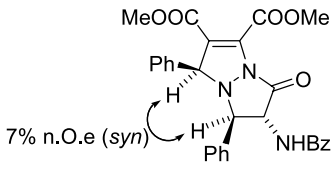


Compounds **7b**, **9a**, **10a**, **13a**, **15e**
rel-(3*R*,5*R*)

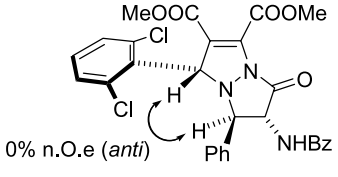


Compounds **8e,f**, **11a,e**, **12a**, **14e**, **16e**, **17e**
rel-(3*R*,5*S*)

R^1-R^4 = H, COOMe



Compound **19a**
rel-(3*R*,5*R*)



Compound **20f**
rel-(3*R*,5*R*)

Figure 6.

15e, NOE supported the *syn*-orientation between *H*–C(3) and *H*–C(5) and, consequently, the (3*R**,5*R**)-configuration. Accordingly, the (3*R**,5*S**)-configuration was assigned to compounds **8e**,**f**, **11a**,**e**, **12a**, **14e**, **16e**, and **17e**, where no NOE between the *anti*-oriented *H*–C(3) and *H*–C(5) was observed (Fig. 6, Table 2).

The configuration at positions 6 and 7 was established on the basis of vicinal coupling constants, $^{3}J_{H5–H6}$ and $^{3}J_{H6–H7}$, by chemical shifts for 6-COOMe protons, as well as by NOESY spectroscopy. Coupling constants, $J_{H5–H6}$ in compounds **7a–d**, **8e**,**f**, **9a–12a**, **13a**,**b**,**d**, **14e–17e** showed the following characteristic values: (a) $J_{H5–H6}=5.3–7.5$ Hz (*cis*)$<J_{H5–H6}=7.9–11.3$ Hz (*trans*) and (b) $J_{H6–H7}=8.7–10.4$ Hz (*cis*)$>J_{H6–H7}=1.1–7.5$ Hz (*trans*). An exception was compound **16e** with a coupling constant, $J_{H5–H6}=10.5$ Hz, for the *cis*-oriented *H*–C(5) and *H*-(6). Interestingly, in compounds **10a**, **12a**, and **16e** with a *cis*-configuration around the C(5)–C(6) bond typical chemical shift for 6-COOMe group was $\delta=3.21–3.36$ ppm, whilst in compounds **7a–d**, **8e**,**f**, and **9a** with *trans*-configuration around the C(5)–C(6) bond typical chemical shift 3.6–3.7 ppm was observed for the 6-COOMe group. In addition to this, the relative configurations at positions 6 and 7 in

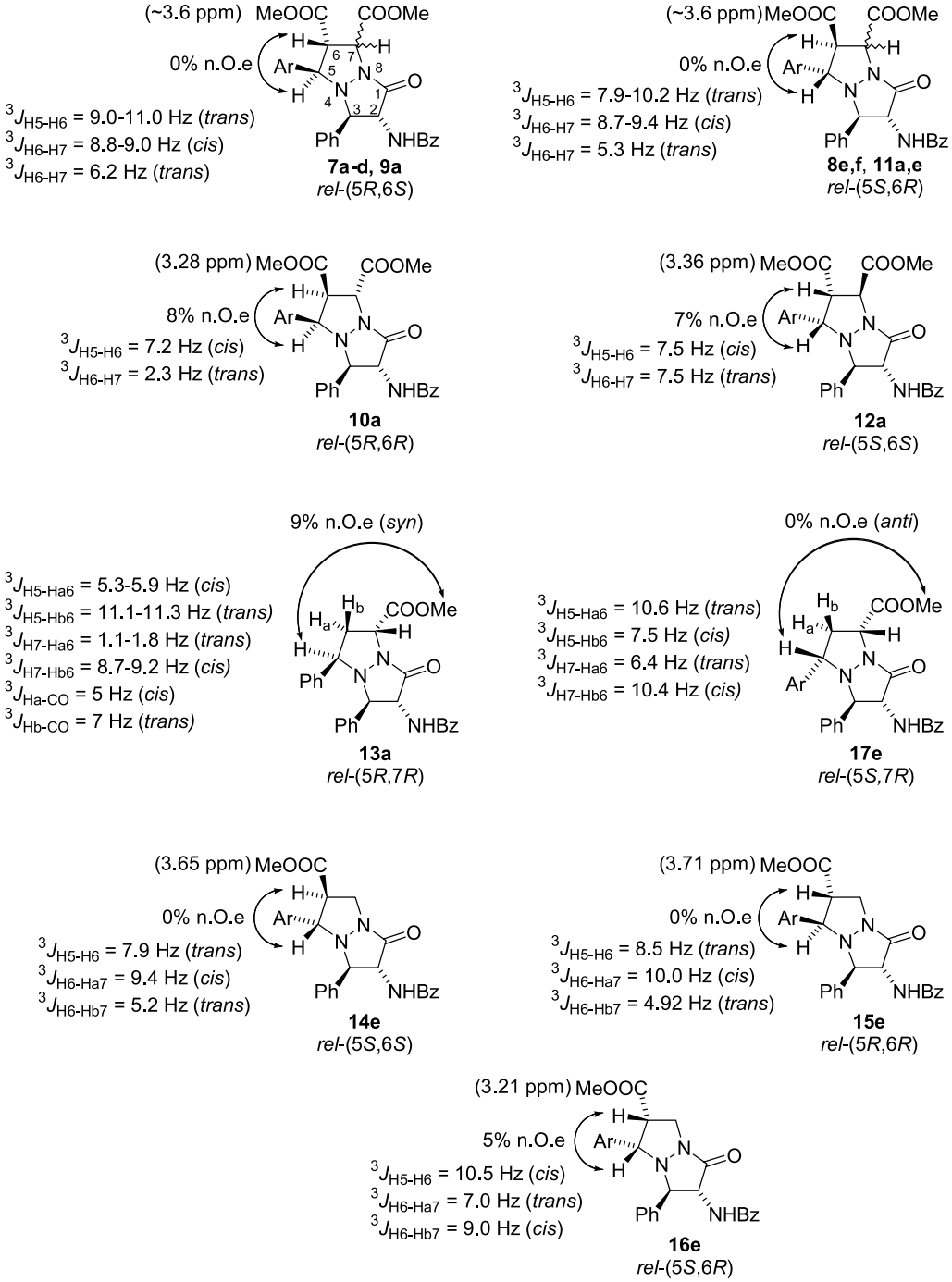


Figure 7.

compounds **7b**, **8e**,**f**, **9a**–**12a**, **13a**,**b**,**d**, and **14e**–**17e** were confirmed by NOESY spectroscopy. Furthermore, the magnitudes of heteronuclear coupling constants,[38–41] $^{3}J_{Hb6-CO}=7$ Hz (*trans*)$>{}^{3}J_{Ha6-CO}=5$ Hz (*cis*), in compound **13a** were also in agreement with the (5*R**,7*R**)-configuration (Fig. 7, Table 2).

Since our previous assignment of configuration of compound **7a** was erroneous,[9] we reinvestigated the configuration of compounds **19a** and **20f**, which were also prepared previously from dipoles **3a**,**f** and dimethyl acetylenedicarboxylate (**18**) (Schemes 2 and 3).[9] Compound **19a** and related *ortho*-unsubstituted cycloadducts exhibit typical chemical shift $\delta\sim5.5$ ppm for *H*–C(5), while in *ortho*-disubstituted compound **20f** chemical shift δ for this proton is 6.48 ppm.[9] Configuration at C(5) in cycloadducts **19a** and **20f** was determined by NOESY spectroscopy. A strong NOE between *H*–C(3) and *H*–C(5) in **19a** was in agreement with previously established (2*R**,3*R**,5*R**)-configuration,[9] whilst in compound **20f**, absence of NOE indicated the opposite sense of configuration at C(5) (Fig. 6, Table 2).

4. Conclusion

The stereochemistry of cycloadditions to azomethine imines **3** is apparently controlled by a stereodirecting phenyl group at position 3, as well as by the *ortho*-substituents at the aromatic ring at position 1′. Experimental evidence on the stereocontrol might be summarized in the following way:

(a) *ortho*-Unsubstituted dipoles **3a**–**d** favoured formation of the major isomers **7a**–**d**, **9a**, **13a**,**b**,**d**, and **19a** with *syn*-oriented *H*–C(3) and *H*–C(5).
(b) *ortho*-Disubstituted dipoles **3e**,**f** favoured formation of the major isomers **8e**,**f**, **11e**, **14e**, and **20f** with *anti*-oriented *H*–C(3) and *H*–C(5).
(c) In all major isomers **7a**–**d**, **8e**,**f**, **9a**, **11e**, and **14e** with a stereocenter at position 6, the *H*–C(5) and *H*–C(6) were always *trans*-oriented, regardless of the substituents at the *Ar*-C(1′) group.
(d) Cycloadditions to dimethyl maleate (**4**) were stereoselective, regardless of the substituents at the *Ar*-C(1′) group of dipole **3**.
(e) Cycloaddition to dimethyl fumarate (**5**) was stereoselective in the case of *ortho*-disubstituted dipole **3e** and non-stereoselective in the case of *ortho*-unsubstituted dipole **3a**.
(f) Cycloadditions to methyl acrylate (**6**) were selective in the case of *ortho*-unsubstituted dipoles **3a**,**b**,**d** and non-selective in the case of *ortho*-disubstituted dipole **3e**.

The results of this study indicate, that by suitable choice and combination of azomethine imines **3** and dipolarophiles, it might be possible to carry out stereoselective diversity-oriented synthesis of 2-acylamino-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazolone-7-carboxylates with variable, yet predictable, configurations. Our current work in this field is focused on extension towards the synthesis of combinatorial libraries of fused pyrazolone peptidomimetics.

5. Experimental

5.1. General

Melting points were determined on a Kofler micro hot stage. The 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 DMSO-d_6 and $CDCl_3$ with TMS as the internal standard, as solvents. The magnitudes of the long range ^{13}C–^{1}H heteronuclear coupling constants, $^{3}J_{C-H}$, were measured by Keeler's method[42,43] from the HMBC correlation spectra. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. Column chromatography was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). Medium pressure liquid chromatography (MPLC) was performed with a Büchi isocratic system with detection on silica gel (Merck, silica gel 60, 0.015–0.035 mm); column dimensions (dry filled): 15×460 mm; backpressure: 10–15 bar; detection: UV 254 nm; sample amount: 100–150 mg of isomeric mixture per each run. The de and the isomer ratios were determined from ^{1}H NMR spectra of the crude reaction mixtures.

Aromatic aldehydes **2a**–**f**, dimethyl maleate (**4**), dimethyl fumarate (**5**), methyl acrylate (**6**), and dimethyl acetylenedicarboxylate (**18**) are commercially available (Fluka AG). (4*R**,5*R**)-4-Benzoylamino-5-phenylpyrazolidin-3-one (**1**), azomethine imines **3a**–**c**,**f**, and cycloadducts **19a** and **20f** were prepared according to the literature procedures.[9]

5.2. General procedure for the synthesis of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-5-phenylpyrazolidin-3-on-1-azomethine imines 3d and 3e

Compounds **3d**,**e** were prepared from (4*R**,5*R**)-4-benzoylamino-5-phenylpyrazolidin-3-one (**1**) and aldehydes **2d**,**e** according to the slightly modified literature procedure.[9] A mixture of **1** (1.4 g, 5 mmol), aldehyde **2d**,**e** (6 mmol), and anhydrous ethanol (20 mL) was heated under reflux for 5 min. Trifluoroacetic acid (10 drops) was added through a reflux condenser, the mixture was heated under reflux for 1 h, and cooled to rt. The precipitate was collected by filtration and washed with Et_2O (15 mL). Compounds **3d** and **3e** were prepared in this manner.

5.2.1. (1*Z*,4*R,5*R**)-4-Benzoylamino-5-phenyl-1-(3,4,5-trimethoxybenzylidene)pyrazolidin-3-on-1-azomethine imine (3d).** This compound was prepared from **1** (1.4 g, 5 mmol) and 3,4,5-trimethoxybenzaldehyde (**2d**) (1.17 g, 6 mmol). Yield: 2.12 g (92%) of a white solid, mp 187–190 °C. EI-MS: $m/z=459$ (M^+). ^{1}H NMR (DMSO-d_6): δ 3.75 (3H, s, OMe); 3.80 (s, 6H, 2×OMe); 4.61 (dd, 1H, $J=5.1$, 7.7 Hz, 4-H); 5.75 (d, 1H, $J=5.4$ Hz, 5-H); 7.32 (s, 1H, 1′-H); 7.51 (m, 8H, 8H of Ph); 7.83 (m, 2H, 2H of Ar); 7.86 (d, 2H, $J=8.3$ Hz, 2H of Ph); 9.21 (d, 1H, $J=7.5$ Hz, NH). ^{13}C NMR ($CDCl_3$): δ 56.2, 59.0, 60.4, 77.2, 98.7, 109.6, 125.0, 127.3, 127.5, 128.5, 129.2, 129.6, 131.8, 133.6, 138.1, 140.9, 152.8, 166.4, 179.4. (Found: C, 67.03; H, 5.54; N, 9.00. $C_{26}H_{25}N_3O_5$ requires: C, 67.96; H, 5.48; N, 9.14.); EI-HRMS: $m/z=459.1794$ (M^+); $C_{26}H_{25}N_3O_5$ requires: $m/z=459.1805$ (M^+); ν_{max} (KBr) 3247, 1665, 1597 cm^{-1}.

5.2.2. (1*Z*,4*R,5*R**)-4-Benzoylamino-5-phenyl-1-(2,4,6-trimethylbenzylidene)pyrazolidin-3-one-1-azomethine imine (3e).** This compound was prepared from **1** (1.4 g, 5 mmol) and 2,4,6-trimethylbenzaldehyde (**2e**, 0.88 g, 6 mmol). Yield: 1.92 g (93%) of a white solid, mp 275–277 °C. ^{1}H NMR (DMSO-d_6): δ 2.10 (s, 6H, 2×Me); 2.25 (3H, s, Me); 4.68 (dd, 1H, J=5.6, 7.9 Hz, 4-H); 5.79 (d, 1H, J=5.6 Hz, 5-H); 6.89 (s, 2H, C_6H_2); 7.48 (m, 9H, 8H of Ph, 1′-H); 7.89 (d, 2H, J=7.9 Hz, 2H of Ph); 9.20 (d, 1H, J=7.5 Hz, NH). (Found: C, 76.00; H, 6.27; N, 10.34. $C_{26}H_{25}N_3O_2$ requires: C, 75.89; H, 6.12; N, 10.21.); ν_{max} (KBr) 3228, 1679, 1659 cm^{-1}.

5.3. General procedure for the preparation of cycloadducts 7a–d, 8e,f, and 13a,b,d

A mixture of azomethine imine **3** (1 mmol), dipolarophile **4** (173 mg, 1.2 mmol) or **6** (103 mg, 1.2 mmol), and anisole (4 mL) was heated under reflux for 4 h. Anisole was evaporated in vacuo to ½ of the initial volume (~2 mL), Et_2O (5 mL) was added, and the precipitate was collected by filtration. Compounds **7a–d**, **8e**,**f**, and **13a**,**b**,**d** were prepared in this manner.

5.3.1. Dimethyl (2*R,3*R**,5*R**,6*S**,7*R**)-2-benzoylamino-3,5-diphenyl-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazole-6,7-dicarboxylate (7a).** Prepared from **4** and **3a** (369 mg, 1 mmol). Yield: 254 mg (49%) of a white solid, lit.[9] yield 64%; mp 190–193 °C; lit.[9] mp 188–190 °C. ^{1}H NMR ($CDCl_3$): δ 3.59 (3H, s, 6-COOMe); 3.85 (3H, s, 7-COOMe); 3.86 (1H, dd, J=8.8, 11.0 Hz, 6-H); 4.37 (1H, d, J=12.0 Hz, 3-H); 4.38 (1H, d, J=10.9 Hz, 5-H); 4.82 (1H, d, J=8.7 Hz, 7-H); 5.57 (1H, dd, J=8.3, 12.1 Hz, 2-H); 6.72 (1H, d, J=8.7 Hz, NH); 6.95–7.05 (6H, m, 6H of Ph); 7.10–7.22 (4H, m, 4H of Ph); 7.30–7.38 (2H, m, 2H of Ph); 7.40–7.50 (1H, m, 1H of Ph); 7.65–7.72 (2H, m, 2H of Ph).

5.3.2. Dimethyl (2*R,3*R**,5*R**,6*S**,7*R**)-2-benzoylamino-5-(4-nitrophenyl)-3-phenyl-1-oxotetra-hydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (7b).** Prepared from **4** and **3b** (414 mg, 1 mmol). Yield: 307 mg (55%) of a yellowish solid; mp 178–181 °C. ^{1}H NMR ($CDCl_3$): δ 3.61 (3H, s, 6-COOMe); 3.77–3.90 (1H, m, 7-COOMe, 6-H); 4.45 (1H, d, J=12.1 Hz, 3-H); 4.55 (1H, d, J=10.9 Hz, 5-H); 4.86 (1H, d, J=8.7 Hz, 7-H); 5.60 (1H, dd, J=8.3, 12.1 Hz, 2-H); 6.93 (1H, d, J=8.3 Hz, NH); 6.95–7.06 (3H, m, 3H of Ar); 7.16–7.24 (2H, m, 2H of Ar); 7.25–7.48 (5H, m, 5H of Ar); 7.67 (2H, br d, J=7.5 Hz, 2H of Ar); 7.87 (2H, d, J=8.3 Hz, 2H of Ar). (Found: C, 61.96; H, 4.66; N, 10.31. $C_{29}H_{26}N_3O_6$ requires: C, 62.36; H, 4.69; N, 10.03.); ν_{max} (KBr) 3307, 1744, 1710, 1665, 1645 cm^{-1}.

5.3.3. Dimethyl (2*R,3*R**,5*R**,6*S**,7*R**)-2-benzoylamino-5-(4-methoxyphenyl)-1-oxo-3-phenyltetra-hydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (7c).** Prepared from **4** and **3c** (399 mg, 1 mmol). Yield: 266 mg (49%) of a white solid; mp 213–216 °C. ^{1}H NMR ($CDCl_3$): δ 3.59 (3H, s, Ar-OMe); 3.65 (3H, s, 6-COOMe); 3.81 (1H, dd, J=8.7, 10.9 Hz, 6-H); 3.85 (3H, s, 7-COOMe); 4.32 (1H, d, J=12.1 Hz, 3-H); 4.34 (1H, br d, J=10.9 Hz, 5-H); 4.81 (1H, dd, J=0.8, 8.7 Hz, 7-H); 5.54 (1H, dd, J=8.7, 12.1 Hz, 2-H); 6.54 (2H, dd, J=2.3, 6.8 Hz, 2H of Ar); 6.58 (1H, d, J=8.3 Hz, NH); 6.97–7.08 (5H, m, 5H of Ar); 7.14–7.22 (2H, m, 2H of Ar); 7.33–7.49 (3H, m, 3H of Ar); 7.68–7.74 (2H, m, 2H of Ar). (Found: C, 66.15; H, 5.58; N, 8.02. $C_{30}H_{29}N_3O_7$ requires: C, 66.29; H, 5.38; N, 7.73.); ν_{max} (KBr) 3415, 1750, 1713, 1665 cm^{-1}.

5.3.4. Dimethyl (2*R,3*R**,5*R**,6*S**,7*R**)-2-benzoylamino-1-oxo-3-phenyl-5-(3,4,5-trimethoxyphenyl)-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (7d).** Prepared from **4** and **3d** (460 mg, 1 mmol). Yield: 412 mg (68%) of a white solid; mp 241–244 °C. ^{1}H NMR ($CDCl_3$): δ 3.62 and 3.66 (6H, 2 s, 1:1, 2×OMe); 3.74–3.83 (7H, m, 2×OMe, 6-H); 3.93 (3H, s, OMe); 4.33 (1H, d, J=11.0 Hz, 5-H); 4.37 (1H, d, J=11.9 Hz, 3-H); 4.81 (1H, br d, J=9.0 Hz, 7-H); 5.62 (1H, dd, J=8.7, 11.9 Hz, 2-H); 6.42 (2H, s, C_6H_2); 6.93 (1H, d, J=8.6 Hz, NH); 7.16–7.25 (3H, m, 3H of Ph); 7.29–7.48 (5H, m, 5H of Ph); 7.67–7.73 (2H, m, 2H of Ph). (Found: C, 63.44; H, 5.50; N, 7.14. $C_{32}H_{33}N_3O_9$ requires: C, 63.67; H, 5.51; N, 6.96.); ν_{max} (KBr) 3400, 1748, 1708, 1664 cm^{-1}.

5.3.5. Dimethyl (2*R,3*R**,5*S**,6*R**,7*S**)-2-benzoylamino-1-oxo-3-phenyl-5-(2,4,6-trimethylphenyl)-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (8e).** Prepared from **4** and **3e** (412 mg, 1 mmol). Yield: 406 mg (73%) of a white solid; mp 240–244 °C. ^{1}H NMR ($CDCl_3$): δ 1.47, 2.16, and 2.58 (9H, 3 s, 1:1:1, 3×Ar-Me); 3.58 (3H, s, 6-COOMe); 3.83 (3H, s, 7-COOMe); 4.30 (1H, dd, J=9.4, 10.2 Hz, 6-H); 4.39 (1H, d, J=5.6 Hz, 3-H); 4.99 (1H, d, J=10.2 Hz, 5-H); 4.92 (1H, dd, J=5.6, 6.8 Hz, 2-H); 5.01 (1H, d, J=9.4 Hz, 7-H); 6.49 and 6.77 (2H, 2 br s, 1: 1, C_6H_2); 7.10 (1H, d, J=6.8 Hz, NH); 7.13–7.26 (5H, m, 5H of Ph); 7.33–7.49 (3H, m, 3H of Ph); 7.70–7.75 (2H, m, 2H of Ph). (Found: C, 68.91; H, 6.06; N, 7.73. $C_{32}H_{33}N_3O_6$ requires: C, 69.17; H, 5.99; N, 7.56.); ν_{max} (KBr) 3286, 1755, 1736, 1734 cm^{-1}.

5.3.6. Dimethyl (2*R,3*R**,5*S**,6*R**,7*S**)-2-benzoylamino-5-(2,6-dichlorophenyl)-1-oxo-3-phenyl-tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (8f).** Prepared from **4** and **3f** (438 mg, 1 mmol). Yield: 472 mg (81%) of a white solid; mp 109–111 °C. ^{1}H NMR ($CDCl_3$): δ 3.68 (3H, s, 6-COOMe); 3.85 (3H, s, 7-COOMe); 4.33 (1H, d, J=9.8 Hz, 3-H); 4.77 (1H, dd, J=8.7, 9.0 Hz, 6-H); 5.16 (1H, dd, J=7.5, 9.8 Hz, 2-H); 5.28 (1H, d, J=9.0 Hz, 5-H); 5.80 (1H, d, J=8.7 Hz, 7-H); 6.51 (1H, d, J=7.5 Hz, NH); 7.03–7.08 (1H, m, 1H of Ar); 7.11–7.20 (5H, m, 5H of Ar); 7.24–7.37 (4H, m, 4H of Ar); 7.39–7.53 (1H, m, 1H of Ar); 7.64–7.70 (2H, m, 2H of Ar). (Found: C, 59.92; H, 4.36; N, 7.25. $C_{29}H_{25}ClN_3O_6$ requires: C, 59.80; H, 4.33; N, 7.21.); ν_{max} (KBr) 3316, 1744, 1713, 1667, 1647 cm^{-1}.

5.3.7. Methyl (2*R,3*R**,5*S**,7*R**)-2-benzoylamino-3,5-diphenyl-1-oxotetrahydro-1*H*,5*H*-pyrazolo-[1,2-*a*]pyrazole-7-carboxylate (13a).** Prepared from **6** and **3a** (369 mg, 1 mmol). Yield: 236 mg (46%) of a white solid; mp 169–174 °C. ^{1}H NMR ($CDCl_3$): δ 2.59 (1H, ddd, J=1.1, 5.3, 13.2 Hz, 6-Ha); 2.81 (1H, ddd, J=9.2, 11.3, 13.2 Hz, 6-Hb); 3.88 (3H, s, 7-COOMe); 4.08 (1H, dd, J=5.3, 11.3 Hz, 5-H); 4.28 (1H, d, J=12.4 Hz, 3-H); 4.58 (1H, dd, J=1.1, 9.0 Hz, 7-H); 5.51 (1H, ddd, J=0.8, 8.3, 12.1 Hz, 2-H); 6.81 (1H, br d, J=8.7 Hz, NH); 6.97–7.48 (13H, m, 13H of Ph); 7.67–7.75 (2H, m, 2H of Ph). ^{13}C NMR

($CDCl_3$): δ 42.8, 53.0, 53.7, 61.4, 68.7, 127.25, 127.33, 127.38, 127.44, 127.50, 127.65, 127.75, 127.80, 127.89, 127.94, 128.00, 128.1, 128.2, 131.5, 133.3, 135.0, 135.9, 163.2, 167.0, 170.2. (Found: C, 71.14; H, 5.56; N, 9.03. $C_{27}H_{25}N_3O_4$ requires: C, 71.19; H, 5.53; N, 9.22.); ν_{max} (KBr) 3415, 1745, 1710, 1650 cm^{-1}.

5.3.8. Methyl (2*R,3*R**,5*S**,7*R**)-2-benzoylamino-5-(4-nitrophenyl)-1-oxo-3-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-7-carboxylate (13b).** Prepared from **6** and **3b** (414 mg, 1 mmol). Yield: 360 mg (72%) of a white solid; mp 237–243 °C. ^1H NMR ($CDCl_3$): δ 2.65 (1H, ddd, J=1.7, 5.8, 13.6 Hz, 6-Ha); 2.76 (1H, ddd, J=8.7, 10.9, 13.6 Hz, 6-Hb); 3.90 (3H, s, 7-COOMe); 4.23 (1H, dd, J=5.9, 11.1 Hz, 5-H); 4.31 (1H, d, J=12.1 Hz, 3-H); 4.60 (1H, dd, J=1.9, 7.5 Hz, 7-H); 5.58 (1H, br dd, J=8.7, 12.1 Hz, 2-H); 6.72 (1H, br d, J=7.9 Hz, NH); 7.00–7.06 (3H, m, 3H of Ar); 7.19–7.24 (3H, m, 3H of Ph); 7.26–7.33 (2H, m, 2H of C_6H_4); 7.35–7.41 (1H, m, 1H of Ph); 7.41–7.49 (1H, m, 1H of Ph); 7.68–7.73 (2H, m, 2H of Ph); 7.86–7.92 (2H, m, 2H of C_6H_4). (Found: C, 64.50; H, 4.74; N, 11.59. $C_{27}H_{24}N_4O_6$ requires: C, 64.79; H, 4.83; N, 11.19.); ν_{max} (KBr) 3326, 1748, 1710, 1665 cm^{-1}.

5.3.9. Methyl (2*R,3*R**,5*S**,7*R**)-2-benzoylamino-3-phenyl-5-(3,4,5-trimethoxyphenyl)-1-oxotetra-hydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-7-carboxylate (13d).** Prepared from **6** and **3d** (460 mg, 1 mmol). Yield: 370 mg (68%) of a white solid; mp 220–224 °C. ^1H NMR ($CDCl_3$): δ 2.59 (1H, ddd, J=1.1, 5.3, 13.2 Hz, 6-Ha); 2.76 (1H, ddd, J=9.2, 11.3, 13.2 Hz, 6-Hb); 3.68 (9H, br s, 3×MeO-Ar); 3.89 (3H, s, 7-COOMe); 4.05 (1H, dd, J=5.3, 11.3 Hz, 5-H); 4.26 (1H, d, J=12.1 Hz, 3-H); 4.56 (1H, br d, J=9.0 Hz, 7-H); 5.53 (1H, br dd, J=8.3, 11.3 Hz, 2-H); 6.33 (2H, s, C_6H_2); 6.76 (1H, br d, J=8.3 Hz, NH); 7.04–7.08 (3H, m, 3H of Ar); 7.23–7.26 (2H, m, 2H of Ar); 7.33–7.39 (2H, m, 2H of Ar); 7.43–7.48 (1H, m, 1H of Ar); 7.69–7.74 (2H, m, 2H of Ar). (Found: C, 65.81; H, 5.74; N, 7.93. $C_{30}H_{31}N_3O_7$ requires: C, 66.04; H, 5.73; N, 7.70.); ν_{max} (KBr) 3259, 1758, 1691, 1665 cm^{-1}.

5.4. Synthesis of cycloadducts 9a–12a

A mixture of **3a** (369 mg, 1 mmol), dimethyl fumarate (**5**) (173 mg, 1.2 mmol), and anisole (5 mL) was heated under reflux for 4 h. Anisole was evaporated in vacuo and the residue was purified by CC (ethyl acetate–petroleum ether, 2:1). Fractions containing single isomers were combined and evaporated in vacuo to give isomerically pure **9a** and **11a**. Fractions containing mixtures of isomers were combined and evaporated in vacuo to give a mixture of **9a**, **10a**, and **12a**, which were separated by MPLC (ethyl acetate–petroleum ether, 1:1). Fractions containing single isomer were combined and evaporated in vacuo to give the second portion of isomerically pure **9a**. Fractions containing mixtures of isomers were combined and evaporated in vacuo to give a mixture of **9a**, **10a**, and **12a**. Repeated separation by MPLC (ethyl acetate–petroleum ether, 2:1) followed by evaporation in vacuo afforded the third portion of isomerically pure **9a** and a mixture of compounds **10a** and **12a**. Pure compounds **9a** and **11a**, obtained upon MPLC, were combined with pure compounds **9a** and **11a**, obtained upon CC. Compounds **9a**, **11a** and a mixture of compounds **10a** and **12a** were prepared in this manner.

5.4.1. Dimethyl (2*R,3*R**,5*R**,6*S**,7*S**)-2-benzoylamino-3,5-diphenyl-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazole-6,7-dicarboxylate (9a).** Yield: 115 mg (22%) of a white solid, mp 94–97 °C. ^1H NMR ($CDCl_3$): δ 3.73 (1H, dd, J=6.4, 9.0 Hz, 6-H); 3.73 (3H, s, 6-COOMe); 3.87 (3H, s, 7-COOMe); 4.33 (1H, d, J=9.0 Hz, 5-H); 4.44 (1H, d, J=8.7 Hz, 3-H); 4.81 (1H, dd, J=7.2, 8.7 Hz, 2-H); 5.25 (1H, d, J=6.0 Hz, 7-H); 6.94 (1H, d, J=6.8 Hz, NH); 7.07–7.33 (10H, m, 10H of Ph); 7.36–7.43 (2H, m, 2H of Ph); 7.45–7.53 (1H, m, 1H of Ph); 7.73–7.79 (2H, m, 2H of Ph). (Found: C, 67.84; H, 5.44; N, 7.89. $C_{29}H_{27}N_3O_6$ requires: C, 67.83; H, 5.30; N, 8.18.); ν_{max} (KBr) 3343, 1742, 1710, 1665 cm^{-1}.

5.4.2. Dimethyl (2*R,3*R**,5*S**,6*R**,7*R**)-2-benzoylamino-3,5-diphenyl-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazole-6,7-dicarboxylate (11a).** Yield: 91 mg (18%) of a white solid, mp 218–220 °C. ^1H NMR ($CDCl_3$): δ 3.67 (3H, s, 6-COOMe); 3.70 (1H, dd, J=5.3, 7.9 Hz, 6-H); 3.90 (3H, s, 7-COOMe); 3.99 (1H, d, J=7.9 Hz, 5-H); 4.87 (1H, d, J=9.8 Hz, 3-H); 5.07 (1H, d, J=5.3 Hz, 7-H); 5.78 (1H, dd, J=8.7, 9.8 Hz, 2-H); 6.80 (1H, d, J=8.7 Hz, NH); 6.86–6.92 (2H, m, 2H of Ph); 6.98–7.12 (6H, m, 6H of Ph); 7.14–7.19 (2H, m, 2H of Ph); 7.36–7.43 (2H, m, 2H of Ph); 7.45–7.52 (1H, m, 1H of Ph); 7.76–7.81 (2H, m, 2H of Ph). (Found: C, 68.03; H, 5.56; N, 7.94. $C_{29}H_{27}N_3O_6$ requires: C, 67.83; H, 5.30; N, 8.18.); ν_{max} (KBr) 3361, 1732, 1665 cm^{-1}.

5.4.3. A mixture of dimethyl (2*R,3*R**,5*R**,6*R**,7*R**)-2-benzoylamino-3,5-diphenyl-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (10a) and dimethyl (2*R**,3*R**,5*S**,6*S**,7*S**)-2-benzoylamino-3,5-diphenyl-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (12a).** Yield: 163 mg (32%) of a colourless solid, **10a**:**12a**=69:31. Crystallisation of isomerically enriched compound **10a** from a mixture of ethyl acetate and petroleum ether afforded a few crystals of pure **10a**, which were used for X-ray structure determination.

NMR data for compound **10a**. ^1H NMR ($CDCl_3$): δ 3.28 (3H, s, 6-COOMe); 3.62 (1H, dd, J=2.3, 7.2 Hz, 6-H); 3.92 (3H, s, 7-COOMe); 4.20 (1H, d, J=11.7 Hz, 3-H); 4.44 (1H, br d, J=7.2 Hz, 5-H); 4.85 (1H, dd, J=1.1, 2.3 Hz, 7-H); 5.56 (1H, dd, J=8.3, 11.7 Hz, 2-H); 6.58 (1H, d, J=8.7 Hz, NH); 6.96–7.54 (13H, m, 13H of Ph); 7.67–7.74 (2H, m, 2H of Ph).

NMR data for compound **12a**. ^1H NMR ($CDCl_3$): δ 3.36 (3H, s, 6-COOMe); 3.73 (1H, d, J=9.4 Hz, 3-H); 3.89 (3H, s, 7-COOMe); 4.32 (1H, t, J=7.5 Hz, 6-H); 4.62 (1H, d, J=7.5 Hz, 5-H); 5.18 (1H, deg t, J=8.9 Hz, 2-H); 5.43 (1H, d, J=7.5 Hz, 7-H); 5.99 (1H, d, J=8.3 Hz, NH); 6.96–7.49 (13H, m, 13H of Ph); 7.53–7.59 (2H, m, 2H of Ph).

5.4.4. Dimethyl (2*R,3*R**,5*S**,6*R**,7*R**)-2-benzoylamino-3-phenyl-5-(2,4,6-trimethylphenyl)-1-oxotetra-hydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6,7-dicarboxylate (11e).** A mixture of **3e** (412 mg, 1 mmol), dimethyl fumarate (**5**) (173 mg, 1.2 mmol), and anisole (5 mL) was heated under reflux for 20 h. Anisole was evaporated in vacuo and the

residue was purified by CC (ethyl acetate–petroleum ether, 1:1). Fractions containing the product were combined and evaporated in vacuo to give **11e**. Yield: 142 mg (26%) of a white solid, mp 230–231 °C. EI-MS: $m/z=555$ (M^+). ^{1}H NMR ($CDCl_3$): δ 1.54, 2.13, and 2.50 (9H, 3 s, 1:1:1, 3× Me-Ar); 3.63 (3H, s, 6-COOMe); 3.85 (1H, dd, $J=5.3$, 9.4 Hz, 6-H); 3.88 (3H, s, 7-COOMe); 4.29 (1H, d, $J=$ 9.0 Hz, 5-H); 4.80 (1H, d, $J=7.9$ Hz, 3-H); 5.12 (1H, d, $J=$ 5.3 Hz, 7-H); 5.67 (1H, deg t, $J=8.1$ Hz, 2-H); 6.38 and 6.69 (2H, 2br s, C_6H_2); 6.75 (1H, d, $J=8.7$ Hz, NH); 7.01–7.13 (3H, m, 3H of Ph); 7.17–7.24 (2H, m, 2H of Ph); 7.30–7.55 (3H, m, 3H of Ph); 7.78–7.83 (2H, m, 2H of Ph). (Found: C, 67.87; H, 6.06; N, 7.22. $C_{32}H_{33}N_3O_6$ requires: C, 69.17; H, 5.99; N, 7.56.); EI-HRMS: $m/z=555.2378$ (M^+); $C_{32}H_{33}N_3O_6$ requires: $m/z=555.2369$ (M^+); ν_{max} (KBr) 3377, 1742, 1665 cm^{-1}.

5.5. Synthesis of cycloadducts 14e–17e

A mixture of **3e** (412 mg, 1 mmol), methyl acrylate (**6**) (103 mg, 1.2 mmol), and anisole (5 mL) was heated under reflux for 15 h. Anisole was evaporated in vacuo and the residue was purified by CC (ethyl acetate–petroleum ether, 2:1). Fractions containing single isomer were combined and evaporated in vacuo to give isomerically pure compound **15e**. Fractions containing mixtures of isomers were combined and evaporated in vacuo to give a mixture of **14e**, **16e**, and **17e**, which were separated by MPLC (ethyl acetate–petroleum ether, 2:3). Fractions containing the products were combined and evaporated in vacuo to give isomerically pure compounds **14e**, **16e**, and **17e**.

5.5.1. Methyl (2*R,3*R**,5*S**,6*S**)-2-benzoylamino-3-phenyl-5-(2,4,6-trimethylphenyl)-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6-carboxylate (14e).** Yield: 92 mg (18%) of a white solid; mp 81–84 °C. EI-MS: $m/z=$ 497 (M^+). ^{1}H NMR ($CDCl_3$): δ 1.58, 2.15, and 2.58 (9H, 3 s, 1:1:1, 3×Me-Ar); 3.60 (1H, ddd, $J=5.3$, 7.9, 9.4 Hz, 6-H); 3.65 (3H, s, 6-COOMe); 3.86 (1H, dd, $J=9.6$, 11.9 Hz, 7-Ha); 4.19 (1H, dd, $J=5.1$, 11.8 Hz, 7-Hb); 4.54 (1H, d, $J=7.9$ Hz, 5-H); 4.78 (1H, d, $J=9.4$ Hz, 3-H); 5.58 (1H, deg t, $J=8.8$ Hz, 2-H); 6.38 and 6.75 (2H, 2br s, 1:1, C_6H_2); 6.78 (1H, br d, $J=8.3$ Hz, NH); 6.99–7.14 (3H, m, 3H of Ph); 7.16–7.21 (2H, m, 2H of Ph); 7.32–7.41 (2H, m, 2H of Ph); 7.42–7.49 (1H, m, 1H of Ph); 7.72–7.78 (2H, m, 2H of Ph). ^{13}C NMR ($CDCl_3$): δ 20.6, 21.0, 21.9, 45.2, 52.0, 52.9, 54.6, 62.7, 65.6, 127.6, 128.2, 128.6, 128.7, 129.5, 130.2, 131.4, 131.9, 132.8, 133.3, 137.1, 137.4, 137.7, 167.6, 172.4, 173.2. (Found: C, 73.90; H, 7.19; N, 7.20. $C_{30}H_{31}N_3O_4$ requires: C, 72.41; H, 6.28; N, 8.44.); EI-HRMS: $m/z=497.2321$ (M^+); $C_{30}H_{31}N_3O_4$ requires: $m/z=$ 497.2315 (M^+); ν_{max} (KBr) 3344, 1738, 1647 cm^{-1}.

5.5.2. Methyl (2*R,3*R**,5*R**,6*R**)-2-benzoylamino-3-phenyl-5-(2,4,6-trimethylphenyl)-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6-carboxylate (15e).** Yield: 77 mg (15%) of a white solid; mp 225–228 °C. ^{1}H NMR ($CDCl_3$): δ 2.11, 2.23, and 2.49 (9H, 3 s, 1:1:1, 3×Me-Ar); 3.71 (3H, s, 6-COOMe); 3.76 (1H, ddd, $J=4.9$, 8.7, 9.8 Hz, 6-H); 3.88 (1H, ddd, $J=1.5$, 10.2, 11.7 Hz, 7-Ha); 4.33 (1H, d, $J=7.2$ Hz, 3-H); 4.35 (1H, dd, $J=4.9$, 11.7 Hz, 7-Hb); 4.80 (1H, d, $J=8.3$ Hz, 5-H); 4.89 (1H, br t, $J=7.0$ Hz, 2-H); 6.61 and 6.63 (2H, 2br s, 1:1, C_6H_2); 6.93 (1H, br d, $J=6.4$ Hz, NH); 7.11–7.20 (3H, m, 3H of Ph); 7.29–7.37 (2H, m, 2H of Ph); 7.38–7.46 (2H, m, 2H of Ph); 7.46–7.54 (1H, m, 1H of Ph); 7.78–7.83 (2H, m, 2H of Ph). (Found: C, 72.65; H, 6.52; N, 8.38. $C_{30}H_{31}N_3O_4$ requires: C, 72.41; H, 6.28; N, 8.44.); ν_{max} (KBr) 3311, 1738, 1705, 1638 cm^{-1}.

5.5.3. Methyl (2*R,3*R**,5*S**,6*R**)-2-benzoylamino-3-phenyl-5-(2,4,6-trimethylphenyl)-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-6-carboxylate (16e).** Yield: 49 mg (10%) of a white solid; mp 88–91 °C. EI-MS: $m/z=$ 497 (M^+). ^{1}H NMR ($CDCl_3$): δ 1.66, 2.15, and 2.49 (9H, 3 s, 1:1:1, 3×Me-Ar); 3.21 (3H, s, 6-COOMe); 3.60 (1H, ddd, $J=7.0$, 9.0, 10.5 Hz, 6-H); 4.10 (1H, dd, $J=7.0$, 12.1 Hz, 7-Ha); 4.13 (1H, dd, $J=9.0$, 12.1 Hz, 7-Hb); 4.35 (1H, d, $J=10.5$ Hz, 5-H); 4.73 (1H, d, $J=6.8$ Hz, 3-H); 5.54 (1H, dd, $J=6.8$, 7.9 Hz, 2-H); 6.48 and 6.66 (2H, 2br s, 1:1, C_6H_2); 6.85 (1H, br d, $J=7.9$ Hz, NH); 7.07–7.20 (5H, m, 5H of Ph); 7.31–7.53 (3H, m, 3H of Ph); 7.75–7.81 (2H, m, 2H of Ph). ^{13}C NMR ($CDCl_3$): δ 20.8, 21.0, 22.9, 43.6, 49.6, 52.0, 57.0, 61.7, 66.9, 127.6, 128.6, 128.7, 128.86, 128.94, 129.0, 131.6, 132.2, 133.1, 133.6, 137.0, 137.4, 137.7, 167.9, 169.6, 171.1. (Found: C, 73.21; H, 6.91; N, 7.66. $C_{30}H_{31}N_3O_4$ requires: C, 72.41; H, 6.28; N, 8.44.); EI-HRMS: $m/z=497.2330$ (M^+); $C_{30}H_{31}N_3O_4$ requires: $m/z=$ 497.2315 (M^+); ν_{max} (KBr) 3402, 1715, 1663 cm^{-1}.

5.5.4. Methyl (2*R,3*R**,5*S**,7*R**)-2-benzoylamino-3-phenyl-5-(2,4,6-trimethylphenyl)-1-oxotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-7-carboxylate (17e).** Yield: 12 mg (2%) of a white solid; mp 103–106 °C. EI-MS: $m/z=$ 497 (M^+). ^{1}H NMR ($CDCl_3$): δ 1.62, 2.14, and 2.51 (9H, 3 s, 1:1:1, 3×Me-Ar); 2.52 (1H, ddd, $J=6.4$, 10.6, 13.2 Hz, 6-Ha); 2.81 (1H, ddd, $J=7.5$, 10.2, 13.6 Hz, 6-Hb); 3.84 (3H, s, 7-COOMe); 4.00 (1H, dd, $J=7.5$, 10.6 Hz, 5-H); 4.72 (1H, dd, $J=6.4$, 10.5 Hz, 7-H); 4.74 (1H, d, $J=6.4$ Hz, 3-H); 5.56 (1H, dd, $J=6.4$, 8.3 Hz, 2-H); 6.46 and 6.69 (2H, 2br s, 1:1, C_6H_2); 6.95 (1H, br d, $J=8.3$ Hz, NH); 7.05–7.20 (5H, m, 5H of Ph); 7.35–7.57 (3H, m, 3H of Ph); 7.79–7.85 (2H, m, 2H of Ph). (Found: C, 72.87; H, 7.12; N, 7.45. $C_{30}H_{31}N_3O_4$ requires: C, 72.41; H, 6.28; N, 8.44.); EI-HRMS: $m/z=497.2320$ (M^+); $C_{30}H_{31}N_3O_4$ requires: $m/z=$ 497.2315 (M^+); ν_{max} (KBr) 3422, 1750–1644 cm^{-1}.

5.6. X-ray structure analysis for compounds 7a, 8f, 10a and 11a

Single crystal X-ray diffraction data of compounds **7a**, **8f**, **10a** and **11a** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[44] DENZO and SCALEPACK[45] were used for indexing and scaling of the data. The structures were solved by means of SIR97.[46] Refinement was done using Xtal3.4[47] program package and the crystallographic plots were prepared by ORTEP III.[48] Crystal structures were refined on F values using the full-matrix least-squares procedure. The non-hydrogen atoms were refined anisotropically in all cases. 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[49] weighting scheme was used in all cases.

Crystallographic data (excluding structure factors) for the

structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 254008-254011. Copies of the data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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Cyclocondensations of (+)-camphor derived enaminones with hydrazine derivatives

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Dedicated to Professor Lubor Fišera, Slovak University of Technology, Bratislava, on the occasion of his 60th anniversary

Abstract—Reactions of 3-[(*E*)-(dimethylamino)methylidene]-(+)-camphor and (1*R*,5*S*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one with hydrazine derivatives were studied. Treatment of 3-[(*E*)-(dimethylamino)methylidene]-(+)-camphor with hydrazines afforded the corresponding fused pyrazoles. Similarly, fused pyrazoles were obtained upon reaction of (1*R*,5*S*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one with *ortho*-unsubstituted phenylhydrazines, while reactions with *ortho*-substituted phenylhydrazines and with hydrazine hydrochloride resulted in 'ring switching' type of transformation to furnish 2-aryl-4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]-1,2-dihydro-3*H*-pyrazol-3-ones.

1. Introduction

Naturally occurring and synthetic pyrazole derivatives have found widespread use in various applications.[1] Similarly, (+)-camphor (**1**) and its derivatives, are among the most frequently employed types of ex-chiral pool starting materials and building blocks, resolving agents, chiral shift reagents in NMR spectroscopy, and ligands in various asymmetric applications.[2] Camphor-functionalized pyrazoles, *N*-substituted (1*R*,7*S*)-1,10,10-trimethyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-dienes (or *N*-substituted (4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methyno-1*H*-indazoles) **2** have been synthesized from 3-formylcamphor and hydrazine derivatives.[3] Kotsuki and co-workers prepared various *N*-(β-hydroxyethyl) substituted (1*R*,7*S*)-1,10,10-trimethyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-dienes **2k**–**m** and **3k**–**m**, which were successfully employed as chiral ligands for enantioselective addition of diethylzinc to benzaldehyde (Fig. 1).[4]

Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates and related enaminones, synthetic equivalents of 1,3-dicarbonyl compounds, have been prepared and used for the preparation of dehydroalanine esters and various heterocyclic systems, including pyrazole derivatives. Various chiral analogs of 3-dimethylaminopropenoates were also prepared from commercially available enantiopure starting materials, such as α-amino acids and (+)-camphor (**1**). The α-amino acid derived chiral enaminones were employed as the key-intermediates and reagents in the synthesis of functionalized heterocycles, for example, in the 'ring switching' synthesis of 3-heteroarylalanine derivatives and related compounds and in the synthesis of heterocyclic analogs of dipeptides.[5,6] Recently, utilization of 3-(dimethylamino)propenoates in combinatorial synthesis has also been reported.[7] In connection with (+)-camphor (**1**) derived enaminones **4** and **5**, we have previously reported stereoselective synthesis of (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3-*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones,[8] and *N*-substituted (1*R*,5*S*)-3-aminomethylidene-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones.[9]

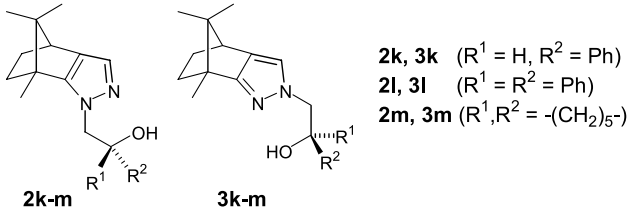

Figure 1.

Keywords: Camphor; Enaminones; Terpenes; Hydrazines; Condensations.
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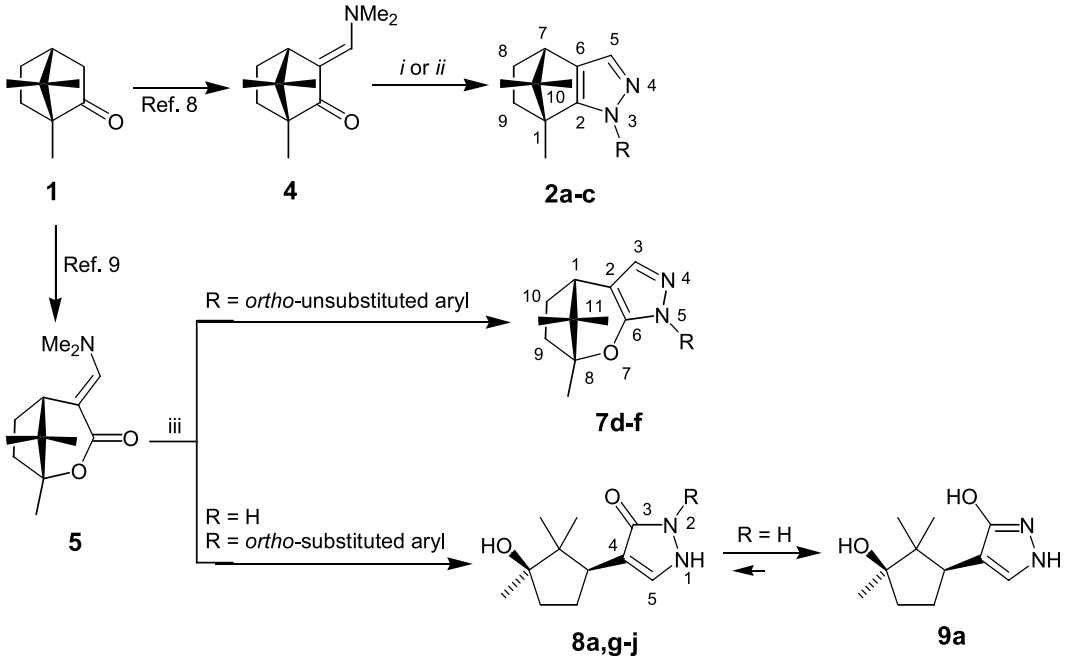
In continuation of our work in the field of (+)-camphor (**1**) derived enaminones, we now report cyclocondensations of (1*R*,4*S*)-3-[(*E*)-(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**4**) and (1*R*,5*S*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**5**) with hydrazine derivatives **6a–i** leading to, either fused pyrazole systems **2** and **7**, or to 4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl] substituted pyrazole derivatives **8** and **9**, as products of a 'ring switching' type transformation.

2. Results and discussion

Starting compounds **4**[8] and **5**[9] were prepared from (+)-camphor (**1**) according to literature procedures. Reaction of **4** with hydrazine hydrochloride (**6a**) in methanol at rt gave (1*R*,7*S*)-1,10,10-trimethyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]-deca-2(6),4-diene (**2a**) in 81% yield. Similarly, treatment of **4** with benzylhydazine dihydrochloride (**6b**) and 6-chloro-3-hydrazinopyridazine (**6c**) in acetic acid under reflux afforded (1*R*,7*S*)-3-benzyl-1,10,10-trimethyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-diene (**2b**) and 6-[(1*R*,7*S*)-1,10,10-trimethyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-dien-3-yl]pyridazin-3(2*H*)-one (**2c**) in 63% and 83% yield, respectively. On the other hand, upon reaction of **5** with phenylhydrazine derivatives **6d–j** in refluxing *n*-propanol, two different types of products were formed, either fused pyrazoles **7**, or cyclopentyl substituted pyrazolones **8**. Thus, treatment of **5** with *ortho*-unsubstituted phenylhydrazines **6d–f** afforded (1*S*,8*R*)-5-aryl-8,11,11-trimethyl-7-oxa-4,5-diazatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-dienes **7d–f** in 74–91% yields, while treatment of **5** with *ortho*-substituted phenylhydrazines **6g–j** furnished 2-aryl-4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]-1,2-dihydro-3*H*-pyrazol-3-ones **8g–j** in 56–70% yields. 'Ring switching' transformation also took place in the case of the reaction of **5** with hydrazine hydrochloride (**6a**), which gave 4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]-1*H*-pyrazol-3-ol (**9a**) in 81% yield (Scheme 1, Table 1).

Formation of pyrazole derivatives **2**, **7–9** can be explained according to the formation of pyrazoles from hydrazine derivatives and 1,3-dicarbonyl compounds and their enamino analogs.[1] Compound **4**, an enamino masked β-keto aldehyde, reacts via initial substitution of the dimethylamino group to give the isomeric enehydrazines **10** and **10′**. The (*Z*)-isomer **10′** then cyclizes into dihydropyrazole **11**, followed by elimination of water to give fused pyrazole **2**. Similarly, compound **5** as an enamino masked β-keto ester is first transformed into a mixture of isomeric enehydrazines **12** and **12′**. The (*Z*)-isomer **12′** then cyclizes into the bicyclic intermediate **13**. From this point on, further reaction can take place in two ways: (a) elimination of water leads to pyrazolo fused lactones **7** (Path A) and (b) elimination of the alcohol moiety leads to 'ring switched' pyrazolones of type **8** (Path B) (Scheme 2).

So far, we do not have an explanation for chemoselectivity of reactions of **5** with hydrazine derivatives **6a**,**d–j**. In the literature, there are several examples, where treatment of β-keto esters with arylhydrazines under acidic conditions afforded 5-alkoxy- and/or 5-hydroxypyrazoles.[1] Since elimination of water is generally facilitated by the protonation of the hydroxy group, while elimination of alcohol can be, either acid-catalysed or base-catalysed, steric factors might control selectivity of cyclisation of bicyclic intermediates **13a**,**d–j** into pyrazole derivatives **7d–f**, **8g–j**, and **9a**. Thus, in the case of intermediates **13d–f** without *ortho*-substituent attached to the aromatic ring, the hydroxy group can undergo protonation and, consequently, elimination of water can take place to give fused pyrazoles **7d–f**. On the other hand, in intermediates **13g–j**, the hydroxy group is hindered by the *ortho*-substituent attached

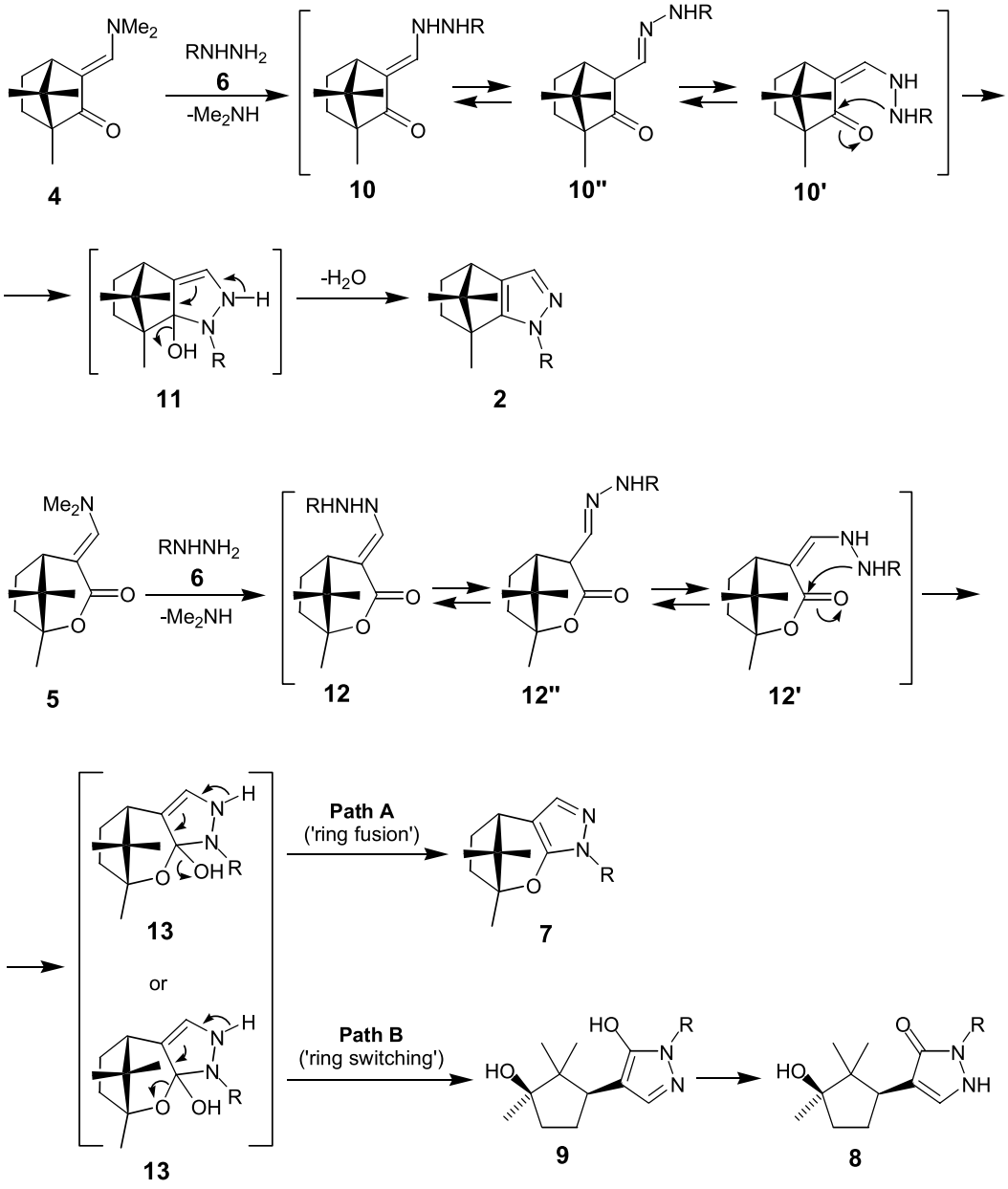


Scheme 1. Reaction conditions: (i) $NH_2NH_2 \cdot HCl$ (**6a**) MeOH, rt; (ii) $PhCH_2NHNH_2 \cdot 2HCl$ (**6b**) or 6-chloro-3-hydrazinopyridazine (**6c**), AcOH, reflux; (iii) R-$NHNH_2 \cdot HCl$ (**6a**,**d–i**) or $C_6F_5NHNH_2 \cdot \frac{1}{2}H_2SO_4$ (**6j**), *n*-PrOH, reflux.

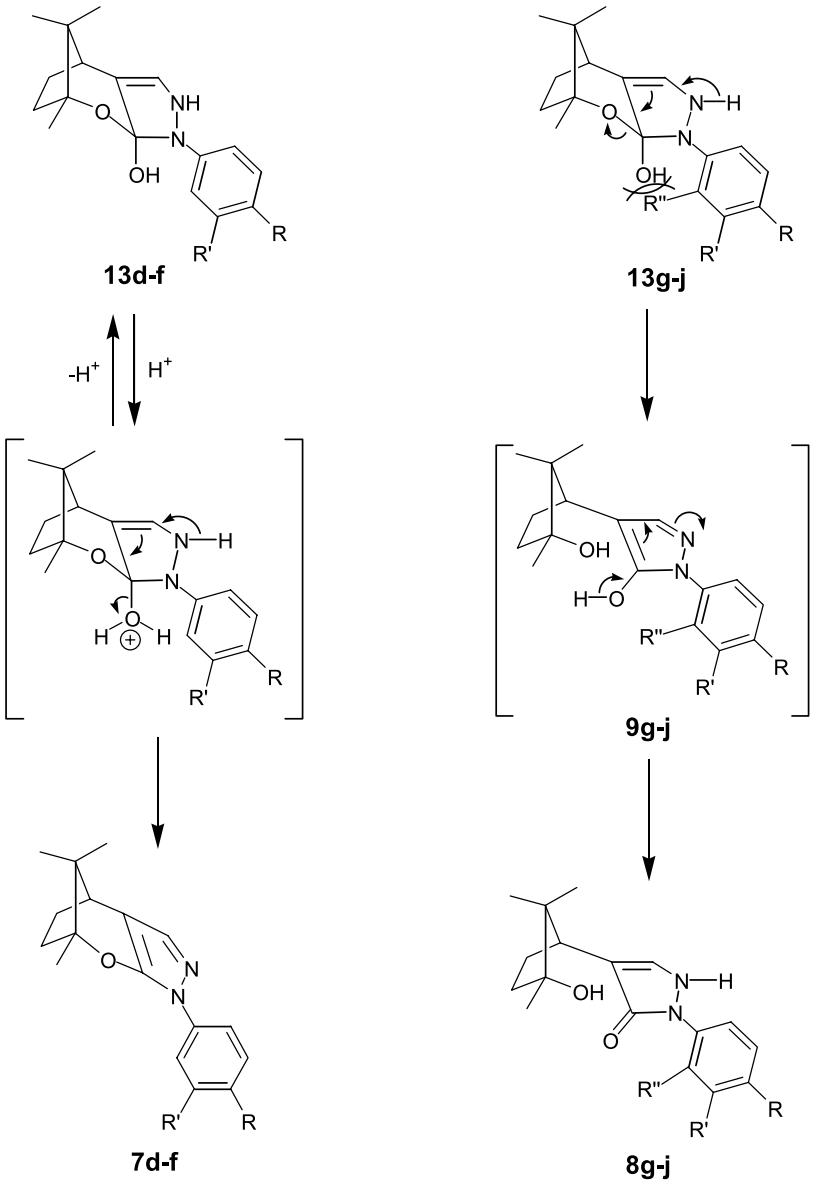
Table 1. Experimental data for compounds **2**, **7**–**9**

Compound	R	Yield (%)			
		2	**7**	**8**	**9**
2a, **6a**, **9a**	H	81			83
2b, **6b**	Benzyl	63			
6c	6-Chloropyridazin-3-yl				
2c	6-Oxo-1,6-dihydropyridazin-3-yl	83			
6d, **7d**	Phenyl		91		
6e, **7e**	3-Methylphenyl		74		
6f, **7f**	4-Methylphenyl		85		
6g, **8g**	2-Methylphenyl			70	
6h, **8h**	2-Chlorophenyl			61	
6i, **8i**	2-Bromophenyl			63	
6j, **8j**	Pentafluorophenyl			56	

to the aromatic ring. Consequently, protonation of the hydroxy group is disfavoured and elimination of alcohol, that is, opening of the lactone ring, takes place to give the hydroxypyrazoles **9g**–**j**, which then tautomerise into the pyrazolones **8g**–**j**. In the case of transformation of **5** into **9a**, which took place upon reaction of **5** with sterically unhindered hydrazine hydrochloride (**6a**), opening of the lactone ring is favoured due to stronger basicity of the



Scheme 2.



Scheme 3.

primary amino group with respect to the arylamino group (Scheme 3).

3. Structure determination

The structures of compounds **2**, **7**–**9** were determined by spectroscopic methods (NMR, IR, MS, HRMS) and/or by analyses for C, H, and N. The structure of compound **9a**, which was not isolated in analytically pure form, was confirmed by ^{13}C NMR and HRMS. Physical and spectral data of known compounds **2a**,**b** were in agreement with the literature data.[3a,e] Spectral data for pyrazoles **2**, **7**–**9** were in agreement with the literature data for related pyrazole[1] and camphor derivatives.[2] IR spectra of compounds **2c** and **8d**–**f** exhibited amide C=O absoption bands at 1681 and 1682–1673 cm^{-1}, respectively, while no C=O absorption was observed in IR spectra of compounds **2a**,**b**, **7d**–**f**, and **9a**. In compound **8g**, NOE between the OH proton and protons of the *ortho*-methyl group in the aryl residue was in agreement with (1*S*,3*R*)-configuration (Fig. 2).

The structure of compound **7d** was determined by X-ray diffraction (Fig. 3).

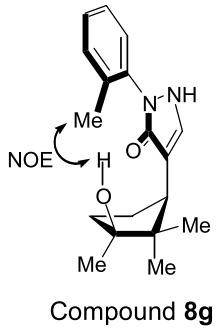


Figure 2.

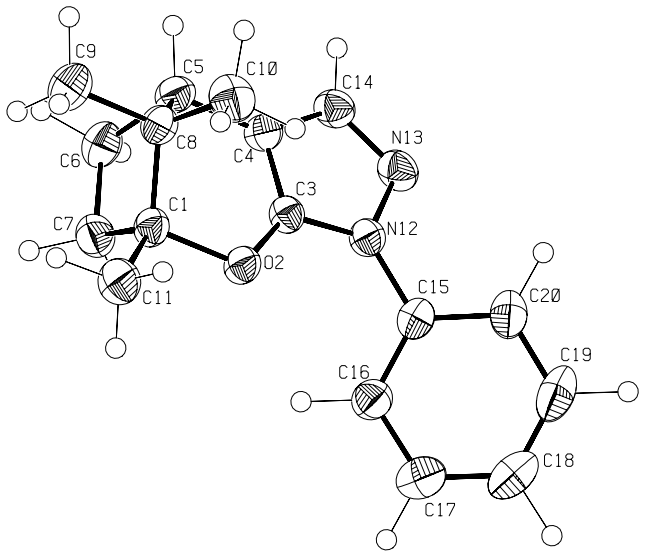


Figure 3. ORTEP view of the asymmetric unit of compound **7d** with labeling of nonhydrogen atoms (ellipsoids are drawn at 50% probability level).

4. Conclusion

In conclusion, (+)-camphor derived enaminones **4** and **5** are easily available reagents, which are suitable for the preparation of terpene-functionalized pyrazole derivatives. Reactions of (1*R*,4*S*)-3-[(*E*)-(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**4**) with hydrazine derivatives **6** lead to 3-substituted (1*R*,7*S*)-1,10,10-trimethyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-dienes **2**. However, in the case of (1*R*,5*S*)-4-[(*E*)-(dimethylamino)-methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**5**), the chemoselectivity was found to be dependent on the type of hydrazine derivative **6** employed. Reactions of **5** with *ortho*-unsubstituted phenylhydrazines **6d–f** afforded fused pyrazole systems **7d–f**, while reactions with hydrazine hydrochloride (**6a**) and *ortho*-substituted phenylhydrazines **6g–j** led to 4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl] substituted pyrazole derivatives **9a** and **8g–j**, respectively, as products of a 'ring switching' type transformation.

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 DMSO-d_6 and $CDCl_3$ as solvents and TMS as the internal standard. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin–Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyser 2400. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm).

Hydrazines **6a**,**b**,**d–j** are commercially available (Fluka AG). (1*R*,4*S*)-3-[(*E*)-(Dimethylamino)-methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**4**),[8] (1*R*,5*S*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**5**),[9] and 6-chloro-3-hydrazinopyridazine (**6c**),[10] were prepared according to the procedures described in the literature.

5.1.1. (1*R*,7*S*)-1,10,10-Trimethyl-3,4-diazatricyclo-[5.2.1.$0^{2,6}$]deca-2(6),4-diene (2a). A mixture of **4** (0.207 g, 1 mmol), hydrazine hydrochloride (**6a**, 0.069 g, 1 mmol), and methanol (4 ml) was stirred at rt for 24 h. Water (6 ml) was added and the precipitate was collected by filtration to give **2a**. Yield: 0.143 g (81%) of yellowish crystals; mp 143–147 °C, lit.[3a] mp 149–150 °C; $[\alpha]_D^{23} = +35.8$ ($c=0.4$, CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ 0.56, 0.91 (6H, 2 s, 1:1, 2Me); 0.98–1.16 (2H, m, CH_2); 1.19 (3H, s, Me); 1.75–1.83 (1H, m, 1H of CH_2); 1.98–2.07 (1H, m, 1H of CH_2); 2.73 (1H, d, $J=3.9$ Hz, H–C(7)); 7.16 (1H, s, H–C(5)); 11.62 (1H, s, H–N(3)). ^{13}C NMR (DMSO-d_6): δ 11.2, 19.7, 20.9, 28.2, 34.1, 47.5, 50.4, 61.4, 120.4, 126.4, 166.5. (Found: C, 74.96; H, 9.36; N, 15.59. $C_{11}H_{16}N_2$ requires: C, 74.96; H, 9.15; N, 15.89.); ν_{max} (KBr): 3415, 3145, 2923, 1586, 1479, 1454, 1415, 1386, 1369, 1286, 1273, 1140, 1084, 1026, 972, 804 cm^{-1}.

5.2. General procedure for the preparation of compounds 2b,c, 7d–f, 8g,h, and 9a

A mixture of enaminone **4** or **5** (1 mmol), hydrazine derivative **6** (1 mmol), and appropriate solvent (~5 ml) was heated under reflux for 2–6 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (CC). Fractions containing the product were combined and evaporated in vacuo to give **2b**,**c**, **7d–f**, **8g**,**h**, and **9a**.

The following compounds were prepared in this manner:

5.2.1. (1*R*,7*S*)-3-Benzyl-1,10,10-trimethyl-3,4-diazatricyclo[5.2.1.$0^{2,6}$]deca-2(6),4-diene (2b). Prepared from **4** (0.207 g, 1 mmol), benzylhydrazine dihydrochloride (**6b**, 0.195 g, 1 mmol), and acetic acid (100%, 6 ml), reflux for 4 h, CC (diethyl ether–petroleum ether, 1:2). Yield: 0.168 g (63%) of colourless oil, lit.[3e] oil; $[\alpha]_D^{22} = -14.9$ ($c=0.29$, CH_2Cl_2). EI-MS: $m/z=266$ (M^+). ^{1}H NMR (DMSO-d_6): δ 0.65, 0.82, 1.13 (9H, 3 s, 1:1:1, 3Me); 0.88–1.00 (2H, m, CH_2); 1.61–1.70 (1H, m, 1H of CH_2); 1.93–2.01 (1H, m, 1H of CH_2); 2.73 (1H, d, $J=3.8$ Hz, H–C(7)); 5.24 (1H, d, $J=16.0$ Hz, 1H of CH_2N); 5.32 (1H, d, $J=16.0$ Hz, 1H of CH_2N); 7.05–7.07 (2H, m, 2H of Ph); 7.09 (1H, s, H–C(5)); 7.22–7.34 (3H, m, 3H of Ph). ^{13}C NMR ($CDCl_3$): δ 11.7, 20.0, 20.7, 28.2, 33.8, 48.0, 52.7, 54.3, 63.2, 127.0, 127.9, 129.0, 129.5, 131.6, 138.6, 153.9. (Found: C, 80.84; H, 8.71; N, 10.51. $C_{18}H_{22}N_2$ requires: C, 81.16; H, 8.32; N, 10.52.); EI-HRMS: $m/z=266.1796$ (M^+); $C_{18}H_{22}N_2O$ requires: $m/z=266.1783$ (M^+); ν_{max} (NaCl): 2957, 2872, 1606, 1522, 1496, 1440, 1383, 1362, 1285, 1194, 1117, 1059, 997, 907 cm^{-1}.

5.2.2. 6-[(1*R*,7*S*)-1,10,10-Trimethyl-3,4-diazatricyclo-[5.2.1.$0^{2,6}$]deca-2(6),4-dien-3-yl]pyridazin-3(2*H*)-one (2c). Prepared from **4** (0.207 g, 1 mmol), 6-chloro-3-hydrazinopyridazine (**6c**, 0.145 g, 1 mmol), and acetic acid (100%, 6 ml), reflux for 4 h, CC (ethyl acetate). Before chromatographic purification, the crude solid product was crystallised from methanol. Yield: 0.124 g (83%) of white

crystals; mp 213–218 °C (from methanol); $[\alpha]_D^{20} = +9.9$ ($c = 0.40$, CH_2Cl_2). ^{1}H NMR (DMSO-d_6): δ 0.71, 0.90 (6H, 2 s, 1:1, 2Me); 0.95–1.03 (1H, m, 1H of CH_2); 1.19–1.27 (1H, m, 1H of CH_2); 1.32 (3H, s, Me); 1.78–1.86 (1H, m, 1H of CH_2); 2.01–2.11 (1H, m, 1H of CH_2); 2.81 (1H, d, J = 3.6 Hz, H–C(7)); 7.05 (1H, d, J = 10.0 Hz, H–C(5′)); 7.44 (1H, s, H–C(5)); 7.92 (1H, d, J = 10.0 Hz, H–C(4′)); 12.92 (1H, s, NH). ^{13}C NMR (DMSO-d_6): δ 13.4, 20.4, 21.0, 28.1, 33.5, 47.4, 54.8, 63.8, 129.6, 132.4, 133.1, 134.8, 142.2, 154.0, 160.8. (Found: C, 66.83; H, 7.09; N, 20.47. $C_{15}H_{18}N_4O$ requires: C, 66.64; H, 6.71; N, 20.73.); ν_{max} (KBr): 3446, 2961, 1681 (C═O), 1613, 1563, 1475, 1448, 1380, 1308, 1242, 1007, 986, 839 cm^{-1}.

5.2.3. (1*S*,8*R*)-5-Phenyl-8,11,11-trimethyl-7-oxa-4,5-diazatricyclo[6.2.1.0^{2,6}]undeca-2(6),3-diene (7d). Prepared from **5** (0.223 g, 1 mmol) and phenylhydrazine hydrochloride (**6d**, 0.145 g, 1 mmol), and anhydrous *n*-propanol (5 ml), reflux for 2 h, CC (ethyl acetate–petroleum ether, 1:3). Yield: 0.224 g (91%) of white crystals; mp 173–177 °C (from ethyl acetate–*n*-hexane); $[\alpha]_D^{25} = -27.6$ ($c = 0.25$, CH_2Cl_2). EI-MS: m/z = 268 (M^+). ^{1}H NMR ($CDCl_3$): δ 0.98, 1.08, 1.44 (9H, 3 s, 1:1:1, 3Me); 1.84–1.91 (1H, m, 1H of CH_2); 1.96–2.14 (2H, m, CH_2); 2.20–2.29 (1H, m, 1H of CH_2); 2.58 (1H, d, J = 4.4 Hz, H–C(1)); 7.19 (1H, tt, J = 1.2, 7.5 Hz, 1H of Ph); 7.25 (1H, s, H–C(3)); 7.36–7.42 (2H, m, 2H of Ph); 7.79–7.81 (2H, m, 2H of Ph). ^{13}C NMR ($CDCl_3$): δ 18.7, 19.5, 24.2, 34.0, 38.1, 43.1, 43.9, 94.2, 107.3, 120.0, 125.7, 129.3, 136.6, 139.5, 149.7. (Found: C, 76.23; H, 7.64; N, 10.35. $C_{17}H_{20}N_2O$ requires: C, 76.09; H, 7.51; N, 10.44.); EI-HRMS: m/z = 268.1585; $C_{17}H_{20}N_2O$ requires: m/z = 268.1576 (M^+). Found: ν_{max} (KBr): 2956, 1595, 1516, 1492, 1455, 1418, 1377, 1088, 1057, 970, 847, 760, 690 cm^{-1}.

5.2.4. (1*S*,8*R*)-5-(3-Methylphenyl)-8,11,11-trimethyl-7-oxa-4,5-diazatricyclo-[6.2.1.0^{2,6}]undeca-2(6),3-diene (7e). Prepared from enaminone **5** (0.223 g, 1 mmol) and (3-methylphenyl)hydrazine hydrochloride (**6e**, 0.159 g, 1 mmol), and anhydrous *n*-propanol (5 ml), reflux for 3 h, CC (ethyl acetate–petroleum ether, 1:4). Yield: 0.209 g (74%) of light orange crystals; mp 75–79 °C; $[\alpha]_D^{21} = -26.3$ ($c = 0.74$, CH_2Cl_2). EI-MS: m/z = 282 (M^+). ^{1}H NMR ($CDCl_3$): δ 0.97, 1.08, 1.43 (9H, 3 s, 1:1:1, 3Me); 1.84–1.91 (1H, m, 1H of CH_2); 1.96–2.14 (2H, m, CH_2); 2.20–2.29 (1H, m, 1H of CH_2); 2.38 (3H, s, *Me*-Ar); 2.57 (1H, d, J = 4.5 Hz, H–C(1)); 7.01 (1H, br d, J = 7.5 Hz, 1H of Ar); 7.24 (1H, s, H–C(3)); 7.27 (1H, br t, J = 7.8 Hz, 1H of Ar); 7.59 (1H, br d, J = 8.3 Hz, 1H of Ar); 7.63 (1H, br s, 1H of Ar). ^{13}C NMR ($CDCl_3$): δ 18.7, 19.5, 21.9, 24.2, 34.0, 38.1, 43.1, 43.9, 94.1, 107.2, 117.1, 120.8, 126.5, 129.0, 136.5, 139.3, 139.4, 149.7. (Found: C, 76.28; H, 7.79; N, 10.16. $C_{18}H_{22}N_2O$ requires: C, 76.56; H, 7.85; N, 9.92.); EI-HRMS: m/z = 282.1740 (M^+); $C_{18}H_{22}N_2O$ requires: m/z = 282.1732 (M^+). ν_{max} (KBr): 2960, 1611, 1597, 1516, 1489, 1460, 1414, 1392, 1380, 1142, 1099, 1069, 975, 884, 854 cm^{-1}.

5.2.5. (1*S*,8*R*)-5-(4-Methylphenyl)-8,11,11-trimethyl-7-oxa-4,5-diazatricyclo-[6.2.1.0^{2,6}]undeca-2(6),3-diene (7f). Prepared from **5** (0.223 g, 1 mmol), (4-methylphenyl)-hydrazine hydrochloride (**6f**, 0.159 g, 1 mmol), and anhydrous *n*-propanol (5 ml), reflux for 4 h, CC (ethyl acetate–petroleum ether, 1:4). Yield: 0.240 g (85%) of white crystals; mp 146–150 °C (from chloroform–*n*-heptane); $[\alpha]_D^{21} = -27.2$ ($c = 0.23$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.97, 1.08, 1.42 (9H, 3 s, 1:1:1, 3Me); 1.83–1.95 (1H, m, 1H of CH_2); 1.95–2.14 (2H, m, CH_2); 2.19–2.28 (1H, m, 1H of CH_2); 2.35 (3H, s, *Me*-Ar); 2.57 (1H, d, J = 4.4 Hz, H–C(1)); 7.19 (2H, br d, J = 8.5 Hz, 2H of Ar); 7.23 (1H, s, H–C(3)); 7.66 (2H, br d, J = 8.5 Hz, 2H of Ar). ^{13}C NMR ($CDCl_3$): δ 18.7, 19.5, 21.3, 24.3, 34.0, 38.1, 43.1, 43.9, 94.0, 107.1, 120.1, 129.8, 135.4, 136.3, 137.1, 149.5. (Found: C, 76.29; H, 8.03; N, 9.76. $C_{18}H_{22}N_2O$ requires: C, 76.56; H, 7.85; N, 9.92.); ν_{max} (KBr): 2972, 1589, 1526, 1458, 1428, 1076, 973, 882, 855, 818 cm^{-1}.

5.2.6. 4-[(1*S*,3*R*)-3-Hydroxy-2,2,3-trimethylcyclopentyl]-2-(2-methylphenyl)-1,2-dihydro-3*H*-pyrazol-3-one (8g). Prepared from **5** (0.223 g, 1 mmol), (2-methylphenyl)hydrazine hydrochloride (**6g**, 0.159 g, 1 mmol), and anhydrous *n*-propanol (5 ml), reflux for 4 h, CC (first: ethyl acetate–petroleum ether, 1:4, then ethyl acetate–petroleum ether, 1:2). Yield: 0.210 g (70%) of white crystals; mp 139–145 °C (from chloroform–*n*-heptane); $[\alpha]_D^{21} = -13.2$ ($c = 0.39$, CH_2Cl_2). EI-MS: m/z = 300 (M^+). ^{1}H NMR ($CDCl_3$): δ 1.00, 1.01, 1.31 (9H, 3 s, 1:1:1, 3Me); 1.59–1.67 (1H, m, 1H of CH_2); 1.93–2.27 (4H, m, 3H of CH_2 and H–C(1′)); 2.16 (3H, s, *Me*-Ar); 5.82 (1H, br s, OH); 6.65 (1H, d, J = 10.4 Hz, H–C(5)); 6.83 (1H, br t, J = 7.3 Hz, 1H of Ar); 6.87 (1H, br d, J = 7.6 Hz, 1H of Ar); 7.07 (1H, br d, J = 7.3 Hz, 1H of Ar); 7.14 (1H, br t, J = 7.6 Hz, 1H of Ar); 8.97 (1H, d, J = 10.4 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 17.4, 18.8, 18.9, 23.8, 31.8, 38.0, 43.8, 50.3, 92.0, 100.0, 112.1, 120.9, 122.2, 127.5, 130.8, 146.7, 151.2, 170.1. (Found: C, 71.94; H, 8.09; N, 9.27. $C_{18}H_{24}N_2O_2$ requires: C, 71.97; H, 8.05; N, 9.33.); EI-HRMS: m/z = 300.1846 (M^+); $C_{18}H_{24}N_2O_2$ requires: m/z = 300.1838 (M^+). ν_{max} (KBr): 3452, 3287, 3256, 2970, 1677 (C═O), 1607, 1426, 1219, 1138, 756 cm^{-1}.

5.2.7. 2-(2-Chlorophenyl)-4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]-1,2-dihydro-3*H*-pyrazol-3-one (8h). Prepared from **5** (0.223 g, 1 mmol), (2-chlorophenyl)-hydrazine hydrochloride (**6h**, 0.179 g, 1 mmol), and anhydrous *n*-propanol (5 ml), reflux for 6 h, CC (first: ethyl acetate–petroleum ether, 1:4). Yield: 0.196 g (61%) of white crystals; mp 177–182 °C (from chloroform–*n*-heptane); $[\alpha]_D^{21} = -9.3$ ($c = 0.31$, CH_2Cl_2). EI-MS: m/z = 320 (M^+). ^{1}H NMR ($CDCl_3$): δ 1.00, 1.01, 1.31 (9H, 3 s, 1:1:1, 3Me); 1.59–1.67 (1H, m, 1H of CH_2); 1.94–2.27 (4H, m, 3H of CH_2 and H–C(1′)); 6.41 (1H, br s, OH); 6.62 (1H, d, J = 10.3 Hz, H–C(5)); 6.82 (1H, dt, J = 1.4, 7.8 Hz, 1H of Ar); 6.94 (1H, dd, J = 1.2, 8.0 Hz, 1H of Ar); 7.18 (1H, br t, J = 7.8 Hz, 1H of Ar); 7.26 (1H, dd, J = 1.3, 7.9 Hz, 1H of Ar); 8.97 (1H, br d, J = 10.3 Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.8, 18.9, 23.8, 31.7, 38.0, 43.8, 50.3, 92.2, 101.0, 113.8, 118.6, 121.4, 128.3, 129.7, 144.7, 150.6, 170.0. (Found: C, 63.62; H, 6.71; N, 8.45. $C_{17}H_{21}ClN_2O_2$ requires: C, 63.65; H, 6.60; N, 8.73.); EI-HRMS: m/z = 320.1301 (M^+). $C_{17}H_{21}ClN_2O_2$ requires: 320.1292 (M^+). ν_{max} (KBr): 3452, 3259, 2983, 1682 (C═O), 1618, 1466, 1215, 1138, 748 cm^{-1}.

5.2.8. 4-[(1*S*,3*R*)-3-Hydroxy-2,2,3-trimethylcyclopentyl]-1*H*-pyrazol-3-ol (9a). Prepared from **5** (0.223 g, 1 mmol), hydrazine hydrochloride (**6a**, 0.069 g, 1 mmol), and anhydrous *n*-propanol (5 ml), reflux for 5 h, CC (chloroform–methanol, 15:1). Yield: 0.175 g (83%) of white crystals; mp

203–210 °C; $[\alpha]_D^{25}=+24.4$ ($c=0.24$, DMSO); +36.2 ($c=0.12$, MeOH). EI-MS $m/z=210$ (M^+). ^{1}H NMR (DMSO-d_6): δ 0.60, 0.76, 1.13 (9H, 3 s, 1:1:1, 3Me); 1.58–1.81 (4H, m, $2CH_2$); 2.74 (1H, br t, $J=9.0$ Hz, H–C(1′)); 4.59 (1H, br s, OH); 7.16 (1H, s, H–C(3)); 9.65 (1H, s, NH); 11.03 (1H, s, HO–C(3)). ^{13}C NMR (DMSO-d_6): δ 19.8, 25.4, 25.6, 27.5, 38.5, 42.9, 47.5, 81.6, 105.7, 129.4, 159.9. (Found: C, 63.09; H, 8.60; N, 12.90. $C_{11}H_{18}N_2O_2$ requires: C, 62.83; H, 8.63; N, 13.32.); EI-HRMS: $m/z=210.1374$ (M^+); $C_{11}H_{18}N_2O_2$ requires: $m/z=210.1368$ (M^+). ν_{max} (KBr): 3481, 3200, 2979, 1524, 1469, 1368, 1144, 1101, 1078, 932 cm^{-1}.

5.2.9. 2-(2-Bromophenyl)-4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]-1,2-dihydro-3*H*-pyrazol-3-one (8i). A mixture of **5** (0.223 g, 1 mmol), (2-bromophenyl)hydrazine hydrochloride **6i** (0.224 g, 1 mmol), and anhydrous *n*-propanol (5 ml) was heated under reflux for 6 h. The reaction mixture was cooled to rt, the precipitate was collected by filtration, and washed with cold *n*-propanol (0 °C, 2 ml) to give **8i**. Yield: 0.230 g (63%) of white crystals; mp 186–194 °C (from chloroform–*n*-heptane); $[\alpha]_D^{21}=-11.2$ ($c=0.22$, CH_2Cl_2). EI-MS: $m/z=364$ (M^+). ^{1}H NMR ($CDCl_3$): δ 1.00, 1.01, 1.31 (9H, 3 s, 1:1:1, 3Me); 1.59–1.68 (1H, m, 1H of CH_2); 1.95–2.27 (4H, m, 3H of CH_2 and H–C(1′)); 6.39 (1H, br s, OH); 6.62 (1H, d, $J=10.4$ Hz, H–C(5)); 6.76 (1H, dt, $J=1.5$, 7.8 Hz, 1H of Ar); 6.93 (1H, dd, $J=1.4$, 8.2 Hz, 1H of Ar); 7.22 (1H, dt, $J=1.1$, 7.8 Hz, 1H of Ar); 7.43 (1H, dd, $J=1.3$, 7.9 Hz, 1H of Ar); 8.99 (1H, br d, $J=10.4$ Hz, NH). ^{13}C NMR ($CDCl_3$): δ 18.8, 18.9, 23.8, 31.7, 38.0, 43.9, 50.3, 92.2, 101.0, 108.1, 114.0, 121.9, 128.9, 132.9, 145.7, 150.6, 170.0. (Found: C, 55.93; H, 5.76; N, 7.38 $C_{17}H_{21}BrN_2O_2$ requires: C, 55.90; H, 5.79; N, 7.67.); EI-HRMS: $m/z=364.0799$ (M+); $C_{17}H_{21}BrN_2O_2$ requires: $m/z=364.0786$ (M^+); ν_{max} (KBr): 3436, 3256, 2943, 1679 (C=O), 1616, 1461, 1213, 1134, 750 cm^{-1}.

5.2.10. 2-Pentafluorophenyl-4-[(1*S*,3*R*)-3-hydroxy-2,2,3-trimethylcyclopentyl]-1,2-dihydro-3*H*-pyrazol-3-one (8j). A solution of sulfuric acid in *n*-propanol (1 M, 0.5 ml, 0.5 mmol) was added to the solution of enamino lactone **5** (0.223 g, 1 mmol) and pentafluorophenylhydrazine (**6j**, 0.198 g, 1 mmol) in anhydrous *n*-propanol (5 ml), and the mixture was heated under reflux for 5 h. Volatile components were evaporated in vacuo and the residue was purified by CC (first: ethyl acetate–petroleum ether, 1:10, then ethyl acetate–petroleum ether, 1:3). Fractions containing the product were combined and evaporated in vacuo to give **8j**. Yield: 0.211 g (56%) of white crystals; mp 163–167 °C (from chloroform–*n*-heptane, with previous melting and solidifying at 139–145 °C); $[\alpha]_D^{21}=+0.9$ ($c=0.316$, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 0.97, 1.00, 1.29 (9H, 3 s, 1:1:1, 3Me); 1.57–1.67 (1H, m, 1H of CH_2); 1.91–2.23 (4H, m, 3H of CH_2 and H–C(1′)); 5.92 (1H, br s, OH); 6.75 (1H, d, $J=10.0$ Hz, H–C(5)); 9.03 (1H, d, $J=10.0$ Hz, NH). (Found: 54.08; H, 4.70; N, 7.19. $C_{17}H_{17}F_5N_2O_2$ requires: C, 54.26; H, 4.55; N, 7.44.); ν_{max} (KBr): 3331, 3295, 2976, 1673 (C=O), 1627, 1520, 1429, 1141, 1018, 966 cm^{-1}.

5.3. X-ray structure determination

Single crystal X-ray diffraction data of compound **7d** were collected at room temperature on a Nonius Kappa CCD diffractometer using the Nonius Collect Software.[11] DENZO and SCALEPACK[12] were used for indexing and scaling of the data. The structure was solved by means of SIR97.[13] Refinement was done using Xtal3.4[14] program package and the crystallographic plot was prepared by ORTEP III[15]. 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[16] weighting scheme was used.

The crystallographic data for compound **7d** have been deposited with the Cambridge Crystallographic Data Center as supplementary material with the deposition number: CCDC 254054. These data can be obtained, free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

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Regioselective cyclization of unsymmetrical dicyanoanilines to novel 2,3-bifunctionalised indole regioisomers and their use in the synthesis of 4,5-dihydro[1,3]oxazino[5,4-*b*]indole-6-carbonitriles☆

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Abstract—Synthesis of novel-2,3-bifunctionalised indole regioisomers (**2/3** and **6/7**) from unsymmetrical dicyanoanilines **1** by regioselective cyclization in two independent ways. Regioisomers **6** are further utilized in synthesis of novel 4,5-dihydro[1,3]-oxazino[5,4-*b*] indole-6-carbonitriles **9**.

1. Introduction

The hetero-ring fused benzene derivatives play a prominent role in synthetic organic chemistry because of their wide range applications in pharmaceutical field. More specifically pyrrole-fused benzene (indole) derivatives have been considered as useful intermediates in drugs, pesticides[1] and also as potential pharmaceuticals.[2a,b] Among the tryptamine derivatives, sumatriptan[3a,b] is a highly selective 5-hydroxy tryptamine receptor-1 (5-HT_{1D}) agonist and a new drug for the treatment of migraine. The tropisetron[3c] is considered as 5-HT_3-receptor selective antagonist for the treatment of nausea and vomiting induced by cancer chemotherapy and radiotherapy. Bopindolol[4,5] is also a potent, long acting β-adrenergic blocker used to treat hypertension and related to the well-known Pindolol. Delaviridin[6] and Ateviridine[7] are in clinical trials, are reverse transcriptase inhibitors and prevent the spread of HIV-1 in human lymphocytes.

N-Heterocyclic indolyl glyoxylamides[8a] and indole quinone[8b] as orally active anticancer agents. Some of the derivatives and analogues[8c] are considered as selective multidrug resistance associated protein inhibitors in multidrug resistance. In addition most important among non-steroidal anti-inflammatory agent is indomethacin.[8d]

A large number of methods for the construction of the indole nucleus have been reported.[9] However, synthesis of indole and indole fused derivatives by novel approach is of current interest due to their promising activity. In this paper, we studied the regioselective cyclization of unsymmetrical 2,6-dicyanoanilines[10] in a way to obtain indole regioisomers in two ways. The influence of substituents on formation of two regioisomers in different proportion and identification of each isomer has been established. The indole derivatives are further used in the synthesis of novel 4,5-dihydro[1,3]-oxazino [5,4-*b*]indole-6 carbonitriles.

2. Results and discussion

The 2,6-dicyano-3-trifluoromethyl-5-phenyl/methyl aniline **1** is considered to be an interesting trifunctional synthon having two cyano groups *ortho* to amine function and possibility for regioselective cyclisation to obtain indole derivatives. Initially the anilines **1** were reacted with ethyl bromoacetate in DMF under basic medium at 110–120 °C and found that the reaction is highly sensitive to temperature and polarity of solvent, as a result several polymeric products are formed. In order to overcome the problem, the similar reaction is carried in acetonitrile at 80–85 °C under basic medium and obtained 2,3-bifunctionalised indole

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Keywords: 2,6-Dicyanoanilines; Ethyl bromoester; Substituted-iodobenzenes; 2,3-Bifunctionalised indole derivatives; Regioisomers; Sandmeyer reaction; Thorpe–Ziegler reaction.
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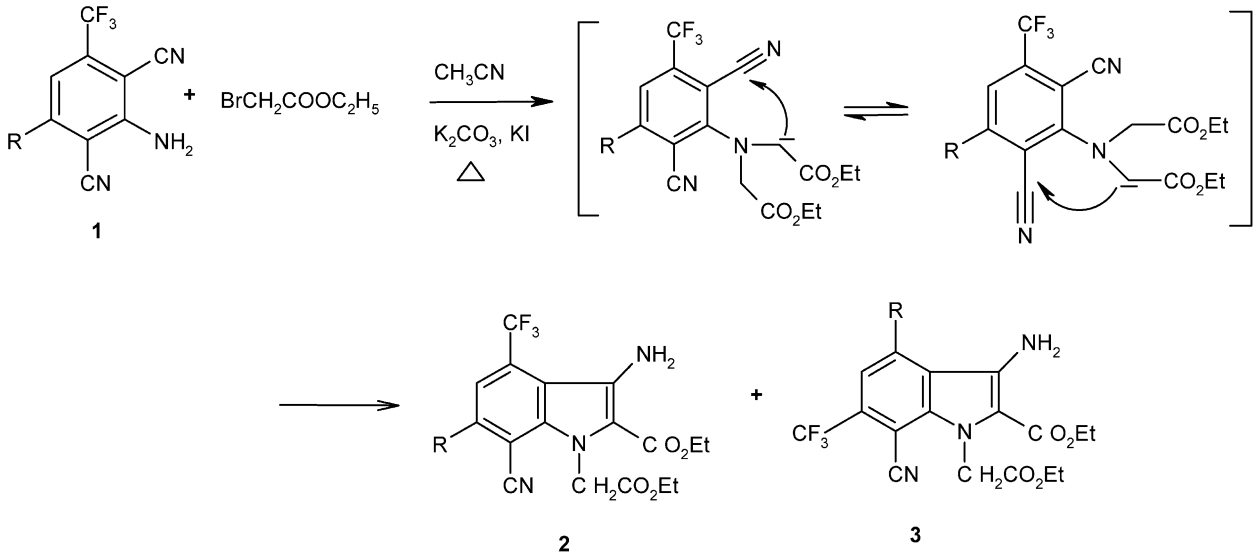


Scheme 1.

regioisomers (**2**,**3**) in different proportion. The reaction details schematically drawn in Scheme 1.

Our earlier experience on alkylation of aniline **1** with ethyl iodide in acetonitrile, potassium carbonate and potassium iodide resulted *N*,*N*-diethylaniline irrespective of mole ratio used. Based on the finding, the following mechanism is formulated. Thus, the reaction is mainly dialkylation of amine function irrespective of the mole ratio of ethyl bromoacetate used and the resultant product is then cyclised by abstraction of a proton from the active methylene by base, followed by attack on one of the nitrile functions in two ways to give two regioisomers in various proportions in a single pot. This type of cyclisation is also called Thorpe–Ziegler[11] reaction. The role of the substituent on the benzene ring during formation of two regioisomers was studied and we found that the phenyl group promotes formation of product **2** as major and product **3** as minor, while methyl group reverses the formation of two isomers. This is attributed to the steric hindrance of phenyl group promotes attack of nucleophile in *para* position rather than *ortho* position. Whereas a methyl group promotes attack of the nucleophile in the *ortho* position. The regioisomers **2**,**3** being very close polarity, a column chromatography method as cited in experimental section is devised to separate them. Each isomer has been identified based on ^{1}H NMR data with reference to the substituents present on benzene ring. A representative pair of isomers is chosen for discussion below.

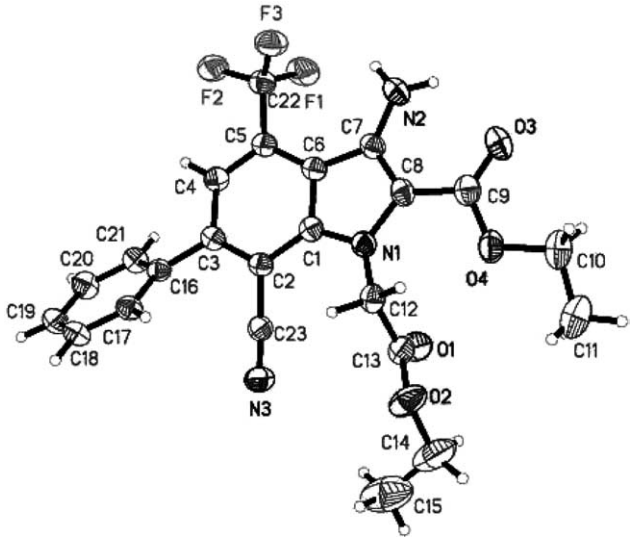
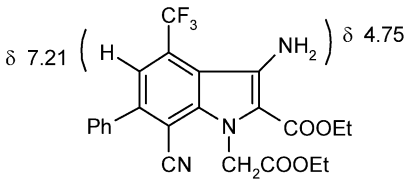


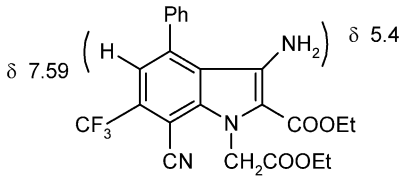
Figure 1. X-ray crystal structure **2b**. Displacement ellipsoids are drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii.

A characteristic difference between two regioisomers **2b** and **3b** is based on chemical shift of NH_2 protons and proton on C-5 carbon in ^{1}H NMR. In isomer **2b** the NH_2 protons appeared as a broad peak at δ 4.75 whereas in isomer **3b** at δ 5.4 and proton on C-5 carbon at δ 7.21 and at δ 7.59,



2b

Chemical shift (up field)



3b

Chemical shift (down field)

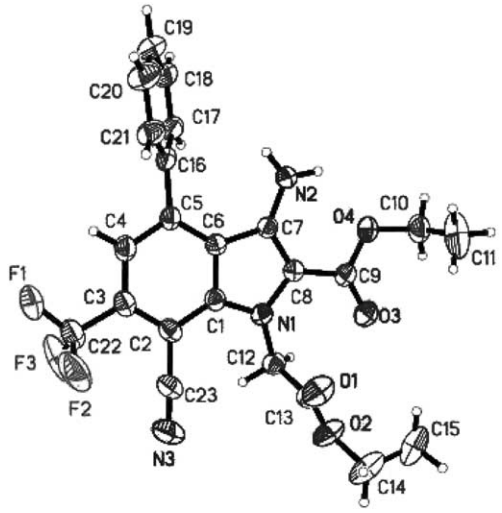


Figure 2. X-ray crystal structure **3b**. Displacement ellipsoids are drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii.

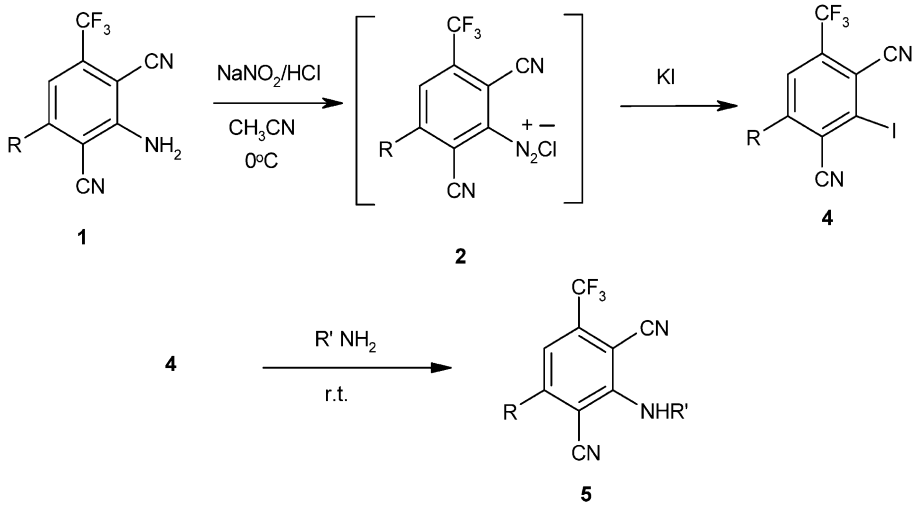
Table 1. Reaction of 2,6-dicyanoanilines with ethyl bromo ester

Entry	Product	R	Ratio (%)	Yield (%)
1	**2a**	CH_3	20	14
2	**3a**	CH_3	80	56
3	**2b**	Ph	85	72
4	**3b**	Ph	15	13

respectively. Based on the facts, it is presumed that the change in chemical shift of NH_2 and proton on C-5 carbon in both the isomers is mainly due to the influence of CF_3 and nitrile groups in benzene ring. The groups CF_3 and CN *para* to each other shifts absorption up field and *ortho* to each other shifts absorption to down field due to electronic effects. ^{13}C NMR data further supports that the CF_3 carbon in **2b** isomer appeared as quartet at δ 126.54 and in **3b** isomer as quartet at δ 123.34 with same coupling constant 272 Hz. However, a clear-cut difference of absorption of *C*–CF_3 is observed. In isomer **2b** the *C*–CF_3 appeared as quartet at δ 132.6 with coupling constant 31 Hz whereas in isomer **3b** the *C*–CF_3 appeared as quartet at δ 126.56 with coupling constant 33 Hz. Thus, the structure of each isomer is determined. It is further confirmed by single crystal X-ray structures determined for both **2b** and **3b** (Figs. 1 and 2).

A similar trend is observed in all the isomers. The products resulted in these reactions have been tabulated in Table 1.

In order to synthesise a number of specified *N*-alkylated indole derivatives and to develop a general methodology for the synthesis of bifunctionalised indole regioisomers an alternate approach is adopted starting from 2,6-dicyanoanilines **1**, as method discussed above is being specific to *N*-acetoxyethyl derivatives due to dialkylation followed by cyclization. Thus compounds **1** were diazotised-using $NaNO_2$/HCl followed by reaction with potassium iodide through Sandmeyer reaction and obtained



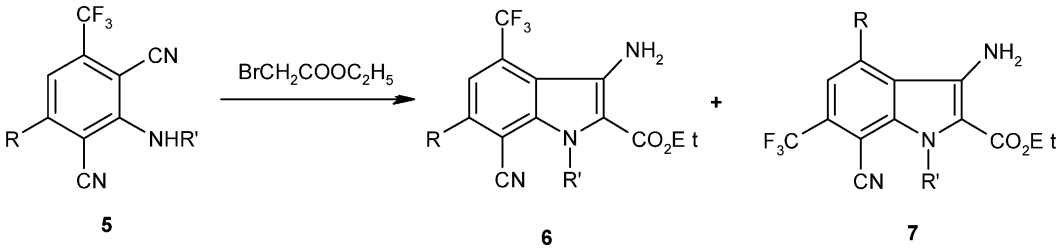
Scheme 2.

Table 2. Preparation of substituted iodobenzenes and anilines

Entry	Product	R	R^1	Yield (%)
5	**4a**	CH_3	—	60
6	**4b**	Ph	—	80
7	**5a**	CH_3	CH_3	45
8	**5b**	CH_3	C_2H_5	58
9	**5c**	CH_3	CH_2Ph	60
10	**5d**	Ph	CH_3	68
11	**5e**	Ph	C_2H_5	70
12	**5f**	Ph	CH_2Ph	78

2,6-dicyano iodo benzenes **4** in good yields. The iodo benzenes **4** are further reacted with various alkyl amines at room temperature to access to number of different substituted anilines **5**. The reaction details presented in Scheme 2 and products are tabulated in Table 2.

Each *N*-substituted aniline **5** on reaction with ethyl bromoacetate in acetonitrile using base gave two regio-isomers of indole derivatives **6** and **7** in definite proportions. The initial reaction is an alkylation of anilines followed by Thorpe–Ziegler cyclisation on nitrile (CN) function to result



Scheme 3.

Table 3. Reaction of substituted anilines with ethyl bromo acetate

Entry	Product	R	R^1	Ratio (%)	Yield (%)
13	**6a**	CH_3	CH_3	23	12
14	**7a**	CH_3	CH_3	77	38
15	**6b**	CH_3	C_2H_5	20	10
16	**7b**	CH_3	C_2H_5	80	42
17	**6c**	CH_3	CH_2Ph	17	10
18	**7c**	CH_3	CH_2Ph	83	50
19	**6d**	Ph	CH_3	90	63
20	**7d**	Ph	CH_3	10	7
21	**6e**	Ph	C_2H_5	89	71
22	**7e**	Ph	C_2H_5	11	9
23	**6f**	Ph	CH_2Ph	93	81
24	**7f**	Ph	CH_2Ph	07	6

products **6** and **7**. The preferential cyclisation to a specified nitrile carbon is mainly depending on substituents present on benzene ring and is similar as established in formation of products **2** and **3**. The reaction details presented in Scheme 3 and products have been tabulated in Table 3.

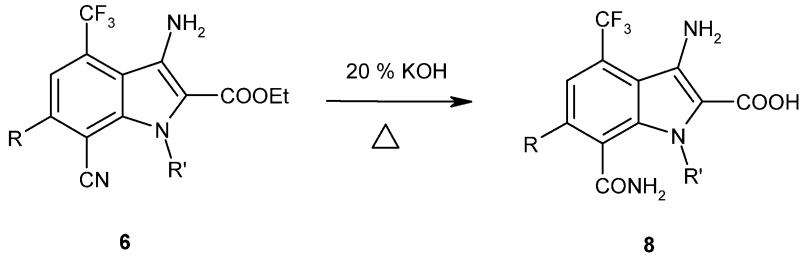
The indole derivatives **6** are further utilized in order to synthesize indole-fused derivatives. Thus, the ethyl-1*H*-indole-2-carboxylates **6** are subjected to alkaline hydrolysis using 20% potassium hydroxide solution on reflux for 2 h. The reaction mixture is cooled to room temperature and diluted with cold water followed by neutralization with glacial acetic acid resulted solid acid product **8**. The product is highly polar and insoluble in most of the organic solvents and identified as 3-amino-7-(aminocarbonyl)-6-substituted-4-trifluoromethyl-1*H*-indole-2-carboxylic acid **8** based on spectral data. The yields are independent of substituents used in benzene as well as in pyrrole ring. During the ester hydrolysis, the nitrile is also hydrolyzed to amide. The compounds are considered as active synthons for further cyclization to obtain tricyclic derivatives (Scheme 4).

The compounds prepared in the above reactions are tabulated in Table 4.

The 3-amino-7-(aminocarbonyl)-6-substituted-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acids **8** are reacted with acetic anhydride at 110 °C to give 1,3-oxazines **9** in good yields. Under the set of conditions, the amide also undergoes dehydration and results in nitrile formation. The number of products formed have been tabulated in Table 5 (Schemes 5 and 6).

3. Conclusion

Regioselective cyclization of 2,6-dicyanoanilines is established based on substituents used as a result bifunctionalised indole regioisomers are formed. Each regioisomer is identified and further utilized to build tricyclic heterocycles.



Scheme 4.

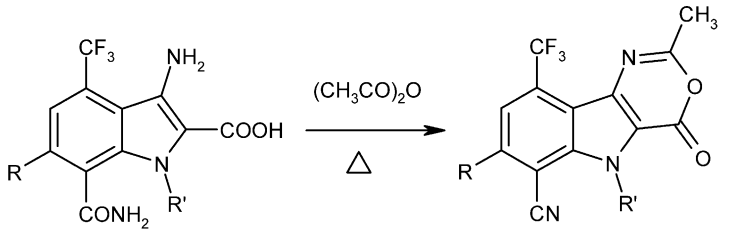
Thus, active functional groups in *ortho* position are fully utilized in anilines to get indoles and further to 1,3-oxazino[5,4-*b*] indoles.

Table 4. Hydrolysis of substituted-1*H*-indole-2-carboxylate

Compound No.	R	R′	Yield (%)
8a	CH_3	CH_3	78
8b	CH_3	$CH_2C_6H_5$	72
8c	CH_3	C_2H_5	68
8d	C_6H_5	CH_3	85
8e	C_6H_5	$CH_2C_6H_5$	81
8f	C_6H_5	C_2H_5	77

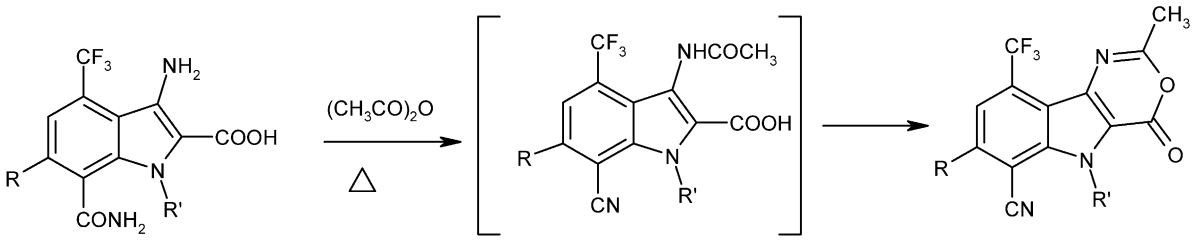
Table 5. Cyclisation of 1*H*-indole-2-carboxylic acids to 1,3-oxazines

Compound No.	R	R′	Yield (%)
9a	CH_3	CH_3	82
9b	CH_3	$CH_2C_6H_5$	80
9c	CH_3	C_2H_5	78
9d	C_6H_5	CH_3	82
9e	C_6H_5	$CH_2C_6H_5$	76
9f	C_6H_5	C_2H_5	78



8 9

Scheme 5.



8 9

Scheme 6.

4. Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker AV 300 and Unity 400 spectrometers, chemical shifts are reported in ppm relative to 0 for TMS melting points were recorded on VMP-AM melting point apparatus and are uncorrected. Elemental analyses were carried out on Elemental Vario EL (Germany) apparatus. IR spectra were recorded on FT-IR Schimadzu Perkin–Elmer 1310 infrared spectrometer. Electron Impact (EI) and Chemical ionization mass spectra (CIMS) were recorded on VG 7070 H eV instrument at 70 eV. During usual workup, all organic extracts were dried over Na_2SO_4 and evaporated. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (Merck); spots were visualized with UV light. Merck silica gel (100–200 mesh) was used for chromatography.

4.1. *N*-1-(2^I-ethoxy-2^I-oxoethyl) 2,3-bifunctionalised-4 or 6-trifluoromethyl indole derivatives (2/3). General procedure

The 2,6-dicyanoanilines **1** (3.48 mmol) were taken in acetonitrile (5 mL) with potassium carbonate (6.96 mmol), potassium iodide (5 mg) and ethyl bromoacetate (6.96 mmol) was added. The reaction mixture was heated to 80–85 °C under stirring in N_2 atmosphere and continued for 12 h. The progress of reaction was monitored by TLC and after completion, the reaction mixture was cooled to room temperature. The solvent (CH_3CN) was evaporated under reduced pressure. The residue was extracted with EtOAc, organic layer was washed with water till the washings were neutral to pH and dried over anhyd Na_2SO_4. The EtOAc was removed by Rotary-evaporator to obtain crude product mixture of two isomers. Each isomer is separated in pure form by column chromatography using silica gel 100–200 mesh size and *n*-hexane–EtOAc (100:3) as eluent.

4.1.1. Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-methyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (2a). 0.19 g, 20% red solid; mp 158 °C; [Found: C, 54.39; H, 4.58; N, 10.53. $C_{18}H_{18}F_3N_3O_4$ requires C, 54.41; H, 4.56; N, 10.57%]; ν_{max} (KBr) 3489, 3371 (NH_2), 2980 (C–H), 2232 (CN), 1735 (CO), 1672 (CO), 1621, 1555, 1324 (C–F), 723 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.32 (3H, t, J=7.3 Hz, CH_3), 1.38 (3H, t, J=7.3 Hz, CH_3), 2.8 (3H, s, CH_3–C (6)), 4.28 (2H, q, J=7.0 Hz, OCH_2), 4.38 (2H, q, J=7.0 Hz, OCH_2), 5.23 (2H, br s, NH_2), 5.58 (2H, s, N–CH_2), 7.06 (1H, s, H–C (5)); *m/z* (LSIMS) 398 (MH^+, 100%), 69 (75%).

4.1.2. Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-methyl-6-(trifluoromethyl)-1*H*-indole-2-carboxylate (3a). 0.77 g, 80% yellow solid; mp 144 °C; [Found: C, 54.42; H, 4.59; N, 10.59. $C_{18}H_{18}F_3N_3O_4$ requires C, 54.41; H, 4.56; N, 10.57%]; ν_{max} (KBr) 3492, 3380 (NH_2), 2982 (C–H), 2241 (CN), 1742 (CO), 1669 (CO), 1619, 1534, 1331 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.36 (3H, t, J=7.3 Hz, CH_3), 1.42 (3H, t, J=7.3 Hz, CH_3), 2.7 (3H, s, CH_3–C (4)), 4.29 (2H, q, J=7.0 Hz, OCH_2), 4.40 (2H, q, J=7.0 Hz, OCH_2), 5.38 (2H, br s, NH_2), 5.6 (2H, s, N–CH_2), 7.31 (1H, s, H–C (5)); *m/z* (LSIMS) 398 (MH^+, 100%), 69 (75%).

4.1.3. Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-6-phenyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (2b). 1.1 g, 85% red solid; mp 148 °C; [Found: C, 60.14; H, 4.38; N, 9.16. $C_{23}H_{20}F_3N_3O_4$ requires C, 60.13; H, 4.39; N,

9.15%]; ν_{max} (KBr) 3492, 3385 (NH_2), 2983 (C–H), 2220 (CN), 1753 (CO), 1694 (CO), 1442, 1259 and 1134 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.32 (3H, t, $J=6.9$ Hz, CH_3) 1.39 (3H, t, $J=6.9$ Hz, CH_3), 4.29 (2H, q, $J=7.0$ Hz, OCH_2), 4.35 (2H, q, $J=7.0$ Hz, OCH_2), 4.75 (2H, br s, NH_2), 5.68 (2H, s, N–CH_2), 7.21 (1H, s, H–C (5)), 7.5 (5H, m, phenyl); δ_C (50 MHz, $CDCl_3$) 14.0, 14.2, 47.3, 47.66, 50.17, 51.76, 60.74, 61.57, 61.76, 90.99, 111.8, 114.6, 117.9, 119.6, 126.5 (q, CF_3, $J=272$ Hz), 128.6, 128.8, 129.2, 132.6 (q, *C*–CF_3, $J=31$ Hz), 137.07, 137.22, 137.87, 142.68, 142.93, 162.05, 168.9, 170.71; *m/z* (LSIMS) 460 (MH^+, 35%).

4.1.4. Ethyl 3-amino-7-cyano-1-(2-ethoxy-2-oxoethyl)-4-phenyl-6-(trifluoromethyl)-1*H*-indole-2-carboxylate (3b). 0.2 g, 15% yellow solid; mp 135 °C; [Found: C, 60.16; H, 4.32; N, 9.19. Anal. Calcd for $C_{23}H_{20}F_3N_3O_4$ requires C, 60.13; H, 4.39; N, 9.15%]; ν_{max} (KBr) 3500, 3361 (NH_2), 2986, 2221 (CN), 1758 (CO), 1678 (CO), 1613, 1437, 1199, 1122 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.31 (3H, t, $J=6.9$ Hz, CH_3) 1.42 (3H, t, $J=6.9$ Hz, CH_3), 4.27 (2H, q, $J=7.0$ Hz, OCH_2), 4.41 (2H, q, $J=7.0$ Hz, OCH_2), 5.41 (2H, br s, NH_2), 5.68 (2H, s, N–CH_2), 7.52 (5H, m, phenyl), 7.59 (1H, s, H–C (5)); δ_C (50 MHz, $CDCl_3$)14.1, 14.23, 47.59, 60.89, 61.75, 97.5, 112.06, 114.57, 116.42, 123.34 (q, CF_3, $J=$ 272 Hz), 126.56 (q, *C*–CF_3, $J=33$ Hz), 129.15, 135.59, 137.61, 138.35, 146.39, 162.15, 168.91; *m/z* (LSIMS) 460 (MH^+, 35%).

4.2. X-ray crystallography

4.2.1. Compound 2b. The crystal belongs to the monoclinic crystal system, space group is $P2_1/c$ (NO.14) with $a=11.3429(8)$ Å, $b=15.9684(11)$ Å, $c=$ 12.9811(9) Å, $\beta=113.329(1)$, $V=2159.0(3)$ Å^3, $\rho_{calc}=$ 1.413 mg m^{-3}, $\lambda=0.71073$ Å, μ(Mo Kα)$=0.115$ mm^{-1}, $F_{000}=952$, $T=273(2)$ K. Data collection yielded 15,353 reflection resulting in 3793 unique, averaged reflection, 3265 with $I>2\sigma(I)$, θ range: 1.96–24.99. Full-matrix least-squares refinement led to a final $R=0.0561$, w$R=0.1331$ and GOOF$=1.144$. Intensity data were measured on Bruker Smart Apex with CCD area detector. CCDC 262067 contains supplementary Crystallographic data for the structure **2b**.

4.2.2. Compound 3b. The crystal belongs to the monoclinic crystal system, space group is $P2_1/c$ (NO.14) with $a=10.2408(6)$ Å, $b=16.9379(10)$ Å, $c=$ 12.7844(7) Å, $\beta=90.425(1)$, $V=2217.5(2)$ Å^3, $\rho_{calc}=$ 1.376 mg m^{-3}, $\lambda=0.71073$ Å, μ(Mo Kα)$=0.112$ mm^{-1}, $F_{000}=952$, $T=273(2)$ K. Data collection yielded 15,735 reflection resulting in 3901 unique, averaged reflection, 3147 with $I>2\sigma(I)$, θ range: 1.99–25.00. Full-matrix least-squares refinement led to a final $R=0.0602$, w$R=0.1668$ and GOOF$=1.036$. Intensity data were measured on Bruker Smart Apex with CCD area detector. CCDC 262068 contains supplementary Crystallographic data for the structure **3b**.

4.3. Substituted iodobenzenes (4). General procedure

To a mixture of 2,6-dicyanoanilines **1** (6.96 mmol), $NaNO_2$ (17.42 mmol) and KI (17.42 mmol) in MeCN (30 mL) at 0 °C was added cold concd HCl (7 mL) drop wise over a period of 30 min, while stirring. The reaction mixture was further stirred at 0 °C for 30 min, warmed to room temperature and the stirring was continued for another 2 h. The solvent was evaporated off and the residue was poured into ice-cold H_2O, the precipitated solid was filtered off, washed with H_2O, and dried. The resulted product is sufficiently pure and is used for further reaction.

4.3.1. 2-Iodo-4-methyl-6-(trifluoromethyl)isophthalonitrile (4a). 1.4 g, 60% colourless solid; mp 68 °C; [Found, C 35.70, H 1.21, N 8.37. $C_{10}H_4F_3IN_2$ requires C 35.71, H 1.20, N 8.34%]; ν_{max} (KBr) 2366, 2238 (CN), 1592, 1150, 706 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.75 (3H, s, CH_3), 7.65 (1H, s, H–C (4)); *m/z* (LSIMS) 336 (M^+, 89%).

4.3.2. 3-Iodo-5-(trifluoromethyl)biphenyl-2,4-dicarbonitrile (4b). 2.22 g, 80% colourless solid; mp 178 °C; [Found: C, 45.29; H, 1.49; N, 7.06. $C_{15}H_6F_3IN_2$ requires C, 45.22; H, 1.51; N, 7.03%]; ν_{max} (KBr) 2234 (CN), 1592, 1539 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.58 (5H, s, aromatic), 7.8 (1H, s, H–C (4)); *m/z* (LSIMS) 398 (M^+, 100%).

4.4. 2,6-Dicyano-3-trifluoromethyl-5-substituted-*N*-substituted anilines (5). General procedure

The iodo compound **4** (2.5 mmol) was suspended in methyl/ethyl/benzyl amine solution (22 mL). The mixture was stirred at room temperature over a period of 6 h. The reaction mixture was partitioned between EtOAc and water; the organic layer was separated, washed with H_2O till washings are neutral to pH and dried over Na_2SO_4. The solvent is removed under reduced pressure and the crude product is purified by column chromatography using Silica gel and hexane–EtOAc (1:50) as eluents.

4.4.1. 4-Methyl-2-(methylamino)-6-(trifluoromethyl)-isophthalonitrile (5a). 0.27 g, 45% pale yellow solid; mp 115 °C; [Found: C, 55.21; H, 3.34; N, 17.53. $C_{11}H_8F_3N_3$ requires C, 55.23; H, 3.37; N, 17.57%]; ν_{max} (KBr) 3331 (NH), 2975 (C–H), 2350, 2232 (CN), 1570, 1121 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.55 (3H, s, CH_3), 3.45 (3H, d, $J=$ 5.1 Hz, N–CH_3), 5.4 (1H, br s, NH), 6.9 (1H, s, H–C (4)); *m/z* (LSIMS) 239 (M^+, 100%).

4.4.2. 2-(Ethylamino)-4-methyl-6-(trifluoromethyl)-isophthalonitrile (5b). 0.37 g, 58% pale yellow solid; mp 59 °C; [Found: C, 56.89; H, 3.93; N, 16.58. $C_{12}H_{10}F_3N_3$ requires C, 56.92; H, 3.98; N, 16.59%]; ν_{max} (KBr) 3338 (NH), 2985 (C–H), 2359, 2225 (CN), 1581, 1133 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.39 (3H, t, CH_3, $J=7.1$ Hz), 2.6 (3H, s, CH_3), 3.9 (2H, qui, $J=6.7$ Hz, N–CH_2), 5.1 (1H, br s, NH), 6.9 (1H, s, H–C (4)); *m/z* (LSIMS) 253 (M^+, 77%), 238.

4.4.3. 2-(Benzylamino)-4-methyl-6-(trifluoromethyl)-isophthalonitrile (5c). 0.47 g, 60% pale yellow solid; mp 100 °C; [Found: C, 64.74; H, 3.79; N, 13.34. $C_{17}H_{12}F_3N_3$ requires C, 64.76; H, 3.83; N, 13.32%]; ν_{max} (KBr) 3329 (NH), 2990 (C–H), 2366, 2288 (CN), 1579, 1165 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.6 (3H, s, CH_3), 4.95 (2H, d, $J=5.1$ Hz, CH_2), 5.42 (1H, br s, NH), 6.97 (1H, s, H–C (4)), 7.4 (5H, s, aromatic H); *m/z* (LSIMS) 315 (M^+, 40%), 91 (100%).

4.4.4. 3-(Methylamino)-5-(trifluoromethyl)biphenyl-2,4-dicarbonitrile (5d). 0.51 g, 68% pale yellow solid; mp 167 °C; [Found: C, 63.73; H, 3.31; N, 13.91. $C_{16}H_{10}F_3N_3$ requires C, 63.79; H, 3.35; N, 13.95%]; ν_{max} (KBr) 3368 (NH), 2223 (CN), 1552, 1476, 1389, 1285 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.48 (3H, d, $J=5.8$ Hz, CH_3), 5.45 (1H, br s, NH), 7.05 (1H, s, H–C (4)), 7.50 (5H, s, aromatic H); *m/z* (LSIMS) 301 (M^+, 100).

4.4.5. 3-(Ethylamino)-5-(trifluoromethyl)biphenyl-2,4-dicarbonitrile (5e). 0.55 g, 70% pale yellow solid; mp 163 °C; [Found: C, 64.72; H, 3.85; N, 13.38. $C_{17}H_{12}F_3N_3$ requires C, 64.76; H, 3.83; N, 13.32%]; ν_{max} (KBr) 3375 (NH), 2977 (C–H), 2219 (CN), 1559, 1457, 1380 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.42 (3H, t, $J=6.9$ Hz, CH_3), 3.92 (2H, qui, $J=6.7$ Hz, CH_2), 5.2 (1H, br s, NH), 7.05 (1H, s, H–C (4)), 7.5 (5H, s, aromatic H); *m/z* (LSIMS) 315 (M^+, 80%), 300.

4.4.6. 3-(Benzylamino)-5-(trifluoromethyl)biphenyl-2,4-dicarbonitrile (5f). 0.74 g, 78% pale yellow solid; mp 143 °C; [Found: C, 70.04; H, 3.76; N, 11.11. $C_{22}H_{14}F_3N_3$ requires C, 70.02; H, 3.74; N, 11.13%]; ν_{max} (KBr) 3378 (NH), 2220 (CN), 1558, 1466, 1382, 1283 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.03 (2H, d, $J=5.8$ Hz, CH_2), 5.58 (1H, br s, NH), 7.18 (1H, s, H–C (4)), 7.4 (5H, s, aromatic H), 7.55 (5H, s, aromatic H); *m/z* (LSIMS) 377 (M^+, 100%), 91 (45%).

4.5. *N*-Alkyl-2-ethylcarboxy-3-amino-4/6-trifluoromethyl-6/4-substituted 7-cyano-indole derivatives (6 and 7). General procedure

The substituted aniline **5** (3.17 mmol) was dissolved in MeCN (9 mL) and anhydrous potassium carbonate (6.34 mmol) followed by ethyl bromoacetate (3.30 mmol) with a catalytic amount of potassium iodide (10 mg) was added to it. The resulting mixture was refluxed for 10–12 h under N_2 atmosphere. The reaction mixture is cooled to room temperature, concentrated in vacuum to remove water miscible acetonitrile. To the residue, ice-cold water was added and extracted with ethyl acetate. The organic layer was washed with brine, followed by water and dried over anhyd Na_2SO_4. Concentrated and chromatographed using Silica gel of 100–200 mesh and hexane–EtOAc, (100:3) as eluents to afford the pure product.

4.5.1. Ethyl 3-amino-7-cyano-1,6-dimethyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (6a). 0.12 g, 23% red solid; mp 174 °C; [Found: C, 55.35; H, 4.39; N, 12.88. $C_{15}H_{14}F_3N_3O_2$ requires C, 55.38; H, 4.34; N, 12.92%]; ν_{max} (KBr) 3502, 3404 (NH_2), 2984 (C–H), 2226 (CN), 1691 (CO), 1614, 1474 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.45 (3H, t, $J=6.9$ Hz, CH_3), 2.82 (3H, s, CH_3), 4.30 (3H, s, N–CH_3), 4.45 (2H, q, $J=6.8$ Hz, OCH_2), 5.2 (2H, br s, NH_2), 7.05 (1H, s, H–C (5)); *m/z* (LSIMS) 326 (MH^+, 42%) 325 (M^+, 100%).

4.5.2. Ethyl 3-amino-7-cyano-1,4-dimethyl-6-(trifluoromethyl)-1*H*-indole-2- carboxylate (7a). 0.4 g, 77% yellow solid; mp 133 °C; [Found: C, 55.31; H, 4.31; N, 12.89. $C_{15}H_{14}F_3N_3O_2$ requires C, 55.38; H, 4.34; N, 12.92%]; ν_{max} (KBr) 3521, 3410 (NH_2), 2892 (C–H), 2218 (CN), 1689 (CO), 1617, 1472 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.45 (3H, t, $J=6.9$ Hz, CH_3), 2.7 (3H, s, CH_3), 4.30 (3H, s, N–CH_3), 4.45 (2H, q, $J=6.8$ Hz, O–CH_2), 5.33 (2H, br s, NH_2) 7.26 (1H, s, H–C (5)); *m/z* (LSIMS) 326 (MH^+, 42%) 325 (M^+, 100%).

4.5.3. Ethyl 3-amino-7-cyano-1-ethyl-6-methyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (6b). 0.11 g, 20% red solid; mp 156 °C; [Found: C, 56.67; H, 4.71; N, 12.32. $C_{16}H_{16}F_3N_3O_2$ requires C, 56.63; H, 4.75; N, 12.38%]; ν_{max} (KBr) 3504, 3408 (NH_2), 2990 (C–H), 2221 (CN), 1690 (CO), 1615, 1615, 1162, 1120 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.45 (6H, t, $J=7.3$ Hz, $2CH_3$), 2.83 (3H, s, CH_3), 4.45 (2H, q, $J=7.0$ Hz, N–CH_2) 4.90 (2H, q, $J=7.0$ Hz, OCH_2), 5.25 (2H, br s, NH_2), 7.07 (1H, s, H–C(5)); *m/z* (LSIMS) 340 (MH^+, 40%) 339 (M^+, 100%).

4.5.4. Ethyl 3-amino-7-cyano-1-ethyl-4-methyl-6-(trifluoromethyl)-1*H*-indole-2-carboxylate (7b). 0.45 g, 80% yellow solid; mp 135 °C; [Found: C, 56.69; H, 4.78; N, 12.32. $C_{16}H_{16}F_3N_3O_2$ requires C, 56.63; H, 4.75; N, 12.38%]; ν_{max} (KBr) 3482, 3401 (NH_2), 2987 (C–H), 2213 (CN), 1682 (CO), 1619 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.45 (6H, t, $J=7.32$ Hz, $2CH_3$), 2.72 (3H, s, CH_3), 4.42 (2H, q, $J=7.0$ Hz, N–CH_2), 4.91 (2H, q, $J=7.0$ Hz, O–CH_2), 5.35 (2H, br s, NH_2), 7.27 (1H, s, H–C (5)); *m/z* (LSIMS) 340 (MH^+, 40%), 339 (M^+, 100%).

4.5.5. Ethyl 3-amino-1-benzyl-7-cyano-6-methyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (6c). 0.13 g, 17% red solid; mp 125 °C; [Found: C, 62.81; H, 4.53; N, 10.49. $C_{21}H_{18}F_3N_3O_2$ requires C, 62.84; H, 4.52; N, 10.46%]; ν_{max} (KBr) 3490, 3372 (NH_2), 2982 (C–H), 2223 (CN), 1677 (CO), 1610, 1524, 1262, 733 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.26 (3H, t, $J=7.3$ Hz, CH_3), 2.87 (3H, s, CH_3), 4.33 (2H, q, $J=6.7$ Hz, O–CH_2), 5.32 (2H, br s, NH_2), 6.17 (2H, s, N–CH_2), 6.9 (2H, m, aromatic H), 7.09 (1H, s, H–C (5)), 7.2 (3H, m, aromatic H); *m/z* (LSIMS) 402 (MH^+, 52%), 401 (M^+, 100%).

4.5.6. Ethyl 3-amino-1-benzyl-7-cyano-4-methyl-6-(trifluoromethyl)-1*H*-indole-2-carboxylate (7c). 0.63 g, 83% yellow solid; mp 139 °C; [Found: C, 62.82; H, 4.55; N, 10.42. $C_{21}H_{18}F_3N_3O_2$ requires C, 62.84; H, 4.52; N, 10.47%]; ν_{max} (KBr) 3491, 3379 (NH_2), 2990 (C–H), 2222 (CN), 1678 (CO), 1611, 1525, 1337, 733 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.28 (3H, t, $J=7.3$ Hz, CH_3), 2.69 (3H, s, CH_3), 4.35 (2H, q, $J=6.7$ Hz, O–CH_2), 5.49 (2H, br s, NH_2), 6.22 (2H, s, N–CH_2), 6.92 (2H, m, aromatic H), 7.25 (1H, s, H–C (5)), 7.30 (3H, m, aromatic H); *m/z* (LSIMS) 402 (MH^+, 55%), 401 (M^+, 100%), 91 (67%).

4.5.7. Ethyl 3-amino-7-cyano-1-methyl-6-phenyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (6d). 0.77 g, 90% red solid; mp 147 °C; [Found: C, 62.06; H, 4.19; N, 10.81. $C_{20}H_{16}F_3N_3O_2$ requires C, 62.01; H, 4.16; N, 10.85%]; ν_{max} (KBr) 3519, 3380 (NH_2), 2979 (C–H), 2218 (CN), 1665 (CO), 1605, 1513, 1443, 620 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.42 (3H, t, $J=6.9$ Hz, CH_3), 4.35 (3H, s, N–CH_3), 4.40 (2H, q, $J=6.9$ Hz, O–CH_2), 4.71 (2H, br s, NH_2), 7.18 (1H, s, H–C (5)), 7.45 (2H, m, aromatic H), 7.52 (3H, m, aromatic H); *m/z* (LSIMS) 388 (MH^+, 49%), 387 (M^+, 100%).

4.5.8. Ethyl 3-amino-7-cyano-1-methyl-4-phenyl-6-(trifluoromethyl)-1*H*-indole-2-carboxylate (7d). 0.08 g, 10% yellow solid; mp 217 °C; [Found: C, 62.05; H, 4.12; N, 10.81. $C_{20}H_{16}F_3N_3O_2$ requires C, 62.01; H, 4.16; N, 10.85%]; ν_{max} (KBr) 3520, 3381 (NH_2), 2980 (C–H), 2219 (CN), 1667 (CO), 1607, 1514, 1445, 621 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.51 (3H, t, $J=6.9$ Hz, CH_3), 4.37 (3H, s, N–CH_3), 4.45 (2H, q, $J=6.9$ Hz, O–CH_2), 5.40 (2H, br s, NH_2), 7.42 (1H, s, H–C (5)), 7.55 (5H, m, aromatic H); *m/z* (LSIMS) 388 (MH^+, 45%), 387 (M^+, 100%).

4.5.9. Ethyl 3-amino-7-cyano-1-ethyl-6-phenyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (6e). 0.9 g, 89% red solid; mp 120 °C; [Found: C, 62.88; H, 4.59; N, 10.41. $C_{21}H_{18}F_3N_3O_2$ requires C, 62.84; H, 4.52; N, 10.47%]; ν_{max} (KBr) 3382 (NH_2), 2960 (C–H), 2221 (CN), 1688 (CO), 1603 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.5 (6H, t, $J=6.9$ Hz, $2CH_3$), 4.40 (2H, q, $J=7.0$ Hz, N–CH_2), 4.7 (2H, br s, NH_2), 4.98 (2H, q, $J=7.0$ Hz, O–CH_2), 7.19 (1H, s, H–C (5)), 7.5 (5H, m, aromatic-H); *m/z* (LSIMS) 402 (MH^+, 72%), 401 (M^+, 100%).

4.5.10. Ethyl 3-amino-7-cyano-1-ethyl-4-phenyl-6-(trifluoromethyl)-1*H*-indole-2-carboxylate (7e). 0.11 g, 11% yellow solid; mp 196 °C; [Found: C, 62.88; H, 4.57; N, 10.43. $C_{21}H_{18}F_3N_3O_2$ requires C, 62.84; H, 4.52; N, 10.47%]; ν_{max} (KBr) 3496, 3366 (NH_2), 2963 (C–H), 2223 (CN), 1667 (CO), 1122 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.5 (6H, t, $J=6.9$ Hz, $2CH_3$), 4.45 (2H, q, $J=7.0$ Hz, N–CH_2), 5.0 (2H, q, $J=7.0$ Hz, O–CH_2), 5.42 (2H, br s, NH_2), 7.4 (1H, s, H–C (5)), 7.57 (5H, m, aromatic-H); *m/z* (LSIMS) 402 (MH^+, 72%), 401 (M^+, 100%).

4.5.11. Ethyl 3-amino-1-benzyl-7-cyano-6-phenyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylate (6f). 1.19 g, 93% red solid; mp 125 °C; [Found: C, 67.36; H, 4.39; N, 9.09. $C_{26}H_{20}F_3N_3O_2$ requires C, 67.38; H, 4.35; N, 9.07%]; ν_{max} (KBr) 3450, 3378 (NH_2), 2923 (C–H), 2232 (CN), 1672 (CO), 1135 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.28 (3H, t, $J=7.1$ Hz, CH_3), 4.30 (2H, q, $J=7.0$ Hz, OCH_2), 4.83 (2H, br s, NH_2), 6.25 (2H, s, N–CH_2), 6.97 (2H, m, aromatic H), 7.23 (1H, s, H–C (5)), 7.25 (3H, m, aromatic H), 7.50 (5H, m, aromatic-H); *m/z* (LSIMS) 464 (MH^+, 60%), 463 (M^+, 100%), 91 (46%).

4.5.12. Ethyl 3-amino-1-benzyl-7-cyano-4-phenyl-6-(trifluoromethyl)-1*H*-indole-2-carboxylate (7f). 0.09 g, 7% yellow solid; mp 159 °C; [Found: C, 67.32; H, 4.31; N, 9.11. $C_{26}H_{20}F_3N_3O_2$ requires C, 67.38; H, 4.35; N, 9.07%]; ν_{max} (KBr) 3451, 3378 (NH_2), 2922 (C–H), 2234 (CN), 1673 (CO), and 1136 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30 (3H, t, $J=7.1$ Hz, CH_3), 4.32 (2H, q, $J=7.0$ Hz, O–CH_2), 5.52 (2H, br s, NH_2) 6.25 (2H, s, N–CH_2), 6.93 (2H, m, aromatic H), 7.25 (3H, m, aromatic H), 7.45 (1H, s, H–C (5)), 7.51 (5H, m, aromatic-H); *m/z* (LSIMS) 464 (MH^+, 72%), 463 (M^+, 100%) 91 (46%).

4.6. Preparation of 3-amino-7-(aminocarbonyl)-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (8a–f)

The ethyl 3-amino-4-trifluoromethyl substituted 1*H*-indole-2-carboxylate (2 mmol) was suspended in 20% potassium hydroxide solution (5 mL) and refluxed for 2 h. Reaction mixture was poured in crushed ice, then neutralised with glacial acetic acid till it shows acidic to litmus paper. Separated solid was filtered, washed with water and dried.

4.6.1. 3-Amino-7-(aminocarbonyl)-1,6-dimethyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (8a). 0.5 g, 78% brown colored solid; mp 168 °C; [Found: C, 49.51; H, 3.81; N, 13.29. $C_{13}H_{12}F_3N_3O_3$ requires C, 49.53; H, 3.84; N, 13.33%]; ν_{max} (KBr) 3414, 2360, 1730, 1670, 1132 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.75 (3H, s, CH_3), 3.92 (3H, s, N–CH_3), 5.4 (2H, br s, NH_2), 6.95 (1H, s, H–C(5)), 7.92 (1H,s, NH, $CONH_2$), 8.19 (1H, s, NH, $CONH_2$); *m/z* (LSIMS) 315 (M^+), 271.

4.6.2. 3-Amino-7-(aminocarbonyl)-1-benzyl-6-methyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (8b). 0.56 g, 72% brown colored solid; mp 157 °C; [Found: C, 58.27; H, 4.11; N, 10.71. $C_{19}H_{16}F_3N_3O_3$ requires C, 58.31; H, 4.12; N, 10.74%]; ν_{max} (KBr) 3444, 2360, 1660, 1117 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.72 (3H, s, CH_3), 5.35 (2H, br s, NH_2), 6.78 (2H, s, N–CH_2), 6.98 (1H, s, H–C(5)), 7.08–7.15 (5H, m, phenyl), 7.82 (1H, s, NH, $CONH_2$), 8.12 (1H, s, NH, $CONH_2$); *m/z* (LSIMS) 392 (MH^+), 391, 347, 91.

4.6.3. 3-Amino-7-(aminocarbonyl)-1-ethyl-6-methyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (8c). 0.45 g, 68% brown colored solid; mp 182 °C; [Found: C, 51.02; H, 4.23; N, 12.72. $C_{14}H_{14}F_3N_3O_3$ requires C, 51.07; H, 4.29; N, 12.76%]; ν_{max} (KBr) 3425, 2372, 1725, 1692, 1135 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.45 (3H, t, CH_3), 2.62 (3H, s, CH_3), 4.3 (2H, q, N–CH_2), 5.20 (2H, br s, NH_2), 7.0 (1H, s, H–C(5)), 7.65 (1H, s, NH, $CONH_2$), 7.9 (1H, s, NH, $CONH_2$); *m/z* (LSIMS) 329 (M^+), 285.

4.6.4. 3-Amino-7-(aminocarbonyl)-1-methyl-6-phenyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (8d). 0.64 g, 85% brown colored solid; mp 178 °C; [Found: C, 57.27; H, 3.72; N, 11.11. $C_{18}H_{14}F_3N_3O_3$ requires C, 57.30; H, 3.74; N, 11.14%]; ν_{max} (KBr) 3448, 2320, 1659, 1370, 1128 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.2 (3H, s, CH_3), 5.15 (2H, br s, NH_2), 6.99 (1H, s, H–C(5)), 7.45 (2H, m, phenyl), 7.55 (3H, m, phenyl), 8.05 (1H, s, NH, $CONH_2$) 8.32 (1H, s, NH, $CONH_2$); *m/z* (LSIMS) 377 (M^+), 333.

4.6.5. 3-Amino-7-(aminocarbonyl)-1-benzyl-6-phenyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (8e). 0.73 g, 81% brown colored solid; mp 150 °C; [Found: C, 63.53; H, 3.97; N, 9.24. $C_{24}H_{18}F_3N_3O_3$ requires C, 63.57; H, 4.00; N, 9.27%]; ν_{max} (KBr) 3446, 2380, 1652, 1381, 1121 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.43 (2H, br s, NH_2), 5.73 (2H, s, N–CH_2), 7.1 (1H, s, H–C(5)), 7.15 (2H, m, phenyl), 7.32 (3H, m, phenyl), 7.5 (5H, m, phenyl), 7.61 (1H, s, NH, $CONH_2$), 7.85 (1H, s, NH, $CONH_2$); *m/z* (LSIMS) 453 (M^+), 409, 91.

4.6.6. 3-Amino-7-(aminocarbonyl)-1-ethyl-6-phenyl-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acid (8f). 0.6 g, 77% brown colored solid; mp 135 °C; [Found: C, 58.27; H, 4.09; N, 10.71. $C_{19}H_{16}F_3N_3O_3$ requires C, 58.31; H, 4.12; N, 10.74%]; ν_{max} (KBr) 3435, 3369, 2380, 1659, 1262 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.23 (3H, t, CH_3), 4.75

(2H, q, N–CH_2), 5.46 (2H, br s, NH_2), 7.01 (1H, s, H–C(5)), 7.41–7.49 (5H, m, phenyl), 7.52 (1H, s, NH, $CONH_2$), 7.89 (1H, s, NH, $CONH_2$); *m/z* (LSIMS) 391 (M^+), 347.

4.7. Preparation of 2-methyl-4-oxo-7-substituted-9-(trifluoromethyl)-4,5-dihydro[1,3] oxazino[5,4-*b*]-6-carbonitriles (9a–f)

The 3-amino-7-(aminocarbonyl)-4-(trifluoromethyl)-1*H*-indole-2-carboxylic acids (1 mmol) were taken in acetic anhydride (2 mL), heated to reflux for 2 h. The reaction mixture was cooled to room temperature and poured into crushed ice. The separated solid was extracted with chloroform dried over sodium sulphate and concentrated. The crude product is purified through column using Silica gel and EtOAc–hexane (5:100) as eluents.

4.7.1. 2,5,7-Trimethyl-4-oxo-9-(trifluoromethyl)-4,5-dihydro[1,3]oxazino[5,4-*b*] indole-6-carbonitrile (9a). 0.26 g, 82% pale yellow colored solid; mp 210 °C; [Found: C, 56.02; H, 3.11; N, 13.03. $C_{15}H_{10}F_3N_3O_2$ requires C, 56.08; H, 3.14; N, 13.08%]; ν_{max} (KBr) 2971, 2223, 1742, 1615, 1122 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.5 (3H, s, CH_3), 2.93 (3H, s, CH_3), 4.55 (3H, s, CH_3), 7.32 (1H, s, H–C(8)); *m/z* (LSIMS) 321 (M^+).

4.7.2. 5-Benzyl-2,7-dimethyl-4-oxo-9-(trifluoromethyl)-4,5-dihydro[1,3]oxazino[5,4-*b*]indole-6-carbonitrile (9b). 0.32 g, 80% pale yellow colored solid; mp 212 °C; [Found: C, 63.43; H, 3.52; N, 10.54. $C_{21}H_{14}F_3N_3O_2$ requires C, 63.48; H, 3.55; N, 10.58%]; ν_{max} (KBr) 2976, 2224, 1747, 1615, 1338, 1127 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.58 (3H, s, CH_3), 3.02 (3H, s, CH_3), 6.35 (2H, s, CH_2), 7.1 (2H, m, phenyl), 7.25 (3H, m, phenyl), 7.41 (1H, s, H–C(8)); *m/z* (LSIMS) 397 (M^+).

4.7.3. 5-Ethyl-2,7-dimethyl-4-oxo-9-(trifluoromethyl)-4,5-dihydro[1,3]oxazino[5,4-*b*]indole-6-carbonitrile (9c). 0.26 g, 78% pale yellow colored solid; mp 198 °C; [Found: C, 57.28; H, 3.59; N, 12.51. $C_{16}H_{12}F_3N_3O_2$ requires C, 57.32; H, 3.61; N, 12.53%]; ν_{max} (KBr) 2983, 2229, 1752, 1622, 1131 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.68 (3H, t, CH_3), 2.51 (3H, s, CH_3), 2.91 (3H, s, CH_3), 4.72 (2H, q, CH_2), 7.35 (1H, s, H–C(8)); *m/z* (LSIMS) 335 (M^+).

4.7.4. 2,5-Dimethyl-4-oxo-7-phenyl-9-(trifluoromethyl)-4,5-dihydro[1,3]oxazino [5,4-*b*]indole-6-carbonitrile (9d). 0.31 g, 82% pale yellow colored solid; mp 220 °C; [Found: C, 62.63; H, 3.11; N, 10.92. $C_{20}H_{12}F_3N_3O_2$ requires C, 62.67; H, 3.16; N, 10.96%]; ν_{max} (KBr) 2222, 1748, 1618, 1217, 1130 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.62 (3H, s, CH_3), 4.7 (3H, s, CH_3), 7.5–7.65 (5H, m, phenyl), 7.71 (1H, s, H–C(8)); *m/z* (LSIMS) 383 (M^+).

4.7.5. 5-Benzyl-2-methyl-4-oxo-7-phenyl-9-(trifluoromethyl)-4,5-dihydro[1,3] oxazino [5,4-*b*]indole-6-carbonitrile (9e). 0.35 g, 76% pale yellow colored solid; mp 232 °C; [Found: C, 67.94; H, 3.48; N, 9.11. $C_{26}H_{16}F_3N_3O_2$ requires C, 67.97; H, 3.51; N, 9.15%]; ν_{max} (KBr) 2228, 1752, 1612, 1214, 1128 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.38 (3H, s, CH_3), 6.43 (2H, s, CH_2), 7.15 (1H, s, H–C(8)), 7.22–7.27 (5H, m, phenyl), 7.49 (3H, m, phenyl), 7.58 (2H, m, phenyl); *m/z* (LSIMS) 459 (M^+).

4.7.6. 5-Ethyl-2-methyl-4-oxo-7-phenyl-9-(trifluoromethyl)-4,5-dihydro[1,3] oxazino[5,4-*b*]indole-6-carbonitrile(9f). 0.3 g, 78% pale yellow colored solid; mp 205 °C; [Found: C, 63.43; H, 3.51; N, 10.54. $C_{21}H_{14}F_3N_3O_2$ requires C, 63.48; H, 3.55; N, 10.58%]; ν_{max} (KBr) 2984, 2207, 1747, 1194 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.65 (3H, t, CH_3), 2.35 (3H, s, CH_3), 5.2 (2H, q, CH_2), 7.4 (1H, s, H–C(8)), 7.43–7.56 (5H, m, phenyl); *m/z* (LSIMS) 397 (M^+).

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Regioselective synthesis of 1-allyl- and 1-arylmethyl uracil and thymine derivatives

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Abstract—2,4-Bis(trimethylsiloxy) pyrimidines **1** with allyl halides and arylmethyl halides in 1,2-dichloroethane in the presence of I_2 regioselectively provide 1-allyl-/1-arylmethyl-uracil and thymine derivatives. The secondary aryl alkyl and diaryl methyl halides with **1** provide chiral 1-arylalkyl/1-(diarylmethyl) uracil/thymine derivatives. The procedure has been extended to the synthesis of fluorescent uracil/thymine derivatives.

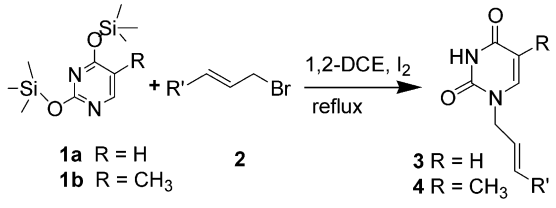
1. Introduction

The nucleoside analogues have been cornerstones for chemotherapy of cancer and viral diseases.[1] However, the clinical toxicities arising due to the various reasons, limited uptake, high susceptibility to catabolism and rapid emergence of resistance towards virus or cancer cells has led to diversification to non-nucleoside inhibitors (NNIs).[2] The NNIs do not interact at the catalytic site of the enzyme but interact in a hydrophobic pocket through π–π or π–HC interactions.[3] These feeble interactions through their multiple interacting features become significant structural force to inhibit the functioning of enzyme.[4] The role of π–π interactions is emphasized in the development of new multi drug resistance modulators[5] as well as in the interactions of olefinic and arene moieties of aromatic amino acids (phenylalanine, tyrosine, tryptophane, which constitute ~8% of the known protein sequence) with the most prevalent biological cations[6,7] Na^+ and K^+. Distinctly, in NNIs the phosphorylation is not an obligatory step for their ability to block the DNA replication and cell growth.

This role of arene moieties and π-bonds in effective participation in biological systems has drawn the attention to the development of synthetic procedures for arene/allyl substituted nucleic bases—uracil and thymine, etc. Such 1-allyl-and 1-arylmethyl nucleobases can prove vital synthons for the development of new drug molecules. However, their synthesis has found scarce attention[8] and available methodologies through base mediated allylation of free nucleic bases[9–11] or Lewis acid catalysed allylation of 2,4-bis(trimethylsiloxy)pyrimidines[2b] suffer with non-regioselectivity of reactions at N-1 and N-3 and poor yields.

2. Results and discussion

In the present manuscript, a simple and general approach for the synthesis of pyrimidine-2,4-diones bearing allyl, arylmethyl, alkyl aryl methyl, diarylmethyl substituents at N-1 is presented (Scheme 1).



Scheme 1.

Refluxing of a solution of **1a**[12] with allyl bromide (1.2 equiv) in 1,2-dichloroethane in the presence of I_2 (5 mol%, catalyst), after usual reaction workup regioselectively provides **3a** (93%), mp 109 °C (lit.[11] mp 110 °C)., M^+ (*m/z*) 152. The structure of **3a** was confirmed by the presence of H-5 and H-6 doublets at δ 5.74 and 7.16 and one 2H doublet at δ 4.38 due to NCH_2 along with the olefinic protons and exchangeable NH (δ 9.68) in its ^1H NMR spectrum. Similarly, **1b** with allyl bromide in 1,2-DCE and I_2 gave **4a** (68%), mp 77 °C, M^+ *m/z* 166. On

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using benzene as solvent, the yields of **3a** (54%) and **4a** (52%) were lowered and in solvents like CH_3CN and $CHCl_3$ the allylation product was not formed. In these reactions, the formation of 1,3-diallyluracil/thymine was not observed even in traces (tlc). Similarly, **1a/1b**[12] with cinnamyl bromide, ethyl 4-bromocrotonate and 1-bromo-2-butene provide respective compounds **3b–d** and **4b–d** in 64–85% yields. (Table 1, entries 2–8).

Table 1. Synthesis of 1-allyluracil and 1-allylthymine derivatives

S. no	R in **1**	R′ in **2/3/4**	Reaction time (h)	Product (yield %)
1	H	H	24	**3a** (93)
2	H	CH_3	24	**3b** (85)
3	H	C_6H_5	36	**3c** (75)
4	H	$CO_2C_2H_5$	36	**3d** (70)
5	CH_3	H	24	**4a** (68)
6	CH_3	CH_3	36	**4b** (67)
7	CH_3	C_6H_5	36	**4c** (68)
8	CH_3	$CO_2C_2H_5$	36	**4d** (64)

The earlier reported Pd (0) catalyzed allylation of uracil and derivatives performed in DMSO[10] or organic aqueous medium (H_2O–CH_3CN) or (H_2O–THF) in the presence of base DBU, and water soluble sulphonated triphenylphosphine P(C_6H_4-m-$SO_3Na)_3$,[11] gave mixture of 1-allyl- and 1,3-diallyluracil derivatives and in general, large excess (4–8 equiv) of the allylating reagent has to be used.

Therefore, the present procedure which requires only equivalent amounts of expensive allylating reagent and provides regioselectively 1-allyl products irrespective of the nature of allyl halide, provides a general and economical procedure for the synthesis of 1-allyl uracil/thymine derivatives.

The presence of benzyl group on the nucleobase due to its higher participation in cation-π and π–π interactions can provide more opportunities for their interactions in biological systems.[13] Further, it is possible to tune these interactions by the presence of electron-withdrawing or electron-donating groups on the aryl rings and the bulk of the substituents. So, the above methodology was extended for the synthesis of 1-(arylmethyl) uracil derivatives.

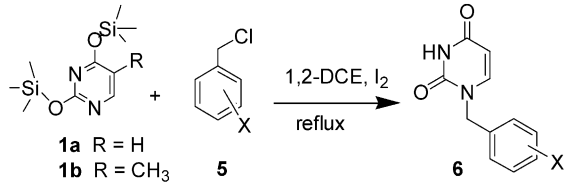
2,4-Bis(trimethylsiloxy) pyrimidine (**1a**) on refluxing with phenylmethyl chloride in 1,2-dichloroethane gave 1-phenylmethyluracil **6a** (87%) mp 160 °C, M^+ *m/z* 203 (Table 2, entry 1) (Scheme 2). Similarly, **1a** and **1b** with substituted aryl-methyl halides provided respective 1-arylmethyluracil/thymine derivatives **6b–6j** in 68–87% yields. In all these cases, the assignment of H-5 and H-6 signals was made on the basis of decoupling of H-5 which appeared at δ 5.54–6.10. It is observed that in cases of **6a–6g** H-6 is present at δ 7.14–7.20 and in **6h**, the C-6H signal is shifted considerably upfield (δ 6.66) which may be attributed to the increased shielding by phenyl ring to H-6 due to the presence of three electron-donating methyl groups at the phenyl moiety.

The reactions of **1** with secondary alkyl halides would provide an opportunity to synthesize the chiral uracil molecules. The role of 4-chlorophenyl methyl group in cetirizine defines the importance of such moieties and the present approach can provide synthons for developing uracil based isosteres of cetirizine.[14] **1** on reaction with secondary chiral and achiral halides provided respective 1-substituted uracil derivatives **9** in 65–80% yields (Table 3, Scheme 3).

Table 2. Synthesis of 1-arylmethyluracil and 1-arylmethylthymine derivatives

S. no	R in **1** and **6**	X in **5/6**	Time (h)	Yield (%)
1	H	H	24	**6a** (87)
2	H	2-Cl[a]	48	**6b** (74)
3	H	3-Cl	72	**6c** (81)
4	H	4-Cl	48	**6d** (81)
5	H	4-F	48	**6e** (70)
6	H	2,4-diCl[a]	36	**6f** (69)
7	H	2-NO_2	36	**6g** (68)
8	H	2,4,6-triMe	36	**6h** (62)
9	CH_3	2-Cl	36	**6i** (87)
10	CH_3	2,4-diCl	36	**6j** (85)

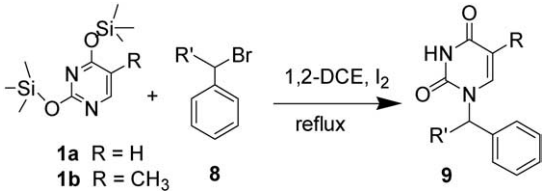
[a] In these cases 1,3-bis(2-chlorophenylmethyl)uracil (**7a**) and 1,3-bis(2,4-dichlorophenylmethyl)uracil (**7b**) derivatives were isolated in <3% yields.



Scheme 2.

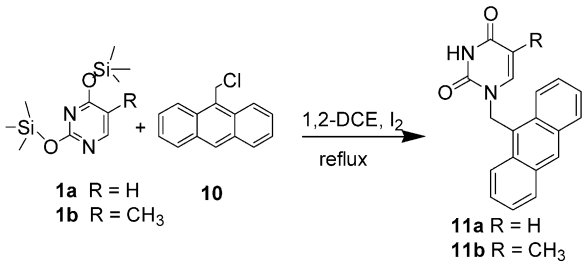
Table 3. Synthesis of 1-diarylalkyl/1-alkyaryl uracil/thymine derivatives

S. no.	R	R′	Reaction time (h)	Yield (%)
1	H	CH_3	36	**9a** (69)
2	H	C_6H_5	36	**9b** (70)
3	H	4-ClC_6H_5	48	**9c** (65)
4	CH_3	CH_3	36	**9d** (78)
5	CH_3	C_6H_5	36	**9e** (80)



Scheme 3.

The presence of a fluorescent moiety[15] on the pyrimidine base could provide a handle to study the interactions of nucleobases through fluorescence measurements. **1a/1b** on reaction with 9-anthracenylmethyl chloride **10** provided **11a** (84%), mp 240 °C, M^+ (*m/z*) 302 and **11b** (80%), mp 260 °C, M^+ *m/z* 316 (Scheme 4). An upfield shift of C-6H ((δ 6.86) from their normal position, i.e. δ 7.14 clearly showed the shielding of H-6 by anthracene moiety. Compounds **11** in their UV–vis spectra showed λ_{max} at 387, 367, 349, 333 nm and their fluorescence spectra gave



Scheme 4.

λ_{max} at 412, 390, 363 nm, the characteristic spectral features of anthracene moiety. On excitation at λ_{max} 365 nm, the solutions of compounds **11** in acetonitrile gave $\phi_f = 0.23 \pm 0.01$.

3. Conclusions

2,4-Bis(trimethylsiloxy)pyrimidines **1** on refluxing with allyl halides and primary and secondary arylalkyl halides provide a simple and general methodology for 1-allyl- and 1-arylmethyl- and 1-diarylmethyl- uracil/thymine derivatives.

4. Experimental

4.1. General

The melting points were determined in capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 200 MHz and JEOL JNM 300 MHz machines. High resolution mass spectra were recorded on micromass (using GC–MS).

4.2. General procedure for the preparation of 1-substituted uracil/thymine derivatives

A solution of 2,4-bis-(trimethylsiloxy)pyrimidine (0.01 mol), allyl/arylmethyl/arylalkyl halide (0.012 mol) and I_2 (20 mg) in 1,2-DCE (20 ml) was refluxed. After completion of the reaction (tlc), the cooled reaction mixture was treated with ethanol (10 ml). The solid separated was filtered and recrystallized from ethanol or acetonitrile to get pure 1-substituted uracil/thymine derivative. In case of reactions with 2-chloro- and 2,4-dichloroarylmethyl chloride, the respective 1,3-bis (arylmethyl)uracils were isolated from filtrate by column chromatography using ethyl acetate and hexane mixtures as eluents.

4.2.1. 1-Allyl-1*H*-pyrimidine-2,4-dione (3a). 93%; White solid, mp 109 °C (ethanol) (lit.[11] mp 110 °C); ^{1}H NMR ($CDCl_3$,): δ 4.38 (d, 2H, $J=7.0$ Hz, NCH_2), 5.22–5.34 (m, 2H, $=CH_2$), 5.74 (1H, d, $J=7.8$ Hz, H-5), 5.81–5.95 (1H, m, =CH), 7.16 (1H, d, $J=7.8$ Hz, H-6), 9.68 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 47.24 (−ve, CH_2), 99.37 (+ve, CH-5), 115.71 (−ve, $=CH_2$), 130.76 (+ve, CH), 143.18 (+ve, CH-6), 148.83 (ab, C), 161.87 (ab, C); ν_{max} (KBr) cm^{-1}: 1693 (C=O), 3566 (NH); HRMS: found 152.0588, $C_7H_8N_2O_2$ requires 152.0586.

4.2.2. 1-But-2-enyl-1*H*-pyrimidine-2,4-dione (3b). 85%; White solid, mp 88 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.76 (3H, d, $J=6.4$ Hz, CH_3), 4.27 (2H, d, $J=6.2$ Hz, NCH_2), 5.46–5.57 (1H, m, =CH), 5.71 (1H, d, $J=8$ Hz, H-5), 5.73–5.83 (1H, m, =CH), 7.18 (1H, d, $J=8$ Hz, H-6), 9.58 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT) ($CDCl_3$): δ 17.65 (+ve, CH_3), 49.39 (−ve, CH_2), 102.16 (+ve, CH-5), 124.20 (+ve, =CH), 131.74 (+ve, =CH), 143.78 (+ve, CH-6), 151.02 (ab, C), 164.28 (ab, C); ν_{max} (KBr) cm^{-1}: 1683 (C=O), 3486 (NH); HRMS found: 166.0745, $C_8H_{10}N_2O_2$ requires 166.0742.

4.2.3. 1-(3-Phenyl-allyl)-1*H*-pyrimidine-2,4-dione (3c). 75%; Light yellow crystals, mp 170 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 4.52 (2H, d, $J=6.2$ Hz, NCH_2), 5.75 (1H, d, $J=8.0$ Hz, H-5), 6.23 (1H, dt, $J_1=6.2$ Hz, $J_2=16$ Hz, =CH), 6.65 (1H, d, $J=16$ Hz, =CH), 7.24 (1H, d, $J=8.0$ Hz, H-6), 7.26–7.38 (5H, m, ArH), 8.77 (1H, b, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 47.52 (−ve, CH_2), 100.12 (+ve, CH-5), 121.88 (+ve, CH), 124.82 (+ve, ArCH), 126.34 (+ve, =CH), 126.94 (+ve, ArCH), 131.65 (+ve, =CH), 134.25 (ab, C),143.05 (+ve, CH-6), 149.40 (ab, C), 162.40 (ab, C); ν_{max} (KBr) (cm^{-1}): 1685 (C=O), 3480 (NH); HRMS found: 228.0898, $C_{13}H_{12}N_2O_2$ requires 228.0899.

4.2.4. 1-(3-Ethoxycarbonyl-allyl)-1*H*-pyrimidine-2,4-dione (3d). 70%; White solid, mp 110 °C (ethanol); ^{1}H NMR ($CDCl_3$,): δ 1.28 (3H, t, $J=7.2$ Hz, CH_3), 4.23 (2H, q, $J=7.2$ Hz, OCH_2), 4.49 (2H, d, $J=6.0$ Hz, NCH_2), 5.76 (1H, d, $J=8.0$ Hz, H-5), 5.87 (1H, d, $J=16$ Hz, =CH), 6.89 (1H, dt, $J_1=6.0$ Hz, $J_2=16$ Hz, =CH), 7.11 (d, $J=8.0$ Hz, H-6), 9.43 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 14.09 (+ve, CH_3), 48.24 (−ve, CH_2), 60.83 (−ve, CH_2), 103.01 (+ve, CH-5), 124.02 (+ve, =CH), 140.14 (+ve, =CH), 143.70 (+ve, CH-6) 150.64 (ab, C), 163.80 (ab, C), 165.16 (ab, C). HRMS found: 224.0798, $C_{10}H_{12}N_2O_4$ requires 224.0797.

4.2.5. 1-Allyl-5-methyl-1*H*-pyrimidine-2,4-dione (4a). 68%; White solid, mp 77 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.90 (3H, s, CH_3). 4.32 (2H, d, $J=6.8$ Hz, NCH_2), 5.21–5.33 (2H, m, $=CH_2$), 5.79–5.88 (1H, m, =CH), 6.95 (1H, s, H-6), 8.35 (1H, s, NH, exchanges with D_2O.); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.25 (+ve, CH_3), 49.70 (−ve, CH_2), 110.92 (ab, C-5), 119.08 (−ve, $=CH_2$), 131.70 (+ve, =CH), 141.21 (+ve, CH-6), 150.99 (ab, C), 164.47 (ab, C); HRMS found: 166.0743, $C_8H_{10}N_2O_2$ requires 166.0742.

4.2.6. 1-But-2-enyl-5-methyl-1*H*-pyrimidine-2,4-dione (4b). 67%; White solid, mp 110 °C (ethanol); ^{1}H NMR ($CDCl_3$,): δ 1.74(3H, d, $J=6.4$ Hz, CH_3), 1.93 (3H, s, CH_3), 4.32 (2H, dd, $J_1=7.0$ Hz, $J_2=24$ Hz NCH_2), 5.31–5.47 (1H, m, =CH), 5.65–5.83 (1H, m, =CH), 6.98 (1H, s, H-6), 8.68 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.24 (+ve, CH_3), 17.64 (+ve, CH_3), 49.15 (−ve, CH_2), 110.55 (ab, C-5), 124.55 (+ve, =CH), 131.23 (+ve, =CH), 139.76 (+ve, CH-6), 151.49

(ab, C), 164.65 (ab, C); HRMS found: 180.0898 $C_9H_{12}N_2O_2$ requires 180.0899.

4.2.7. 1-(3-Phenyl-allyl)-5-methyl-1*H*-pyrimidine-2,4-dione (4c). 68%; Light yellow crystals, mp 208 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.86 (3H, s, CH_3), 4.49 (d, J=6.4 Hz, 2H, NCH_2), 6.24 (1H, dt, J_1=6.4 Hz, J_2=15.8 Hz, =CH), 6.62 (1H, d, J=15.8 Hz, =CH), 7.04 (1H, s, H-6), 7.21–7.34 (5H, m, ArH), 8.68 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 11.83 (+ve, CH_3), 48.74 (−ve, CH_2), 109.94 (ab, C-5), 122.75 (+ve, ArCH), 126.03 (+ve, ArCH), 127.61 (+ve, =CH), 128.13 (+ve, ArCH), 133.29 (+ve, =CH), 135.45 (ab, C), 139.63 (+ve, CH-6), 150.82 (ab, C), 164.42 (ab, C); HRMS found: 241.1051 $C_{14}H_{14}N_2O_2$ requires 241.1055.

4.2.8. 1-(3-Ethoxycarbonyl-allyl)-5-methyl-1*H*-pyrimidine-2,4-dione (4d). 64%; White solid, mp 105 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, J=7.2 Hz, CH_3), 1.92 (3H, s, CH_3), 4.20 (2H, q, J=7.2 Hz, OCH_2), 4.48 (2H, dd, J_1=5.2 Hz, J_2=1.8 Hz, NCH_2), 5.91 (1H, dt, J_1=1.8 Hz, J_2=16 Hz, =CH), 6.88 (1H, dt, J_1=5.2 Hz, J_2=16 Hz, =CH), 6.96 (1H, s, H-6), 8.50 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.18 (+ve, CH_3), 14.05 (+ve, CH_3), 50.44 (−ve, CH_2), 60.67 (−ve, CH_2), 110.99 (ab, C-5), 123.69 (+ve, CH), 139.58 (+ve, CH), 140.58 (+ve, CH), 150.82 (ab, C), 164.57 (ab, C), 165.45 (ab, C); HRMS found: 238.0957 $C_{11}H_{14}N_2O_4$ requires 238.0954.

4.2.9. 1-Benzyl-1*H*-pyrimidine-2,4-dione (6a). 87%; White solid, mp 160 °C (ethanol), ^{1}H NMR ($CDCl_3$): δ 4.94 (2H, NCH_2), 5.72 (1H, d, J=7.9 Hz, H-5), 7.17 (1H, d, J=7.9 Hz, H-6), 7.31–7.42 (5H, m, ArH), 9.01 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA): δ 52.30 (−ve, CH_2), 102.67 (+ve, CH-5), 128.16 (+ve, ArCH), 129.17 (+ve, ArCH), 129.37 (+ve, ArCH), 133.48 (ab, ArC), 146.04 (+ve, CH-6), 151.94 (ab, C), 166.19 (ab, C); HRMS found: 202.0741, $C_{11}H_{10}N_2O_2$ requires 202.0742.

4.2.10. 1-(2-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6b). 74%; White solid, mp 210 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 5.11 (2H, s, NCH_2), 6.04 (1H, d, J=7.8 Hz, H-5), 7.25–7.47 (4H, m, ArH), 7.54 (1H, d, J=7.8 Hz, H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 49.98 (−ve, CH_2), 102.28 (+ve, CH-5), 127.70 (+ve, ArCH), 130.23 (+ve, ArCH), 130.74 (+ve, ArCH), 131.09 (ab, ArC), 131.34 (+ve, ArCH), 133.86 (ab, ArC), 146.23(+ve, CH-6), 151.66 (ab, C), 166.17 (ab, C); HRMS found: 236.0358 $C_{11}H_9^{35}ClN_2O_2$ requires 236.0353. found 238.0327 $C_{11}H_9^{37}ClN_2O_2$ requires 238.0323.

4.2.11. 1-(3-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6c). 81%; White solid, mp 140 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 4.87 (2H, s, NCH_2), 5.69 (1H, d, J=7.8 Hz, H-5), 7.18 (1H, d, J=7.8 Hz, H-6), 7.25–7.35 (4H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 51.84 (−ve, CH_2), 102.96 (+ve, CH-5), 126.24 (+ve, ArCH), 128.23 (+ve, ArCH), 129.51 (+ve, ArCH), 130.77 (+ve, ArCH), 131.5 (ab, ArC), 135.41 (ab, ArC), 146.09 (+ve, CH-6), 152.00 (ab, C), 166.40 (ab, C); HRMS found: 236.0351, $C_{11}H_9^{35}ClN_2O_2$ requires 236.0353. found 238.0323 $C_{11}H_9^{37}ClN_2O_2$ requires 238.0323.

4.2.12. 1-(4-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6d). 81%; White solid, mp 180 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 4.94 (2H, s, NCH_2), 5.97 (1H, d, J=7.8 Hz, H-5), 7.25–7.37 (5H, m, 4×ArH, H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 51.83 (−ve, NCH_2), 102.76 (+ve, CH-5), 129.59 (+ve, ArCH), 129.63(+ve, ArCH), 131.98 (ab, ArC), 135.40 (ab, ArC), 146.27 (+ve, CH-6), 151.99 (ab, C), 166.47 (ab, C); HRMS found: 236.0352, $C_{11}H_9^{35}ClN_2O_2$ requires 236.0353. found 238.0325 $C_{11}H_9^{37}ClN_2O_2$ requires 238.0323.

4.2.13. 1-(4-Fluorobenzyl)-1*H*-pyrimidine-2,4-dione (6e). 70%; White solid, mp 230 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 4.97 (2H, s, NCH_2), 6.04 (1H, d, J=7.8 Hz, H-5), 7.10 (2H, t, J=8.4 Hz, $(CH)_2CF$), 7.28–7.38 (2H, m, 2×ArH), 7.43 (1H, d, J=7.8 Hz, H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 51.71 (−ve, NCH_2), 102.71 (+ve, CH-5), 116.34 (+ve, d, J=21.6 Hz, ^{2}CH-CF), 129.40 (ab, d, J=3 Hz, ^{4}C-F), 130.29 (+ve, d, J=8.7 Hz, ^{3}CH-CF), 145.98 (+ve, CH-6), 151.90 (ab, C), 161.452, 164.75 (ab, d, J=247 Hz, C-F), 166.33 (ab, C); HRMS found: 220.0645, $C_{11}H_9FN_2O_2$ requires 220.0648.

4.2.14. 1-(2,4-Dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (6f). 69%; White solid, mp 140 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 5.09 (2H, s, NCH_2), 6.00 (1H, d, J=7.8 Hz, H-5), 7.25–7.46 (3H, m, ArH), 7.51 (1H, d, J=7.8 Hz, H-6); ^{13}C(normal/DEPT-135) ($CDCl_3$+TFA): δ 49.72 (−ve, NCH_2), 102.32 (+ve, CH-5), 128.03 (+ve, ArCH), 129.70 (ab, ArC), 130.08 (+ve, ArCH), 132.29 (+ve, ArCH), 134.54 (ab, ArC), 136.18 (ab, ArC), 146.23 (+ve, CH-6), 151.61(ab, C), 166.12 (ab, C); HRMS found: 292.9853 (M^++Na) $C_{11}H_8^{35}Cl_2N_2O_2Na$ requires 292.9855.

4.2.15. 1-(2-Nitrobenzyl)-1*H*-pyrimidine-2,4-dione (6g). 68%; Light yellow solid, mp 120 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA) δ: 5.12 (2H, s, NCH_2), 6.04 (1H, d, J=7.8 Hz, H-5), 7.41 (1H, d, J=8.0 Hz, ArH-3), 7.55 (1H, d, J=7.8 Hz, H-6), 7.59 (1H, t, J=8.0 Hz, ArH-4), 772 (1H, t, J=8.0 Hz, ArH-5), 8.15 (1H, t, J=8.0 Hz, ArH-3); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA) δ: 50.09 (−ve, CH_2), 102.82 (+ve, C-5), 125.88 (+ve, ArCH), 130.17 (+ve, ArCH), 130.36 (+ve, ArCH), 134.56 (+ve, ArCH), 135.08 (ab, ArC), 146.86 (+ve, CH-6), 147.87 (ab, C), 151.62 (ab, C), 166.26 (ab, C); HRMS found: 247.0654 $C_{11}H_9N_3O_4$ requires 247.0593.

4.2.16. 1-(2,4,6-Trimethylbenzyl)-1*H*-pyrimidine-2,4-dione (6h). 62%; White solid, mp 230 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 2.24 (6H, s, 2×CH_3), 2.30 (3H, s, CH_3), 4.90 (2H, s, NCH_2), 5.54 (1H, d, J=8.0 Hz, H-5), 6.66 (1H, d, J=8.0 Hz, H-6), 6.93 (2H, s, ArH), 9.12 (1H, b, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 19.73 (+ve, CH_3), 21.02 (+ve, CH_3), 44.81 (−ve, CH_2), 101.94 (+ve, CH-5), 126.27 (ab, ArC), 129.82 (+ve, ArCH), 138.27 (ab, ArC), 139.24 (ab, ArC), 141.36 (+ve, CH-6), 151.68 (ab, C), 162.08 (ab, C); HRMS found: 244.1213, $C_{14}H_{16}N_2O_2$ requires 244.1212.

4.2.17. 1-(2-Chlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (6i). 87%; White soild, mp 132 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 1.97 (3H, s, CH_3), 5.12 (2H, s, NCH_2), 7.28–7.51 (5H, m, 4×ArH+H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.94 (+ve, CH_3), 50.01 (−ve, CH_2), 112.32 (ab, C-5), 127.82 (+ve, ArCH), 130.38 (+ve, ArCH), 130.90 (+ve, ArCH), 131.10 (ab, ArC), 133.90 (ab, ArC), 142.66 (+ve, CH-6), 152.46 (ab, C), 166.66 (ab, C); HRMS found: 250.0513 $C_{12}H_{11}^{35}ClN_2O_2$ requires 250.0509. found: 252.0488 $C_{12}H_{11}^{37}ClN_2O_2$ requires 252.0479.

4.2.18. 1-(2,4-Dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (6j). 85%; White solid, mp 140 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 1.99 (3H, s, CH_3), 5.09 (2H, s, NCH_2), 7.32–7.51 (5 H, m, 4×ArH+H-6); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.98 (+ve, CH_3), 49.48 (−ve, CH_2), 108.73 (ab, C-5), 127.95 (+ve, ArCH), 129.85 (ab, ArC), 129.98 (+ve, ArCH), 131.81 (+ve, ArCH), 134.53 (ab, ArC), 136.24 (ab, ArC), 142.29 (+ve, CH-6), 152.33 (ab, C), 166.41 (ab, C); HRMS found: 284.0119, $C_{12}H_{10}^{35}Cl_2N_2O_2$ requires 284.0119. found 286.0094, $C_{12}H_{10}^{35}Cl^{37}ClN_2O_2$ requires 286.0089.

4.2.19. 1,3-Bis(2-chlorobenzyl)-1*H*,3*H*-pyrimidine-2,4-dione (7a). White solid, mp 74 °C; FAB Mass *m/z* 361, 363, 365 (100: 62: 10) (M^+); ^{1}H NMR ($CDCl_3$): δ 4.97 (2H, s, CH_2), 5.22 (2H, s, CH_2), 5.74 (1H, d, J=7.8 Hz, 5-H), 6.91–7.01(1H, m, ArH), 7.11–7.17 (2H, m, ArH), 7.24–7.43 (4H, m, 5 ArH, C-6H), ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 42.23 (−ve, CH_2), 49.95 (−ve, CH_2), 101.81 (+ve, CH), 126.59 (+ve, ArCH), 126.73 (+ve, ArCH), 127.42 (+ve, ArCH), 128.23 (+ve, ArCH), 129.55 (+ve, ArCH), 129.97 (+ve, ArCH), 130.57 (+ve, ArCH), 132.94 (+ve, ArCH), 132.58 (ab, C), 132.94 (ab, C),133.58 (ab, C), 133.93 (ab, C), 142.31 (+ve, CH), 151.49 (ab, C), 162.63 (ab, C).(found: C, 59.63; H, 3.62; N, 7.42%; $C_{18}H_{14}Cl_2N_2O_2$ requires C, 59.66; H, 3.86; N, 7.73%).

4.2.20. 1,3-Bis(2,4-dichlorobenzyl)-1*H*,3*H*-pyrimidine-2,4-dione (7b). 72%; White solid, mp 72 °C; FAB mass *m/z* 429, 431, 433, 435 (78:100: 50:12) (M^+); ^{1}H NMR ($CDCl_3$): δ 5.01 (2H, s, CH_2), 5.21 (2H, s, CH_2), 5.85 (1H, d, J=7.8 Hz, C5H), 6.91(1H, d, J=8.0 Hz, ArH), 7.15 (1H, d, J=8.0 Hz, ArH), 7.24–7.51 (5H, m, 4×ArH, C-6H). The decoupling of C-5H doublet at δ 5.85 converts δ 7.37 doublet into singlet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 41.88 (−ve, CH_2), 49.71 (−ve, CH_2), 101.97 (+ve, CH), 127.07 (+ve, ArCH), 127.80 (+ve, ArCH), 127.99 (+ve, ArCH), 129.41 (+ve, ArCH), 129.82 (+ve, ArCH), 131.11 (ab, C), 131.71 (+ve, ArCH), 132.31 (ab, C), 133.46 (ab, C), 133.73 (ab, C), 134.28 (ab, C), 135.39 (ab, C), 142.40 (+ve, CH), 151.41 (ab, C), 162.49 (ab, C). (Found: C, 49.84; H, 2.42; N, 6.21%. $C_{18}H_{12}Cl_4N_2O_2$ requires C, 50.12; H, 2.78; N, 6.50%).

4.2.21. 1-(1-Phenyl-ethyl)-1*H*-pyrimidine-2,4-dione (9a). 69%; White solid, mp 85 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.70 (3H, d, J=7.2 Hz, CH_3), 5.66 (1H, d, J=8.0 Hz, H-5), 5.99 (1H, q, J=7.2 Hz, CH), 7.03 (1H, d, J=8.0 Hz, H-6), 7.24-7.37 (5H, m, ArH), 9.26 (1H, bs, NH, exchanges with D_2O); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 18.33 (+ve, CH_3), 53.20 (+ve, CH), 102.66 (+ve, CH-5), 127.18 (+ve, ArCH), 128.32 (+ve, ArCH), 128.99 (+ve, ArCH), 138.57 (ab, ArC), 141.05 (+ve, CH-6), 151.28 (ab, C), 163.72 (ab, C); HRMS found: 216.0901 $C_{12}H_{12}N_2O_2$ requires 216.0899.

4.2.22. 1-Benzhydryl-1*H*-pyrimidine-2,4-dione (9b). 70%; White solid, mp 180 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 5.67 (1H, d, J=7.8 Hz, H-5), 7.07 (1H, d, J=7.0 Hz, H-6), 7.13–7.36 (11H, m, ArH+CH), 9.53 (1H, bs, ArH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ: 62.19 (+ve, CH), 102.06 (+ve, C-5), 128.38 (+ve, ArCH), 128.44 (+ve, ArCH), 129.00 (+ve, ArCH), 137.49 (ab, C), 142.39 (+ve, CH-6), 151.21 (ab, C), 163.71 (ab, C; HRMS found: 278.1055, $C_{17}H_{14}N_2O_2$ requires 278.1055.

4.2.23. 1-(4-Chlorophenyl phenyl methyl)-1*H*-pyrimidine-2,4-dione (9c). 65%; Thick yellow oil; ^{1}H NMR ($CDCl_3$): δ 5.68 (1H, d, J=8.4 Hz, H-5), 7.06 (1H, d, J=8.4 Hz, CH-6), 7.11–7.42 (10H, m, 9×ArH+CH), 9.47(1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 61.32 (+ve, CH), 102.31 (+ve, CH-5), 126.49 (+ve, ArCH), 128.38 (+ve, ArCH), 128.74 (+ve, ArCH), 129.21 (+ve, ArCH), 129.60 (+ve, ArCH), 134.45 (ab, ArC), 136.06 (ab, ArC), 141.95 (+ve, CH-6) 151.13 9 (ab, C), 163.46 (ab, C).

4.2.24. 1-(1-Phenyl-ethyl)-5-methyl-1*H*-pyrimidine-2,4-dione (9d). 78%; White solid, mp 110 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.69 (3H, d, J=7.0 Hz, CH_3), 1.84 (3H, s, CH_3), 6.02 (1H, q, J=7.0 Hz, CH), 6.82 (1H, s, H-6), 7.27–7.39 (5H, m, ArH), 9.58 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 11.94 (+ve, CH_3), 17.99 (+ve, CH_3), 55.66 (+ve, CH), 112.67 (ab, C-5), 127.38 (+ve, ArCH), 129.42 (+ve, ArCH), 129.60 (+ve, ArCH), 137. 37 (ab, ArC), 140.35 (+ve, CH-6), 152.58 (ab, C=O)), 166.80 (ab, C=O); HRMS found: 230.1057 $C_{13}H_{14}N_2O_2$ requires 230.1055.

4.2.25. 1-Benzhydryl-5-methyl-1*H*-pyrimidine-2,4-dione (9e). 80%; White solid, mp 180 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.93 (3H, s, CH_3), 6.88 (1H,s, CH), 7.07 (1H, s, H-6), 7.14–7.41 (10H, m, ArH), 9.52 (1H, b, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.18 (+ve, CH_3), 64.19 (+ve, CH), 111.96 (ab, C-5), 128.51 (+ve, ArCH), 129.26 (+ve, ArCH), 129.50 (+ve, ArCH), 136.28 (ab, ArC), 143.02 (+ve, CH-6), 152.61 (ab, C=O), 166.53 (ab, C=O); HRMS found: 292.1214, $C_{18}H_{16}N_2O_2$ requires 292.1212.

4.2.26. 1-Anthracen-9-ylmethyl-1*H*-pyrimidine-2,4-dione (11a). 84%; Yellow solid, mp 240 °C (ethanol); UV–vis (CH_3CN): λ_{max} 387(ε 6300), 367(ε 7100), 349(ε 4800), 333(ε 2400); ^{1}H NMR ($CDCl_3$+TFA) δ: 5.71 (1H, d, J=7.8 Hz, H-5), 5.97 (2H, s, NCH_2), 6.86 (1H, d, J=8.0 Hz, H-6), 7.56-7.68 (4H, m, ArH), 8.06 (2H, d, J=8.4 Hz, ArH), 8.10 (2H, d, J=8.4 Hz, ArH), 8.64 (1H, s, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 43.34 (−ve, NCH_2), 102.01 (+ve, CH-5), 120.95 (ab, ArC), 122.07 (+ve, ArCH), 125.90 (+ve, ArCH), 128.70 (+ve, ArCH), 130.04 (+ve, ArCH), 131.18 (+ve, ArCH), 131.56 (ab, ArC), 131.68 (ab, ArC), 145.21(+ve, CH-6), 153.47 (ab, C=O), 167.47 (ab, C=O); HRMS found: 302.1056, $C_{19}H_{14}N_2O_2$ requires 302.1055.

4.2.27. 1-Anthracen-9-ylmethyl-5-methyl-1*H*-pyrimidine-2,4-dione (11b). 80%; Yellow solid, mp 260 °C (ethanol); UV–vis (CH_3CN): λ_{max} 387(ε 7500), 367(ε 7800), 349(ε 4800), 333(ε 1600); ^1H NMR ($CDCl_3$+TFA): δ 1.58 (3H, s, CH_3), 5.92 (2H, s, NCH_2), 6.65 (1H, s, H-6), 7.53–7.69 (4H, m, ArH), 8.06 (4H, t, J=8.4 Hz, ArH), 8.64 (1H, s, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.95 (+ve, CH_3), 43.22 (−ve, CH_2), 111.96 (ab, CH-5), 121.85 (ab,ArC), 122.20 (+ve, ArCH), 125.61 (+ve, ArCH), 128.32 (+ve, ArCH), 129.74 (+ve, ArCH), 130.67 (+ve, ArCH), 131.44 (ab, ArC), 131.46 (ab, ArC), 140.01 (+ve, CH-6), 152.40 (ab, C=O), 166.21 (ab, C=O); HRMS found: 316.1207, $C_{20}H_{16}N_2O_2$ requires 316.1212.

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Nitroaldol-reaction of aldehydes in the presence of non-activated Mg:Al 2:1 hydrotalcite; a possible new mechanism for the formation of 2-aryl-1,3-dinitropropanes

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Abstract—Commercially available, non-activated 2:1 Mg:Al hydrotalcite catalyzes the nitroaldol reaction between a variety of aromatic and aliphatic aldehydes and simple nitroalkanes such as nitromethane and nitroethane. A new mechanism is proposed for the formation of the 1,3-dinitropropanes. The *threo*/*erythro* diastereoselectivity of the nitroethane-adducts was determined by ^{1}H NMR spectroscopy and was found to range from 50:50 to 70:30. The substituents of the aromatic aldehydes influenced the isomer ratio.

1. Introduction

The Henry reaction, which is also known as nitroaldol addition, is a fundamental reaction in organic chemistry.[1] The 2-nitroalkanols formed are an important class of compounds often used as key intermediates in the synthesis of numerous products. They are particularly versatile intermediates for the synthesis of nitroalkenes, 2-amino-alcohols and 2-nitro-ketones. They are also useful intermediates in the synthesis of valuable pharmaceuticals and pharmaceutical intermediates such as (*S*)-propanolol,[2] or (*S*)-(−)-pindolol,[3] antibiotics (e.g., ezomycin,[4] tunicamycin[5]), natural products such as the sex pheromone of the Douglas Fir Tussock moth[6] or cyclopeptide alkaloids.[7] Moreover, 2-nitroalkanol derivatives are important as fungicides.[8] Due to their versatility, a considerable amount of work about their synthesis has been reported.

Several organic and inorganic catalysts have been described in the literature for the preparation of 2-nitroalcohols from nitroalkane and carbonyl derivatives. These include alkali metal hydroxides, alkaline earth oxides, carbonates, bicarbonates, alkoxides, quaternary ammonium salts. Both protic and aprotic solvents and solvent-free conditions have been used. The development of new catalysts for the Henry reaction needs to avoid competitive reactions such as aldol condensation, epimerization of stereogenic centers created during the reaction, the Cannizzaro reaction, the Tishchenko reaction, and the Nef-type reaction. Moreover, 2-nitro-alcohols may be dehydrated to the nitroalkenes that readily polymerize. Since the Henry reaction creates stereogenic centers in the products, considerable effort has also been directed toward the development of enantioselective versions.[9,10] A lot of various new catalysts have recently been developed, like Amberlyst A-21,[11] benzyltrimethyl-ammonium hydroxide,[12] rhodium complex,[13] proaza-phosphatranes,[14] Mg–Al–O–*t*Bu hydrotalcite,[15] heterobimetallic complexes with lanthanide BINOL system,[16] or guanidines.[17]

Nevertheless, the development of new catalyst and procedure of the Henry reaction has been constantly in focus, because of the need to reduce the amount of toxic waste materials and byproducts, to develop new asymmetric catalyst, and to use less toxic, 'green' promoters.

Nowadays, the use and design of environmental-friendly solid acid and solid base catalysts has become an important research target. These materials have a lot of useful properties, for example, high versatility, easy treatment and work-up, mild experimental conditions, high yield and selectivity, they are inexpensive and often reusable. Hydrotalcites (HT), the anionic layered double hydroxides (LDHs) have potential application as

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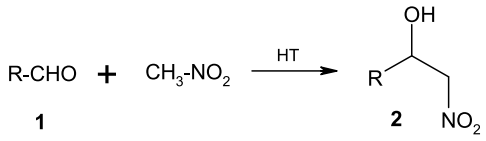


Scheme 1.

Table 1. Effect of solvent on the reaction between 3-nitrobenzaldehyde **1f** and nitromethane using non-activated Mg:Al 2:1 HT

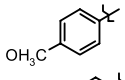
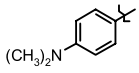
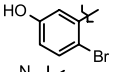
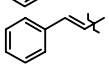
Entry	Solvent	Temperature (°C)	Time (h)	Conversion (%)[a]
1	Ethanol	20	1	46
2	Tetrahydrofuran	20	1	40
3	Nitromethane	20	1	65
4	Nitromethane	20	3.5	75
5	Nitromethane	20	5	95

[a] Determined by ^{1}H NMR, based on the starting aldehyde.

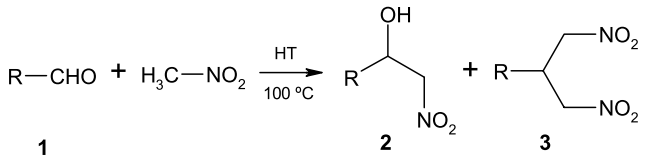
adsorbents, anion-exchangers and basic catalysts. These materials can be described by the formula $[M(II)_{(1-x)}M(III)_x(OH)_2]^{x+}(A^{m-}_{x/m})nH_2O$, where M(II) is a divalent ion like Mg, Cu, Ni, Co, Mn, Zn; M(III) is a trivalent ion like Al, Fe, Cr, Ga; A is the compensating anion like OH^-, Cl^-, NO_3^-, CO_3^{2-}, SO_4^{2-} and x is in the range of 0.1–0.33, closely resembles that of brucite, $Mg(OH)_2$. In HT a number of the divalent cations are replaced by trivalent cations, resulting in positively charged layers. Charge-balancing anions and water molecules are situated in the interlayers.[18] Numerous studies on their structure,[19] physical properties[20] and their catalytic activity have been reported, for example, in Michael addition,[21] Knoevenagel condensation,[22] or Meerwein–Ponndorf–Verley reduction.[23]

In this paper, we present the development of an eco-friendly, simple and convenient, catalytic diastereoselective method for the synthesis of 2-nitroalkanols from nitroalkanes and aldehydes, catalyzed by commercially available Mg:Al 2:1 hydrotalcite. Our research target was to

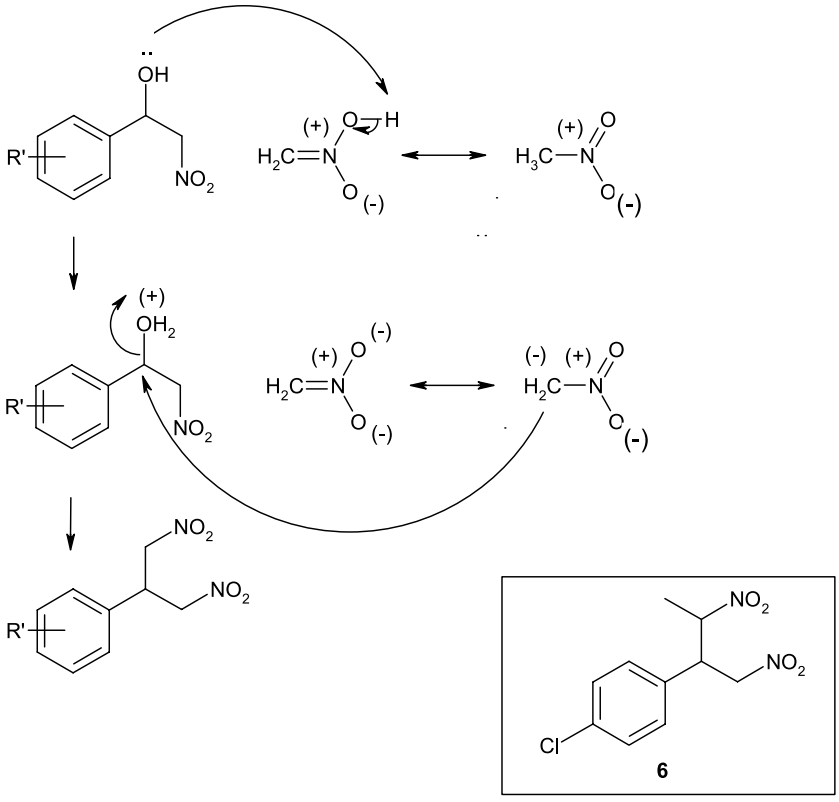
Table 2. Henry reaction between various aldehydes and nitromethane using Mg:Al 2:1 HT

2	R	Temperature (°C)	Time (h)	Conversion[a] (%)[b]
2a[27]		20	5	80 (74)[b]
2b		20	5	100 (91)[b]
2c		20	5	100 (95)[b]
2d		20	5	30
		100	5	8
2e[28]		20	5	70 (62)[b]
2f[29]		20	5	100 (95)[b] (94)[c]
2g[30]		20	5	60 (54)[b]
2h[15]		20	5	86 (80)[b]
2i[31]		20	5	43
2j[29]		20	5	8
		20	10	8
2k		20	5	47
2l[27]		20	5	100 (94)[b]
2m[30]		20	5	10
2n[32]		20	5	52
2o[32]	CH_3	20	5	(67)[b]
2p[27]	CH_3–CH_2	20	5	(90)[b]
2q[32]	$(CH_3)_3$–C	20	5	40

[a] Determined by ^{1}H NMR, based on the starting aldehyde.
[b] Isolated yield in parenthesis.
[c] Isolated yield after third cycle.



Scheme 2.



Scheme 3.

investigate the catalytic activity of this type of hydrotalcite, which does not need inert atmosphere, can be easily handled and does not require high-temperature pretreatment or long procedures like rehydration to be activated.

2. Results and discussion

Based on the data provided by the manufacturer the commercial Mg:Al 2:1 hydrotalcite (HAS-type) has the molecular formula $[Mg_4Al_2(OH)_{12}]CO_3$, its specific surface (BET) is 80 m^2/g, and the pH of its 5% suspension (filtered) is 8.6. The elemental analysis of the product dried at 110 °C for 2 h gave Al_2O_3 20.5%, MgO 33.8%, CO_2 11.0%, $Cl^- < 0.1\%$, $SO_4^{2-} < 0.1\%$, $Na^+ < 0.5\%$.

To our best knowledge until now only patents had published the use of these materials as catalysts for some polymerisation reactions.[24,25] Recently we described the synthesis of 4-hydroxyaryl piperidinols from bis-Mannich bases using this catalyst.[26]

First, we examined the reaction of 3-nitrobenzaldehyde and nitromethane (Scheme 1) in the presence of the catalyst (6 mol%).

The reaction was carried out at room temperature in ethanol, tetrahydrofuran, and nitromethane (Table 1). In the first two cases (entries 1, 2), the conversions were rather similar. Not surprisingly the use of nitromethane as solvent (20 mol equiv) gave the best results. Increasing the reaction time led to significant increase in the conversion (see entries 4 and 5). Without HT no reaction was observed.

We investigated the reactivity of a variety of aldehydes under the same reaction conditions as for **1f**, and the appropriate 2-nitroalcohols **2** were generally obtained in good to excellent yield. The results are summarized in Table 2. Compounds **2b**,**c**,**d**,**k** have not been described in the literature yet. Their structures were confirmed by their spectroscopic data and elemental analysis (see Section 4). The derivatives of benzaldehydes bearing electron-withdrawing groups **1b**,**c**,**f** and pyridine-2-carbaldehyde **1 l** were more reactive, giving 100% conversion, than those with electron-donating groups **1d**,**g**,**i**,**j**. Especially with salicylaldehyde **1d** and *p*-dimethylaminobenzaldehyde **1j** the conversions were very low, even after modification of the reaction conditions like reaction temperature, or reaction time, respectively.

Reaction of salicylaldehyde **1d** with nitromethane in the presence of HT at 100 °C for 5 h gave a reaction mixture of the nitroalcohol and an unknown product in a ratio of 3:1. This was separated by column chromatography, using

dichloromethane as eluent, yielding a dark yellow solid. The mass spectrometry showed that the new product was the 1,3-dinitro-compound **3a**. The ^{1}H and ^{13}C NMR spectra also confirmed this structure. Repetition of this reaction in boiling toluene with 1 equiv of nitromethane gave the same product mixture.

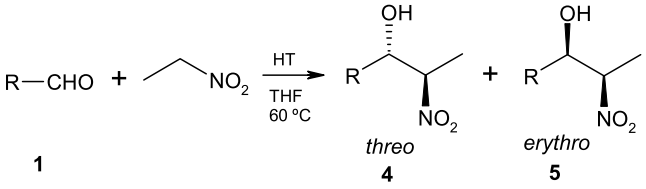
Some related 1,3-dinitro-compounds have already been described in the literature.[33–36] The mechanism of their formation was assumed to be a three-step base-catalysed reaction as follows: (1) nitroaldol addition to form the nitroalcohol; (2) dehydration of this to give the corresponding nitrostyrene; (3) Michael-addition of nitromethane to the nitrostyrene.[33,35] However, during our synthesis we could not isolate the nitrostyrene or even detect its formation. This is in good agreement with the statements in the literature that hydrotalcites are usually unable to induce dehydration in aldol-type reactions, and with the results reported by Choudary et al.[15,39] for the Henry reaction (Scheme 2).

When the pure Henry-product **2h** was heated in boiling toluene in the presence of HT, no formation of the appropriate nitrostyrene was detected, the starting material could be recovered.

In addition, reacting the pure 3,β-dinitro-styrene (prepared by the traditional NaOH/methanol method) with nitromethane in the presence of HT in boiling nitromethane, the conversion was quite slow, we observed the total consumption of the styrene only after 3 h boiling.

If the formation of the 1,3-dinitro-compound had occurred via the nitrostyrene and the formation of this latter had been so slow, we should have detected the formation of the nitrostyrene either by TLC of the reaction mixture or by NMR. This means that in the case of HT, another mechanism for the formation of the 1,3-dinitro-compounds should be supposed. Since nitromethane has a tautomeric *aci* form (Scheme 3) this could protonate the Henry-product, this protonation would be followed by the loss of water and the cation thus formed would be attacked by the anion of nitromethane. Scheme 3 shows this supposed reaction pathway. For the verification of this hypothesis we reacted **2h** with nitroethane at 100 °C for 5 h. ^{1}H NMR investigation of the crude reaction product showed the presence of the appropriate dinitro compound **6** (ca. 30%, Scheme 3) and no nitrostyrene. The reaction was quite slow but this can be explained with the lower pK_a value of nitroethane than nitromethane (8.456 and 10.211 at 25 °C, respectively[37]).

When nitroethane was used, the nitroaldol addition of various aldehydes (Scheme 4) in THF as solvent at 60 °C in the presence of catalytic amount of Mg:Al HT (2:1) (6 mol%) gave the corresponding nitroalcohols in good yields within 6.5 h (Table 3).



Scheme 4.

The reaction can be applied both to aromatic and aliphatic aldehydes. The highest diastereoselectivity was obtained with *ortho*-substituted aldehydes **1b**,**c**,**d** and with pyridine-2-carbaldehyde **1h**. The *threo*/*erythro* diastereoselectivity was determined by ^{1}H NMR spectroscopy. In their ^{1}H NMR spectra the extent of vicinal coupling constants of the products between the α-N–C–H and the α-O–C–H verify the formation of isomers. In the case of *threo* isomers $J=7$–9 Hz, and *erythro* isomers $J=3.2$–4 Hz.[38] In some cases we obtained an excess of the *erythro*-isomer. It is interesting to note the significant difference in the diastereoselectivity for *ortho*-chlorobenzaldehyde with nitroethane compared with the data reported by Bulbule et al.,[38] where 100% *threo* isomer was obtained.

In these reactions none of the appropriate 1,3-dinitro compounds were observed. This can be explained with the lower reaction temperature and the use of THF as solvent, since in this case a small excess of nitroethane was used. In the experiments with nitromethane the 1,3-dinitro compounds were not observed if a solvent other than nitromethane was used.

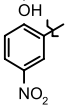
The catalyst was recovered from the reaction mixture by simple filtration, washed with nitromethane and treated at 120 °C for 1 h. This could be successfully reused under the above-reported conditions. These results show that Mg:Al 2:1 hydrotalcite was reusable for three cycles without loss of activity (Table 2, **2f**).

Table 3. Reaction of nitromethane and aldehydes with Mg:Al 2:1 HT at 100 °C

3	R	Conversion (%)	Time (h)	Yield of **3** (%)[a]
3a		30	5	10
3b		70	5	20
3c		100	5	20

[a] Determined by ^{1}H NMR.

Table 4. Diastereoselective synthesis of 2-nitroalcohols catalysed by Mg:Al 2:1 HT

4	R	Temperature (°C)	Conversion[a] (%)[b]	*Erythro–threo*[c] (%)
4a[38]		60	62	40:60
4b[38]		60	86	66:34
4c		60	85	70:30
4d		60	32	70:30
4e		60	57	30:70
4f[38]		60	(81)[b]	50:50
4g[31]		60	60	45:55
4h[40]		60	100 (95)[b]	65:35
4i[41]	CH_3	20	(64)[b]	47:53
4j[42]	CH_3–CH_2	60	(92)[b]	48:52

[a] Determined by ^{1}H NMR, based on the starting aldehyde.
[b] Isolated yield in parenthesis.
[c] Calculated by ^{1}H NMR.

3. Conclusion

In summary, we have shown that commercially available non-activated Mg:Al 2:1 hydrotalcite is a highly efficient basic catalyst for the Henry reaction. In the reaction with nitromethane at room temperature we obtained only 2-nitroalcohols in good to excellent yields. By increasing the temperature to 100 °C 1,3-dinitro compounds were obtained. The advantages of our method developed are the following: the reaction is eco-friendly since it minimises harmful reagents; the experimental and work-up procedure is very simple; the catalyst does not require any complicated pre-treatment and is recyclable, and this method realises a new application for the commercial HT product.

4. Experimental

4.1. General

Commercially available starting materials were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avanche 300 (300 MHz) and Bruker Avance DRX-500 (500 MHz) spectrometer using TMS as internal standard. Melting points were determined on Gallenkamp apparatus and were uncorrected. IR spectra were recorded on a Perkin–Elmer Model 1600 instrument. TLC was performed on Merck Kieselgel plates (60 F_{254}) with an eluent: hexane–acetone 4:1. Column chromatography was carried out on Merck Kieselgel 60–240 mesh using dichloromethane as eluent. The spectral and physical data of the known compounds were identical with those reported in the literature (for references see Tables 2 and 4). The new compounds gave satisfactory elemental analysis.

4.2. Characterization of hydrotalcite

The Mg:Al 2:1 hydrotalcite was the commercially product of Süd-Chemie AG, München (HSA-type). The catalyst was dried at 120 °C for 1 h before use.

The presence of the pure hydrotalcite structure was confirmed by XRD pattern, and by thermogravimetry. The XRD pattern of the HT sample exhibits the characteristic reflections corresponding to a ordered-crystalline layered structure (Fig. 1).[16] From the (003) reflection ($2\Theta = 11.46°$) we calculated the 7.72 Å basal interlayer spacing. Correspondingly, from the (110) reflection ($2\Theta = 60.41°$) the brucite-like layer thickness is 3.06 Å.

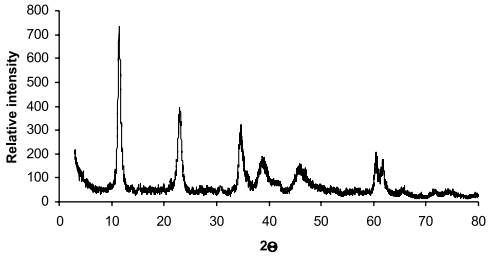


Figure 1.

X-ray diffraction (XRD) pattern was recorded on Philips PW 1050/81 instrument with Cu Kα_1 radiation (λ = 1.54184 Å) equipped with EVA Diffract-AT (Siemens Socabim) software. The samples were step-scanned in steps of 0.02° (2Θ) in the range from 3 to 70°. Thermogravimetric measurements (TG) were performed using Setaram Labsys TG equipment (Setaram, France) with 10.9 mg test material at a heating rate of 10 K min^{-1} in the temperature range 20–700 °C in nitrogen atmosphere. The

parameters obtained corresponded to those reported in the literature.[15]

4.3. General procedure for the Henry reaction of nitromethane and various aldehydes

A mixture of the aldehyde (5 mmol) and hydrotalcite (0.13 g) in nitromethane (5.6 ml, 0.1 mol) was stirred at room temperature for 5 h. The catalyst was filtered off and washed with nitromethane (3 ml). The filtrate was evaporated, and the residue, if necessary, was washed with saturated aq $NaHSO_3$ (2×10 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated to give the corresponding nitroalcohol derivative. The known products were characterized by comparing the ^1H NMR and melting point data with those reported in the literature (for references see Table 2).

4.4. Spectral data of the new compounds

4.4.1. 1-(2-Chlorophenyl)-2-nitro-ethanol (2b). 0.92 g (91%), yellow oil, IR (neat): 1377, 1555, 3530 ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.35 (1H, br s, OH), 4.43 (1H, dd, $J_1=2$ Hz, $J_2=9$ Hz, CH_2), 4.64 (1H, dd, $J_1=2$ Hz, $J_2=11.5$ Hz, CH_2), 5.81 (1H, d, $J=9.5$ Hz, *CH*OH), 7.26–7.39 (3H, m, Ph), 7.62–7.63 (1H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 71.2, 86.3, 127.9, 128.5, 130.7, 131.1, 132.7, 136.5. MS (EI): *m/z* (%) 201 (M^+, 5), 185 (7), 183 (21), 156 (8), 154 (24), 143 (100), 141 (33), 110 (26). $C_8H_8NO_3Cl$. Anal. Calcd C 47.64, H 6.95, N 3.98. Found C 47.86, H 7.06, N 4.07.

4.4.2. 1-(2-Bromophenyl)-2-nitro-ethanol (2c). 1.17 g (95%), yellow oil, IR (neat): 1368, 1550, 3511 ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.12 (1H, br s, OH), 4.45 (1H, dd, $J_1=3.5$ Hz, $J_2=9.5$ Hz, CH_2), 4.67 (1H, dd, $J_1=2.5$ Hz, $J_2=11.5$ Hz, CH_2), 5.81 (1H, d, $J=9.5$ Hz, *CH*OH), 7.21–7.26 (1H, m, Ph), 7.38–7.41 (1H, m, Ph), 7.56–7.61 (1H, m, Ph), 7.65–7.68 (1H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 71.4, 87.2, 128.1, 128.8, 130.9, 131.4, 132.9, 137.1. MS (EI): *m/z* (%) 246 (M^+, 2), 230 (8), 228 (7), 200 (6), 198 (6), 185 (14), 183 (14), 156 (100). $C_8H_8NO_3Br$. Anal. Calcd C 38.95, H 3.25, N 5.68. Found C 39.09, H 3.41, N 5.73.

4.4.3. 1-(2-Hydroxyphenyl)-2-nitro-ethanol (2d). 0.27 g (30%), yellow oil, IR (neat): 1382, 1558, 3528 ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.31 (1H, s, OH), 4.61 (1H, dd, $J_1=3$ Hz, $J_2=10.5$ Hz, CH_2), 4.76 (1H, dd, $J_1=3$ Hz, $J_2=10$ Hz, CH_2), 5.61 (1H, d, $J=9.5$ Hz, *CH*OH), 6.98–7.04 (2H, m, Ph), 7.5–7.57 (2H, m, Ph), 11.02 (1H, s, Ph*OH*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 70.9, 84.5, 127.4, 128.4, 128.9, 130.6, 131.1, 135.4. MS (EI): *m/z* (%) 183 (M^+, 2), 165 (7), 136 (15), 123 (100), 93 (10). $C_8H_9NO_4$. Anal. Calcd C 52.46, H 7.65, N 4.92. Found C 52.63, H 7.78, N 5.06.

4.4.4. 1-(2-Hydroxy-5-bromophenyl)-2-nitro-ethanol (2k). 0.66 g (47%), yellow oil, IR (neat): 1382, 1557, 3518 ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.61 (1H, br s, OH), 4.59 (1H, dd, $J_1=3$ Hz, $J_2=10.5$ Hz, CH_2), 4.71 (1H, dd, $J_1=3$ Hz, $J_2=10$ Hz, CH_2), 5.59 (1H, d, $J=10$ Hz, *CH*OH), 6.69 (1H, d, $J=9$ Hz, Ph), 7.32–7.36 (1H, m, Ph), 7.65–7.69 (1H, d, $J=2$ Hz, Ph), 10.93 (1H, s, Ph*OH*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 71.2, 88.1, 127.8, 128.5, 130.1, 130.8, 132.9, 136.4. MS (EI): *m/z* (%) 279 (M^+, 5), 261 (6), 232 (15), 214 (21), 172 (36). $C_8H_8NO_4Br$. Anal. Calcd C 36.64, H 5.34, N 3.05. Found C 36.87, H 5.29, N 3.16.

4.5. General procedure for the reaction of nitroethane and various aldehydes

A mixture of the aldehyde (5 mmol) and nitroethane (6 mmol) with hydrotalcite (0.13 g) in THF (10 ml) was stirred at 60 °C for 6.5 h. Then the catalyst was filtered off and washed with THF (3 ml). The filtrate was evaporated, and the residue, if necessary, was washed with saturated aq $NaHSO_3$ (2×10 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated to give the corresponding nitroalcohol derivative. The *threo*/*erythro* diastereoselectivity of the products was determined by ^1H NMR spectroscopy based on the vicinal coupling constants of the products between the α-N–C–H and the α-O–C–H (see Table 4). The known products were characterized by comparing the ^1H NMR and melting points data with those reported in the literature (for references see Table 4).

4.6. Spectral data of the new compounds

4.6.1. 1-(2-Bromophenyl)-2-nitro-propan-1-ol (4c). 1.11 g (85%), yellow oil, IR (neat): 1372, 1548, 3520 ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.45 (3H, d, $J=6.6$ Hz, CH_3), 1.47 (3H, d, $J=6.3$ Hz, CH_3), 3.23 (1H, br s, OH), 4.9 (1H, m, *CH*CH_3), 5.6 (1H, d, $J=8.4$ Hz, *threo-CH*OH), 5.81 (1H, d, $J=4.4$ Hz, *erythro-CH*OH), 7.28–7.64 (3H, m, Ph), 7.9 (1H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 16.1, 72.5, 73.9, 84.0, 88.3, 127.2, 128.2, 130.3, 132.1, 133.3, 137.5. MS (EI): *m/z* (%) 260 (M^+, 2), 243 (21), 213 (15), 196 (100), 186 (29), 155 (44). $C_9H_{10}NO_3Br$. Anal. Calcd C 41.54, H 3.80, N 5.38. Found C 41.82, H 3.95, N 5.56.

4.6.2. 1-(2-Fluorophenyl)-2-nitro-propan-1-ol (4d). 0.32 g (32%), yellow oil, IR (neat): 1366, 1540, 3540 ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.38 (3H, d, $J=6.9$ Hz, CH_3), 1.47 (3H, d, $J=6.9$ Hz, CH_3), 3.97 (1H, m, OH), 4.84 (1H, m, *CH*CH_3), 5.42 (1H, d, $J=9.1$ Hz, *threo-CH*OH), 5.74 (1H, d, $J=3.3$ Hz, *erythro-CH*OH), 7.11–7.61 (3H, m, Ph), 7.85 (1H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 16.3, 73.1, 74.6, 87.8, 88.9, 128.2, 128.9, 131.4, 131.7, 133.1, 137.8. MS (EI): *m/z* (%) 199 (M^+, 5), 181 (20), 152 (100), 134 (38), 125 (28), 95 (10). $C_9H_{10}NO_3F$. Anal. Calcd C 54.27, H 5.03, N 7.04. Found C 54.49, H 5.26, N 6.96.

4.6.3. 1-(3-Hydroxyphenyl)-2-nitro-propan-1-ol (4e). 0.56 g (57%), yellow oil, IR (neat): 1352, 1522, 3532 ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.31 (3H, d, $J=6.6$ Hz, CH_3), 1.48 (3H, d, $J=6.6$ Hz, CH_3), 3.49 (1H, m, OH), 4.71 (1H, m, *CH*CH_3), 4.95 (1H, d, $J=9$ Hz, *threo-CH*OH), 5.34 (1H, d, $J=3.6$ Hz, *erythro-CH*OH), 6.77–7.12 (4H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 16.4, 73.3, 75.3, 87.6, 88.2, 122.1, 124.1, 130.4, 131.8, 133.4, 137.5. MS (EI): *m/z* (%) 197 (M^+, 2), 179 (5), 132 (15), 123 (68), 121 (100), 105 (15), 93 (10). $C_9H_{11}NO_4$. Anal. Calcd C 54.82, H 5.58, N 7.11. Found C 54.99, H 5.72, N 7.38.

4.7. General procedure for the synthesis of 1,3-dinitro compounds

A mixture of the aldehyde (5 mmol) and hydrotalcite (0.13 g) in nitromethane (5.6 ml, 0.1 mol) was stirred at 100 °C for 5 h. Then the catalyst was filtered off and washed with nitromethane (3 ml). The solvent was evaporated, the residue was purified by column chromatography (eluent: dichloromethane) to give the new compounds.

4.7.1. 2-(2-Hydroxyphenyl)-1,3-dinitro-propane (3a). 0.34 g (30%), dark yellow oil, IR (neat): 1380, 1556, 3482 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.37–4.45 (1H, m, CH), 4.83–4.88 (4H, m, CH_2), 5.91 (1H, br s, OH), 6.73 (1H, d, $J=7.8$ Hz, Ph), 6.85–6.90 (1H, m, Ph), 7.10–7.19 (2H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 40.3, 76.6, 111.9, 125.2, 128.1, 131.5, 132.0, 154.4. MS (EI): *m/z* (%) 226 (M^+, 10), 210 (12), 192 (15), 162 (5), 150 (29), 149 (83), 117 (6), 77 (20), 60 (4). $C_9H_{10}N_2O_5$. Anal. Calcd C 47.79, H 4.42, N 12.39. Found C 47.25, H 4.11, N 12.09.

4.7.2. 2-(4-Chlorophenyl)-1,3-dinitro-propane (3b). 0.86 g (70%), yellow oil, IR (neat): 1374, 1548 ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.30–4.35 (1H, m, CH), 4.74–4.78 (4H, m, CH_2), 7.18 (2H, d, $J=6.3$ Hz, Ph), 7.35 (2H, d, $J=8.4$ Hz, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 41.2, 76.6, 128.8, 129.9, 130.3, 135.3. MS (EI): *m/z* (%) 244 (M^+, 15), 197 (30), 151 (38), 137 (41), 125 (27), 115 (100), 112 (10), 89 (16), 77 (22). $C_9H_9N_2O_4Cl$. Anal. Calcd C 44.17, H 3.68, N 11.45. Found C 43.87, H 3.32, N 11.09.

4.7.3. 2-(3-Nitrophenyl)-1,3-dinitro-propane (3c). 1.28 g (100%), dark yellow oil, IR (neat): 1365, 1584 ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.52–4.55 (1H, m, CH), 4.89–4.93 (4H, m, CH_2), 7.62–7.66 (1H, m, Ph), 7.76–7.79 (1H, m, Ph), 8.17–8.20 (1H, m, Ph), 8.20–8.24 (1H, s, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 40.8, 77.3, 124.4, 128.6, 130.4, 134.8, 137.5, 148.79. $C_9H_9N_3O_6$. Anal. Calcd C 42.35, H 3.53, N 16.47. Found C 42.02, H 3.23, N 16.11.

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Slipping of a histidine improved the peroxidase activity of a de novo designed polypeptide packing an iron porphyrin

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Abstract—Polypeptides with two histidines and an iron porphyrin (**1H**^{40}–**7H**^{46}) were synthesized with a variety of positions of a histidine. In **4H**^{43}, histidine (H^{43}) was in the hydrophobic region of an α-helix. The other polypeptides were of slightly or substantially distorted conformation. In the pH 7.2 buffer solution, two histidines of the polypeptide coordinated the iron porphyrin regardless of their positions. Some polypeptides (**1H**^{40}, **3H**^{42}, and **5H**^{44}) showed an enhanced catalytic activity in the peroxidase reaction using cumene hydroperoxide compared to that of **4H**^{43}, whereas some polypeptides (**2H**^{41} and **6H**^{45}) were ineffective catalysts. The distortion of the peptide conformation by the addition of MeOH was also effective for the peroxidase reaction.

1. Introduction

Biological studies have elucidated the reaction mechanisms of the natural heme oxygenases, peroxidases, and cytochrome P-450s.[1–3] Natural heme is located at the interior hydrophobic site of the protein. Protein not only tethers heme but also controls the activity of heme by providing ligand(s) to the iron porphyrin. The interaction between the peroxide (ROOH) and protein is also important and great efforts have been devoted to uncover the mechanisms of the peroxide activation.[4] So far, a large amount of polypeptides conjugating the iron porphyrins have been synthesized in order to understand and possibly reproduce the enzymatic activity.[5] In aqueous media, the hydrophobic interactions of the porphyrin with the polypeptide[6,7] and the coordination of histidine(s) to the iron porphyrin[8] are both important for a stable conjugate. Various groups have utilized the amphiphilic α-helical peptides, which cover both sides of the porphyrin with the coordination of histidine(s) to the iron porphyrins.[9–11] We have also synthesized a polypeptide linking the iron porphyrin that folded into a 4α-helix bundle structure. Unexpectedly, the catalytic oxidation smoothly occurred when the polypeptide was scarcely denaturated from the originally designed α-helix bundle.[7] Polypeptides might lower the accessibility of the substrate from the active center (iron porphyrin). Polypeptides might restrict the dissociation of His ligand(s) from the iron porphyrin. This result suggested to us a hypothesis that it was unfavorable for the catalytic reaction to pack the porphyrin tightly from both sides by the α-helical peptides, that is, the catalytic oxidation favored a loose surrounding of heme. Mimicking the naturally occurring heme packed by the α-helices and β-sheets,[12] we adopted a βα-unit (the sequenced β-segment and α-segment) to cover each face of the porphyrin. The 49-mer polypeptide, thus designed as the βαβα-type structure, was an effective catalyst in a peroxidase reaction.[13,14] To further improve the catalytic activity, we slipped a His residue from the center of the hydrophobic region of an α-helix. We examined the effects of this His slipping for the peptide structure and the catalytic activity.

2. Results and discussion

2.1. Syntheses of polypeptides packing the iron porphyrins with a variety of His positions

The 49-mer polypeptides packing the iron porphyrins, **1H**^{40}, **2H**^{41}, **3H**^{42}, **5H**^{44}, **6H**^{45}, and **7H**^{46} (Fig. 1) were designed by slipping His from our original βαβα-type peptide, **4H**^{43} (Fig. 2).[13] Polypeptide **4H**^{43} was made of (1) the first segment possibly taking the β-structure, O(p)EVKV, which tethered the iron porphyrin at the ornithine side chain (O(p) is the iron porphyrin-linked ornithine).[15] This segment was made of an alternative hydrophobic (Val and porphyrin-linked ornithine)/ionic (Glu and Lys) sequence.[16] (2) The

Keywords: Iron porphyrin; Oxidation; Catalyst; Polypeptide; Peroxidase.
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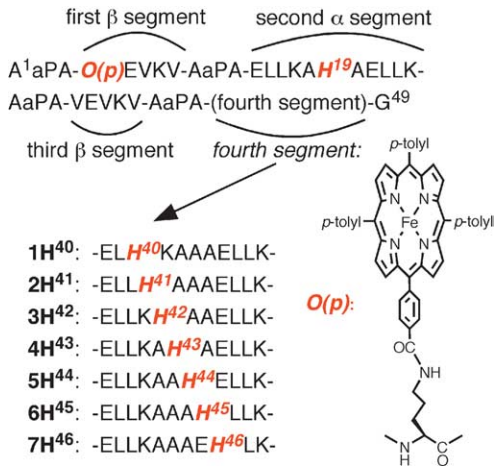


Figure 1. Polypeptides **1H[40]–7H[46]** (A, Ala; a, D-Ala; E, Glu; G, Gly; H, His; K, Lys; L, Leu; *O*(*p*), ornithine linking the iron porphyrin at the side chain; P, Pro; V, Val).

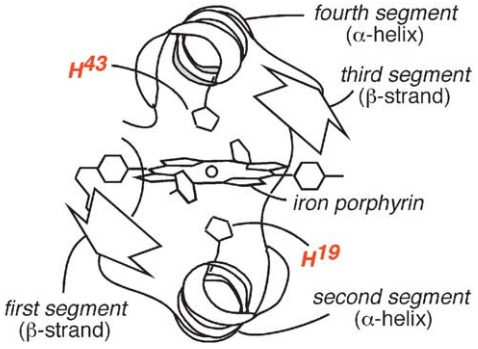


Figure 2. Supposed βαβα-structure of **4H[43]**.

second segment taking the α-helix structure, ELLKAHAELLK. Figure 3a, a wheel diagram of the α-helix viewed from its top, showed the amphiphilicity of this α-helix. Four leucines formed the hydrophobic face to surround H[19]. The ionic Glu and Lys formed the hydrophilic face on the opposite side.[17] (3) The third segment, VEVKV, possibly taking the β-structure, and (4) the fourth segment taking the α-helix structure, ELLKAHAELLK, which again bore H[43] at its hydrophobic region. The -AaPA- spacers ('a' denotes the D-alanine residue) linked these β-, α-, β-, and α-segments in this order. These 5-residual β-segments and 11-residual α-segments (≈1.2–1.5 nm) were designed to cover

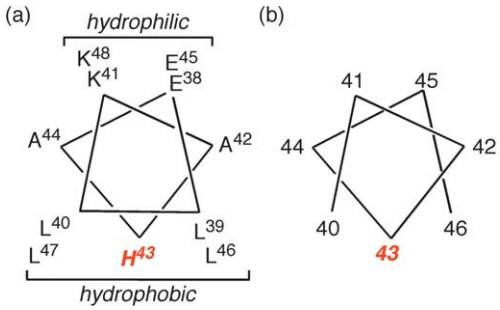


Figure 3. (a) The fourth α-helx segment of **4H[43]** showing the hydrophilic and hydrophobic faces. (b) The positions of His in **1H[40]–7H[46]** assuming that these segments are α-helical (for the actual secondary structure, see text).

the porphyrin (≈1.0 nm). When H[19] and H[43] coordinated the iron porphyrin, the hydrophobic faces of two α-helices would cover both sides of the porphyrin. The two amphiphilic β-strands might come close to the α-helices, constructing an outer hydrophobic/inner hydrophobic structure packing the porphyrin (Fig. 2). However, no direct information for the conformation of the β-strands was obtained, therefore, we denoted **4H[43]** as the βαβα-'type' peptide.

In the new series of the polypeptides packing the iron porphyrins (**1H[40]**, **2H[41]**, **3H[42]**, **5H[44]**, **6H[45]**, and **7H[46]**), the second His residue, H[43] of **4H[43]**, was slipped into H[40], H[41], H[42], H[44], H[45], and H[46], respectively (Fig. 1). Figure 3b shows a hypothetical α-helix wheel diagram of the fourth segments of **1H[40]–3H[42]** and **5H[44]–7H[46]** (note; these fourth segments are actually not α-helical, see below), depicting the positions of His in these peptides. In **1H[40]** and **7H[46]** (H[40] and H[46], respectively), His is at the close position as that of **4H[43]**. However, in **2H[41]** and **6H[45]**, His (H[41] and H[45], respectively) is at a different side in this α-helix wheel. This diagram suggested that the structure of the fourth segments of **2H[41]** and **6H[45]** significantly differed from **4H[43]**, if His of these peptides (H[41] and H[45]) coordinated to the iron porphyrin.

These polypeptides with porphyrins were synthesized via the solid-phase syntheses of the polypeptide fragments and the solution-phase couplings of the fragments. On the *p*-nitrobenzophenone oxime resin, the protected peptide fragments, for instance, Boc-Ala-His(Bom)-Ala-Glu(O-*c*Hex)-Leu-Leu-Lys(ClZ)-Gly-OBzl (**9**, Boc-(42-49)-OBzl, see Section 4) were synthesized via the Boc strategy.[7,18] The protected peptide fragments were successively condensed; the Boc-deprotection of **9** and subsequent coupling with Boc-(35-41)-OH (**10**) in DMF using EDC·HCl/HOBt·H_2O as the condensation reagents yielded Boc-(35-49)-OBzl (**14**). The deprotection/coupling was repeated to obtain the protected full-length 49-mer peptide, Z-(1-49)-OBzl (**18**) bearing the free-base porphyrin. A novel Boc-amino acid bearing the free-base porphyrin at the side chain, N^{α}-Boc-N^{δ}-[4-(10,15,20-tritolylporphyrin-5-yl)benzoyl]ornithine (**8**, see Fig. 1 for the iron complex), was used in the porphyrin-containing fragment. The protected 49-mer polypeptide (**18**) was deprotected with HF (CAUTION)[19]-anisole, yielding the precursor polypeptide with a free-base porphyrin, **4H[43]** (free-base). Finally, the iron insertion with $Fe(OAc)_2$ yielded the polypeptide packing iron(III) porphyrin, **4H[43]**. The other polypeptides **1H[40]–3H[42]** and **5H[44]–7H[46]** were synthesized in a similar manner. These polypeptides were purified by size exclusion chromatographies using Sephadex® LH-20 or LH-60 eluting with DMF for the protected peptides and Sephadex® G-50 eluting with aqueous 40% AcOH for the deprotected peptides. The precursor peptide with the free-base porphyrin was successfully characterized by the reversed phase HPLC using a C4 column and mass spectroscopy (FAB-MS or MALDI-TOF-MS). The polypeptide with the iron(III) porphyrin was characterized by the reversed phase HPLC. Unfortunately, ^{1}H NMR signals of the peptide were too broad to assign even before iron insertion.

UV–vis spectra of **1H[40]–7H[46]** in an aqueous buffer solution

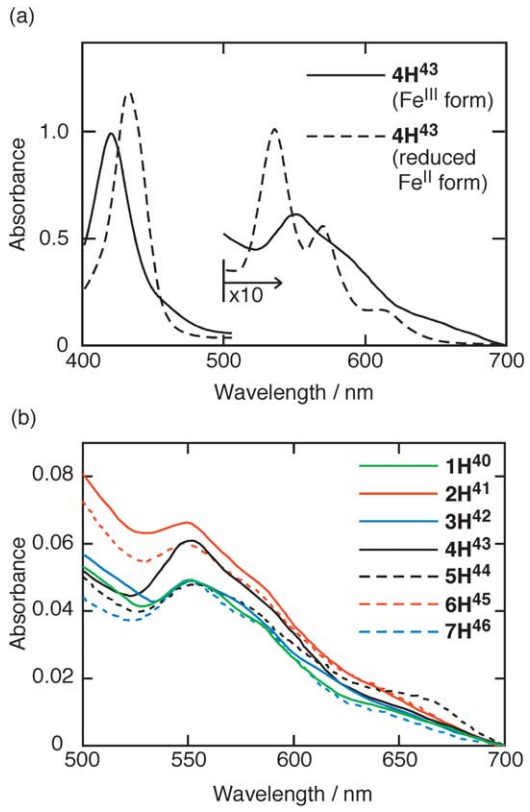


Figure 4. UV–vis spectra of (a) **4H^{43}** (Fe(III) form, solid line) and its reduced Fe(II) form (dashed line), (b) the Q-band region of **1H^{40}–7H^{46}**. [Peptide] = 10 μM in Tris·HCl buffer (20 mM, pH 7.2).

(pH 7.2, 20 mM Tris·HCl) were similar to each other. The Soret bands appeared at 420 nm (see Fig. 4a for **4H^{43}**) and Q-bands as broad peaks at around 550 nm with a shoulder at 575 nm (Fig. 4b for **1H^{40}–7H^{46}**). Such a narrow and weak Soret band and broad Q-band are the characteristics of low spin iron(III) porphyrins.[9,11,20,21] The iron(III) porphyrin is of low spin when two strong ligands coordinate. For instance, $[(TPP)Fe(III)(imidazole)_2]^+$ shows its absorption at 416, 548, and 580 (sh) nm in CH_2Cl_2.[20] Thus, the UV–vis spectra of **1H^{40}–7H^{46}** (Fig. 4) suggested that all these polypeptides contained the low spin iron(III) porphyrins. This fact suggested that the strong ligands, two histidines, coordinated to both faces of the iron porphyrins. When these polypeptides were treated with $Na_2S_2O_4$, the iron(III) porphyrins were reduced to generate iron(II) porphyrins (Fig. 4a). The reduced **4H^{43}** showed absorptions at 434, 537, and 570 nm with a red-shifted Soret band and the obvious α- and β-band structures in the Q-band region. This spectrum suggested that the reduced **4H^{43}** contained the low spin iron(II) porphyrin, again coordinated by two histidines.[11,21,22] The other polypeptides with iron porphyrins, **1H^{40}–3H^{42}** and **5H^{44}–7H^{46}** showed similar spectral changes in the UV–vis measurements upon reduction by $Na_2S_2O_4$. Thus, two histidines seemed to coordinate the iron porphyrins of **1H^{40}–7H^{46}** regardless of the peptide sequences and the oxidation states of the iron ions. The UV–vis spectra described above were independent of the examined peptide concentration (0.5–15 μM), suggesting that these polypeptides were monomeric in the pH 7.2 buffer solution.

UV–vis spectra described above suggested that two histidines coordinated to iron(III) in all the polypeptides, although the position of His was varied from H^{40} to H^{46} in the fourth segment (Fig. 1). The coordination of the second His residue (H^{40}–H^{42} and H^{44}–H^{46}) to the iron porphyrin should distort the βαβα-type structure of the original peptide, **4H^{43}**. For instance, if H^{41} of **2H^{41}** coordinated iron while maintaining the α-helical structure of the fourth segment, the hydrophilic amino acids such as Glu^{45} (Fig. 3) coming close to the porphyrin was unlikely. In fact, the CD spectra of the amide region showed that the contents of the α-helix structure (α-helicity) in **1H^{40}–3H^{42}** and **5H^{44}–7H^{46}** were substantially decreased (Fig. 5). As reported earlier, the βαβα-type peptide, **4H^{43}**, showed the CD spectrum with the double minima at 204 and 222 nm, which was a characteristic of the α-helix peptide.[13] From the molar ellipticity per residue ($[\theta]_{MRW}$) value at 222 nm ($[\theta]_{222} = -13\,000$ deg. cm^2 dmol^{-1} per residue), the α-helicity of **4H^{43}** was calculated to be 33%. This meant that 18 amino acid residues of the 49-mer polypeptide were involved in the α-helix.[13,23] Namely, nine amino acids of the 11-residual α-helix segments (the second and fourth segments) of **4H^{43}** formed the helix. Indeed, β-sheet polypeptides are also known to show a negative CD band at 216 nm with a relatively low intensity.[24] However, we could not get any information about the conformation of the β-strands because the CD spectrum was occupied by the intense Cotton effects derived from the α-helices. Therefore, we tentatively evaluated the conformation of the polypeptide assuming that the $[\theta]_{222}$ value only reflected the α-helix structure. Thus, the α-helix contents of **1H^{40}**, **2H^{41}**, **3H^{42}**, **5H^{44}**, **6H^{45}**, and **7H^{46}** from their CD spectra (Fig. 5) were estimated to be 14, 13, 15, 16, 24, and 28%, respectively (Table 1). The substantial drop in the α-helicity in **1H^{40}**, **2H^{41}**, **3H^{42}**, and **5H^{44}** showed that the coordination of the second His (H^{40}, H^{41}, H^{42}, and H^{44}) to the iron porphyrin distorted the molecular conformation. However, the coordination of His near the C-terminus (H^{45} and H^{46}) did not substantially affect the α-helical structure of the fourth segment.

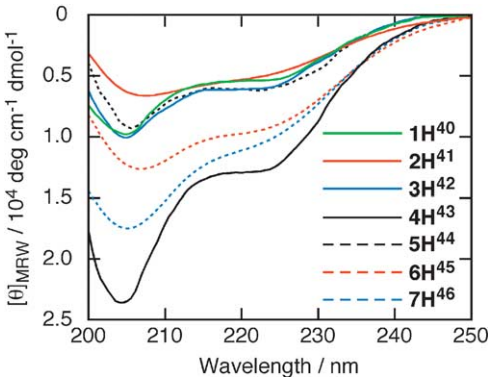


Figure 5. CD spectra of **1H^{40}–7H^{46}**. [Peptide] = 10 μM in Tris·HCl buffer solution (20 mM, pH 7.2).

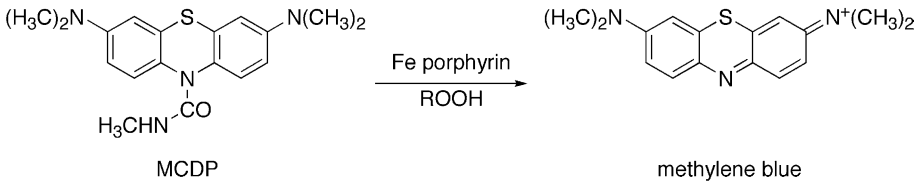
2.2. Catalytic oxidation by the polypeptide packing the iron porphyrin

Natural peroxidases utilize H_2O_2 or alkyl peroxides as the oxidants and catalyze the oxidation reactions of a wide variety of substrates.[1] Here we used cumene hydroperoxide

Table 1. The α-helicity and the Michaelis–Menten parameter in the MCDP oxidation catalyzed by the polypeptide packing iron porphyrin[a]

Catalyst	α-Helicity %	Cumene hydroperoxide (CPO)		H_2O_2	
		K_M mM	k_{cat}/K_M mM^{-1} s^{-1}	K_M mM	k_{cat}/K_M mM^{-1} s^{-1}
1H[40]	14	15	100	20	68
2H[41]	13	62	30	21	22
3H[42]	15	14	110	13	52
4H[43]	33	25	62	20	27
5H[44]	16	16	110	24	23
6H[45]	24	57	19	50	25
7H[46]	28	33	38	67	9

[a] [polypeptide]=0.5 μM, [MCDP]=0.2 mM, [oxidant]=1–100 mM in Tris·HCl buffer (20 mM, pH 7.2) at 25 °C.



MCDP methylene blue

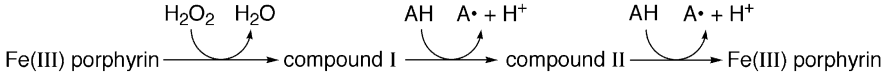
Scheme 1.

(CPO) or H_2O_2 as the oxidant and 10-*N*-methylcarbamoyl-3,7-bis(dimethylamino)-10*H*-phenothiazine (MCDP, Kyowa Medex Co., Ltd.) as the substrate.[25,26] MCDP is a peroxidase sensitive dye which generates 3,7-bis(dimethylamino)phenothiazinium ion (methylene blue) as an oxidized product in the presence of peroxidase and peroxide (Scheme 1). The catalytic oxidation of MCDP is easily followed by the UV–vis absorption of methylene blue (λ_{max}=666 nm, ε=96 000 at 25 °C). When an excess amount of CHP (20 mM) was added as the oxidant to the aqueous buffer solution (20 mM Tris·HCl, pH 7.2) containing **4H**[43] (0.50 μM) and MCDP (0.20 mM) at 25 °C, the reaction mixture immediately turned blue with the formation of methylene blue. By monitoring the increase in Abs_{666}, the initial rate of the MCDP oxidation catalyzed by **4H**[43] under these conditions was obtained, v_0=0.23 μM s^{-1}.

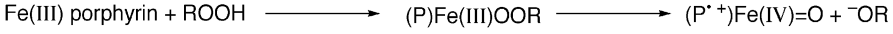
Generally, the reaction of the iron porphyrin with the peroxide and the substrate proceeds as in Scheme 2.[1] The reaction between the iron(III) porphyrin and the peroxide (ROOH) first generates a two electron oxidized species (compound I). The one-electron oxidation of a reaction substrate (AH) then twice takes place. Both compound I and its one-electron reduced species, compound II, are actually the catalytic active species. The complexes between the catalytic active species (compounds I and II) with the substrate are very short lived and difficult to detect, therefore, the formation of compound I should be the rate determining step in the catalytic cycle. In fact, the initial reaction rate (v_0) of the oxidation of MCDP catalyzed by **1H**[40]–**7H**[46] depended on the concentration of the oxidant, CHP ([CHP]), and did not depend on the concentration of the substrate, MCDP. The reaction kinetics was analyzed by the Michaelis–Menten equation. The plot of $1/[v_0]$ versus 1/[CHP] (Lineweaver–Burk plot) showed a linear relationship. Thus, the Michaelis–Menten parameters (K_M and k_{cat}/K_M) for the catalytic oxidations by **1H**[40]–**7H**[46] with CPO and H_2O_2 were collected by varying the concentration of the oxidants in the 1.0–100 mM range (Table 1).

Table 1 shows several features of the catalytic activities of the polypeptides packing iron porphyrins. First, comparing the reactions with **1H**[40]–**7H**[46] using CPO and H_2O_2 as the oxidants, the reactions with CPO had higher k_{cat}/K_M values, that is, the higher apparent second-order reaction rate constants. The oxidation reaction by the peroxide involves the heterolysis of the O–O bond of the ROO-Fe(III) intermediate (Scheme 3).[27] Because the basicities of the leaving groups ($C_6H_5C(CH_3)_2O^-$ for CPO and HO^- for H_2O_2) are similar,[28] the formation of the ROO-Fe(III) intermediate might be important. This fact implied that the hydrophobic interaction between CPO and the polypeptide (**1H**[40]–**7H**[46]) possibly accelerated the formation of ROO-Fe(III) intermediates.

The second feature of the catalytic reactions shown in Table 1 is that **1H**[40], **3H**[42], and **5H**[44] showed enhanced catalytic activities (k_{cat}/K_M) using CPO compared to that of **4H**[43]. **4H**[43] is our original polypeptide with two α-helices on both faces of the porphyrin. In these polypeptides with the higher catalytic activities (**1H**[40], **3H**[42], and **5H**[44]), the fourth segments were distorted due to the His coordination, which might affect the smooth generation of ROO-Fe(III) intermediate. The reason why **5H**[44] showed enhanced



Scheme 2.



Scheme 3.

catalytic activities using CPO and weak catalytic activities using H_2O_2 is yet not clear. It is interesting that peptides **2H**[41] and **6H**[45] showed large K_M values (62 and 57 mM, respectively), which suggested that these catalysts were only active at high CPO concentrations. Although H^{46} is at the close position to H^{43} in the helix wheel diagram (Fig. 3), **7H**[46] showed a weak catalytic activity (k_{cat}/K_M) compared to that of **4H**[43]. Thus, some polypeptides with disordered secondary structures (**1H**[40], **3H**[42], and **5H**[44]) showed the improved catalytic activity.

Although the slipping of His successfully distorted the βαβα-type structure of **4H**[43] as described above, another approach, the addition of MeOH to the solvent, was also effective for the improvement of the catalytic activity. Because MeOH stabilizes an α-helix and also weakens the hydrophobic interactions, the addition of MeOH changed the molecular structure of the polypeptides packing the iron porphyrins. Figure 6 shows the initial rates (v_0) of the oxidations of MCDP catalyzed by **1H**[40]–**7H**[46] in the aqueous buffer solution (20 mM Tris·HCl, pH 7.2) containing various amounts of MeOH. Because the reaction mechanism of the MCDP oxidation in this buffer–MeOH system was not clear, we did not analyze the reactions by the Michaelis–Menten equation but simply assessed it using the initial reaction rates. For every catalyst (**1H**[40]–**7H**[46]), the initial rate v_0 increased with the addition of MeOH up to 40 vol% and decreased with the large MeOH content, showing the bell-shaped profiles. For instance, v_0 catalyzed by **3H**[42] was 0.33 μM s^{-1} in the aqueous buffer solution without MeOH and 0.65 μM s^{-1} in the buffer solution–40% MeOH. The other polypeptides with the iron porphyrins also showed an improved activity in the buffer solution–40% MeOH. For instance, the v_0 values of **1H**[40], **4H**[43], and **5H**[44] are 0.61, 0.59, and 0.55 μM s^{-1}, respectively. It is interesting that the catalytic activities of **2H**[41], **6H**[45], and **7H**[46] in 40% MeOH are less effective than the other polypeptides in the same solvent system, similar to the case in the buffer solution.

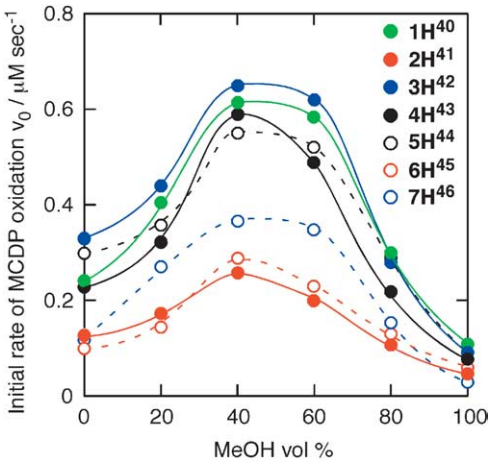


Figure 6. Initial rate of MCDP oxidation v_0 versus MeOH vol% in the solvent. [Peptide]=0.5 μM, [MCDP]=0.2 mM, [CPO]=20 mM in Tris·HCl buffer (20 mM, pH 7.2) containing MeOH.

The reason why the polypeptides showed such higher catalytic activities in the buffer solution–40% MeOH is not yet clear. In MeOH, **3H**[42] showed the typical UV–vis spectrum for the high spin iron(III) porphyrin, with a Soret band at 416 nm and broad Q bands at 540 and 640 nm (Fig. 7).[20,21] Weak ligands such as MeOH might coordinate to the high spin iron(III) porphyrin. As we reported in an earlier CD study, the α-helicity of the βαβα-type peptide with the iron porphyrin (**4H**[43]) increased in MeOH up to 80%.[13] Probably the helix-stabilizing solvent, MeOH, changed the conformation of the β-segment to α-helix. Due to this change in the peptide structure and the weakened hydrophobic interaction between the peptide and porphyrin, histidines might be forced to dissociate in MeOH, generating the high spin iron(III) porphyrin. The catalytic activities of every polypeptide were low in MeOH (Fig. 6), suggesting that the catalytic reactions were disfavored when two histidines were completely dissociated. In the buffer solution–40% MeOH, **3H**[42] showed some unidentified absorptions at 568 and 609 (sh) nm (Fig. 7). This fact might be concerned with the fact that the catalytic activity of **3H**[42] was the highest in the buffer solution–40% MeOH. In the buffer solution–40% MeOH, two histidines might not be completely dissociated from the iron porphyrin. The other peptides with iron porphyrins, **1H**[40]–**2H**[41] and **4H**[43]–**6H**[46] showed similar spectroscopic results upon titrating their buffer solutions with MeOH.

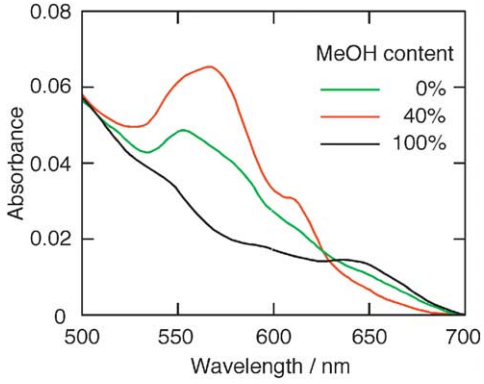


Figure 7. UV–vis spectra of **3H**[42] (10 μM) in Tris·HCl buffer solution (20 mM, pH 7.2), buffer solution/40% MeOH, and 100% MeOH.

3. Conclusion

As a challenge to improve the activity of the artificial hemoprotein, the position of His in the de novo designed βαβα-type polypeptide packing the iron porphyrin (**4H**[43]) was varied from H^{40}–H^{46} (polypeptide **1H**[40] to **7H**[46]). Regardless of the position of His, two histidines seemed to coordinate the iron porphyrin in the pH 7.2 buffer solution, showing UV–vis spectra typical of the low spin iron(III) porphyrin. In **4H**[43], H^{43} was at the center of the hydrophobic region of the α-helix, which would stabilize the peptide–porphyrin packing. However, **1H**[40], **3H**[42], and **5H**[44] bearing histidines not at the center of the hydrophobic region showed an enhanced catalytic activity in the peroxidase reaction. Thus, when the peptide conformation was loosened by the slipping of His in **1H**[40], **3H**[42], and **5H**[44], their peroxidase activities were moderately enhanced. The distortion of the peptide conformations by the addition of MeOH was also effective for the enhancement of the peroxidase activity. Controlling the accessibility of peroxide to the iron porphyrin packed by a polypeptide would

be one of the keys for the further development of artificial heme enzymes. The paramagnetic NMR and ESR spectra should be used to further characterize the polypeptides packing the iron porphyrins.

4. Experimental

4.1. General

Amino acid derivatives and reagents were from the commercial sources except for 10-(*N*-methylcarbamoy1)-3,7-bis(dimethylamino)-10*H*-phenothiazine (MCDP) from Kyowa Medex Co., Ltd. HPLC analyses were carried out using a Hitachi L-6300 pump and an L-4200 UV–vis detector with a Wakopak C4 column (4.6×150 mm) eluted at a 1.0 mL min^{-1} flow rate with a linear gradient of 37–100% CH_3CN/0.1% TFA over 30 min and then with 100% CH_3CN/0.1% TFA (R_t^1) or with a linear gradient of 10–100% CH_3CN/0.1% TFA over 30 min (R_t^2). ^1H NMR spectrum was measured on a JEOL JNM α-500 spectrometer (500 MHz), in which the chemical shifts were determined with respect to internal TMS. FAB-MS were measured on a JEOL JMS-SX 102A mass spectrometer and MALDI-TOF-MS on a Shimadzu Kratos Compact III, using 2,2′-dithiodiethanol and sinapic acid as matrixes, respectively, unless otherwise noted. UV–vis and CD spectra were recorded with a Hitachi U-2010 spectrophotometer and with a JASCO J-820 spectropolarimeter, respectively.

4.2. Synthesis of a βαβα-type polypeptide packing an iron porphyrin, 4H[43]

4.2.1. N^{α}-Boc-N^{δ}-[4-(10,15,20-tritolylporphyrin-5-yl)-benzoyl]ornithine (8, Boc-ornithine(por)-OH). In $CHCl_3$ (100 mL)-dioxane (30 mL), 4-(10,15,20-tritolylporphyrin-5-yl)benzoic acid[29] (1.8 g, 2.5 mmo1), dicyclohexylcarbodiimide (0.55 g, 2.6 mmo1), and *N*-hydroxysuccinimide (0.30 g, 2.6 mmol) were mixed at 0 °C and stirred overnight. Then, N^{α}-Boc-ornithine (1.1 g, 4.5 mmo1) and Et_3N (0.95 mL, 6.8 mmol) in DMF (10 mL)–H_2O (10 mL) was added at 0 °C and the mixture was further stirred at room temperature overnight. Purification by silica gel column chromatography ($CHCl_3$–1% MeOH) yielded **8** (2.1 g, 2.3 mmol, 90%). ^1H NMR (DMSO-d_6); δ 12.80 (br, 1H), 8.91 (s, 8H), 8.44 (m, 3H), 8.37 (d, J=8 Hz, 2H), 8.16 (m, 6H), 7.66 (m, 6H), 6.74 (m, 1H), 4.11 (m, 1H), 3.57 (m, 2H), 2.68 (s, 9H), 1.95–1.63 (m, 4H), 1.43 (s, 9H), −2.75 (br, 1H). FAB-MS (3-nitrobenzyl alcohol); *m/z* 915 $(M+H)^+$.

4.2.2. Solid-phase synthesis of the protected peptide fragments. Boc-Ala-His(Bom)-Ala-Glu(O*c*Hex)-Leu-Leu-Lys(ClZ)-Gly-OBzl (9), Boc-D-Ala-Pro-Ala-Glu(O-*c*Hex)-Leu-Leu-Lys(ClZ)-OH (10), Boc-Ala-D-Ala-Pro-Ala-Val-Glu(O*c*Hex)-Val-Lys(ClZ)-Val-Ala-OH (11), Boc-Ala-His(Bom)-Ala-Glu(O*c*Hex)-Leu-Leu-Lys(ClZ)-OH (12), and Z-Ala-D-Ala-Pro-Ala-ornithine(por)-Glu(O*c*Hex)-Val-Lys(ClZ)-Val-Ala-OH (13). These protected peptide fragments were prepared via the standard solid-phase peptide syntheses on the *p*-nitrobenzophenone oxime resin (2.0 g resin, ∼0.6 mmol peptide) using the coupling reagents EDC·HCl/HOBt·H_2O.[7,18] For the synthesis of **13**, the Boc amino acid **8** was used. The obtained crude peptides were reprecipitated from EtOH–diethyl ether. **9** (91%): HPLC; R_t^1 18.47 min, FAB-MS; *m/z* 1399 $(M+H)^+$. **10** (91%): R_t^1 19.48 min, FAB-MS; *m/z* 1114 $(M-H+Na)^+$. **11** (88%): R_t^1 17.00 min, FAB-MS; *m/z* 1327 $(M-H+Na)^+$. **12** (91%): R_t^1 14.82 min, FAB-MS; *m/z* 1154 $(M-H+Na)^+$. **13** (88%): R_t^1 19.08 min, FAB-MS; *m/z* 2059 $(M-H+Na)^+$.

4.2.3. Solution-phase coupling of the peptide fragments. *Z*-(1-49)-OBzl (18). After the removal of *N*-terminal Boc of **9** (TFA, 0 °C, 30 min), H-(42-49)-OBzl·TFA thus obtained (1.6 g, 1.1 mmol) was coupled with **10** (1.2 g, 1.1 mmol) using EDC·HCl (0.32 g, 1.7 mmol), HOBt·H_2O (0.26 g, 1.7 mmol), and Et_3N (0.19 mL, 1.3 mmo1) in 10 ml DMF (0 °C, overnight). After concentration, the precipitate was washed by H_2O, 10% aqueous citric acid, and 4% aqueous $NaHCO_3$. The reprecipitation from EtOH–diethyl ether yield Boc-(35-49)-OBzl (**14**, 2.0 g, 0.84 mmol, 76%): HPLC; R_t^1 28.84 min, FAB-MS; *m/z* 2374 $(M+H)^+$. The polypeptides below were prepared similarly. Boc-(25-49)-OBzl (**15**); Boc removal of **14**, coupling with **11**, and purification using a Sephadex® LH-20 column (2×90 cm, DMF), 82%, R_t^1 34.86 min, FAB-MS; *m/z* 3561 $(M+H)^+$. Boc-(18-49)-OBzl (**16**); Boc removal of **15**, coupling with **12**, and purification using a Sephadex® LH-60 column (2×90 cm, DMF), 62%, R_t^1 37.36 min, TOF-MS; *m/z* 4661.4, calcd for $C_{233}H_{343}N_{40}O_{53}Cl_3$ $(M-Cl+H)^+$, *m/z* 4658.9. Boc-(11-49)-OBzl (**17**); Boc removal of **16**, coupling with **10**, and LH-60 purification, 63%, R_t^1 40.32 min, TOF-MS; *m/z* 5666.9, calcd for $C_{281}H_{416}N_{48}O_{64}Cl_5$ $(M+H)^+$, *m/z* 5668.0. *Z*-(1-49)-OBzl (**18**); Boc removal of **17**, coupling with **13**, and LH-60 purification, 66%, R_t^1 43.10 min, TOF-MS; *m/z* 7604.7, calcd for $C_{389}H_{536}N_{64}O_{79}Cl_6Na$ $(M+Na)^+$, *m/z* 7608.7.

4.2.4. HF deprotection to yield the metal-free precursor, 4H[43] (free-base). The protected 49-mer peptide **18** (0.20 g, 26 μmol) was treated with anhydrous HF (CAUTION, 15 mL)[19]–anisole (1.5 mL) at 0 °C for 90 min. After removal of HF, the crude peptide was extracted with aqueous 10% AcOH, washed with diethyl ether, and lyophilized. Purification of the crude peptide using a Sephadex® G-50 column (2×90 cm, aqueous 40% AcOH) yielded pure peptide, **4H[43]** (free-base) (0.11 g, 20 μmol, 76%): HPLC; R_t^2 20.38 min, TOF-MS; *m/z* 5618.9, calcd for $C_{274}H_{419}N_{64}O_{63}$ $(M+H)^+$, *m/z* 5617.8.

4.2.5. Iron insertion. To the solution of **4H[43]** (free-base) (95 mg, 17 μmol) in AcOH (15 mL), iron(II) acetate (0.30 g, 1.7 mmol) was added and stirred overnight at 30 °C under Ar (until the disappearance of the UV–vis peak at 660 nm). Purification using a Sephadex® G-50 column yielded **4H[43]** (the iron complex, 90 mg, 16 μmo1, 94%): R_t^2 21.55 min.

4.3. Synthesis of the polypeptides packing an iron porphyrin, 1H[40], 2H[41], 3H[42], 5H[44], 6H[45], and 7H[46]

The solution-phase couplings of the peptide fragments as described in Section 4.2.3 for **4H[43]** afforded these polypeptides, by using some different peptide fragments for these His-slipped 49-mer peptides (see below). After HF deprotection and purification, the iron ion was inserted

into the precursor polypeptides bearing the free-base porphyrins in a similar manner to that of **4H**[43].

4.3.1. 1H[40]**.** Using Boc-D-Ala-Pro-Ala-Glu(O*c*Hex)-Leu-His(Bom)-Lys(ClZ)-OH instead of **10** and using Boc-Ala-Ala-Ala-Glu(O*c*Hex)-Leu-Leu-Lys(ClZ)-Gly-OBzl instead of **9**. **1H**[40] (free-base); R_t^2 20.51 min, TOF-MS; found *m/z* 5574.9, calcd *m/z* 5575.7 $(M+H)^+$. **1H**[40]; R_t^2 22.02 min.

4.3.2. 2H[41]**.** Using Boc-D-Ala-Pro-Ala-Glu(O*c*Hex)-Leu-Leu-His(Bom)-OH instead of **10** and using Boc-Ala-Ala-Ala-Glu(O*c*Hex)-Leu-Leu-Lys(ClZ)-Gly-OBzl instead of **9**. **2H**[41] (free-base); R_t^2 19.17 min, TOF-MS; *m/z* 5561.7, calcd *m/z* 5560.7 $(M+H)^+$. **2H**[41]; R_t^2 20.54 min.

4.3.3. 3H[42]**.** Using Boc-His(Bom)-Ala-Ala-Glu(O*c*Hex)-Leu-Leu-Lys(CIZ)-Gly-OBzl instead of **9**. **3H**[42] (free-base); R_t^2 21.64 min, TOF-MS; *m/z* 5618.0, calcd *m/z* 5617.8 $(M+H)^+$. **3H**[42]; R_t^2 23.44 min.

4.3.4. 5H[44]**.** Using Boc-Ala-Ala-His(Bom)-Glu(O*c*Hex)-Leu-Leu-Lys(ClZ)-Gly-OBzl instead of **9**. **5H**[44] (free-base); R_t^2 20.36 min, TOF-MS; *m/z* 5617.7, calcd *m/z* 5617.8 $(M+H)^+$. **5H**[44]; R_t^2 21.66 min.

4.3.5. 6H[45]**.** Using Boc-Ala-Ala-Ala-His(Bom)-Leu-Leu-Lys(ClZ)-Gly-OBzl instead of **9**. **6H**[45] (free-base); R_t^2 21.42 min, TOF-MS; *m/z* 5556.9, calcd *m/z* 5559.7 $(M+H)^+$. **6H**[45]; R_t^2 22.42 min.

4.3.6. 7H[46]**.** Using Boc-Ala-Ala-Ala-Glu(O*c*Hex)-His-(Bom)-Leu-Lys(CIZ)-Gly-OBzl instead of **9**. **7H**[46] (free-base); R_t^2 22.78 min, TOF-MS; *m/z* 5576.0, calcd *m/z* 5575.7 $(M+H)^+$. **7H**[46]; R_t^2 24.88 min.

4.4. Kinetic measurements for the peroxidase activity

Typically, 5.0 μL of a peptide solution in MeOH (0.10 mM, determined using $\varepsilon_{416}=103\,000\ M^{-1}\,cm^{-1}$ in MeOH for **4H**[43]) and 20 μL of a MCDP solution in DMF (10 mM) were mixed into a 1.0 mL of pH 7.2 buffer solution (20 mM Tris·HCl) in a quartz cuvette of a 10 mm path length, and then 20 μL of CHP solution in MeOH (1.0 M) or aqueous H_2O_2 (1.0 M) was added at 25 °C. The final conditions were [peptide]=0.50 μM, [MCDP]=0.20 mM, and [oxidant]=20 mM in a buffer solution–2.5% MeOH–2% DMF. The progress of MCDP oxidation was followed by the increase in absorption of the oxidized product, methylene blue ($\varepsilon_{666}=96\,000\ M^{-1}\,cm^{-1}$) for ~15 min to collect the initial rates (v_0). The apparent Michaelis–Menten parameters (k_{cat}, K_M, and k_{cat}/K_M) were obtained from the Lineweaver–Burk equation (the plot of $1/v_0$ versus 1/[oxidant]) with varying the [oxidant] in 1.0–100 mM range.

Acknowledgements

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15. Abbreviations are according to IUPAC-IUB commission: IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), *Eur. J. Biochem.* **1984**, *138*, 9–37. Other abbreviations; a (in the peptide sequence), D-alanine; BOM, benzyloxymethyl; ClZ, 2-Cl-benzyloxycarbonyl; CPO, cumene hydroperoxide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide; HOBt, 1-hydroxybenzotriazole; MCDP, 10-*N*-methylcarbamoyl-3,7-bis(dimethylamino)-10*H*-phenothiazine; O(p), side-chain (iron) porphyrin-linked ornithine; TPP, tetraphenylporphyrinato dianion; Tris, tris(hydroxymethyl)aminomethane.
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Three-component reactions involving zwitterionic intermediates for the construction of heterocyclic systems: one pot synthesis of highly functionalized γ-iminolactones

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Abstract—The highly reactive 1:1 intermediate generated in the reaction between an alkyl isocyanide and a dialkyl acetylenedicarboxylate is trapped by alkylphenylglyoxylate to yield γ-iminolactones in good yields.

1. Introduction

Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention from the vantage point of combinatorial chemistry.[1,2] Of pivotal importance in this area are the isocyanide-based MCRs such as the versatile Ugi and Passerini reactions.[3,4]

The reactivity of nucleophilic carbenes such as isocyanides towards dimethyl acetylenedicarboxylate (DMAD) is well documented.[5,6] The reaction of isocyanides with carbon–carbon triple bonds occurs in a stepwise manner through a zwitterionic intermediate, the ultimate fate of which appears to be dictated by the nature of the original triple-bonded substrate.[6–8]

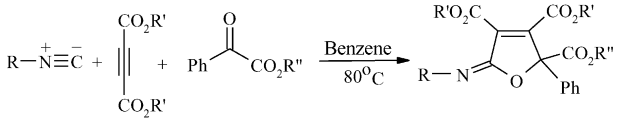
The initially formed zwitterionic intermediate has been shown to undergo further reaction with DMAD and isocyanide in different molar proportions, leading to a variety of complex heterocyclic compounds and these reactions have been the subject of detailed investigation by a number of research groups.[9–16]

In the context of our general interest in the synthesis of heterocyclic compounds by the reaction of dipolar species with carbonyl compound,[17–19] we were intrigued by the possibility of trapping the zwitterionic intermediate derived from isocyanides and dialkyl acetylenedicarboxylates with alkyl phenylglyoxylate. It is noteworthy that previous attempts to trap zwitterionic intermediate with various olefinic dipolarofiles have failed.[12,13] The preliminary results of our investigations validating the usefulness of this process, leading to a novel γ-iminolactones synthesis are presented here.

2. Results and discussion

Thus, alkylisocyanides **1** and acetylenic esters **2** in the presence of alkyl phenylglyoxylate **3** undergo a cycloaddition reaction in benzene at 80 °C to produce γ-iminolactones **4** in good to excellent yields (Scheme 1).

On the basis of the well established chemistry of isocyanides,[6,7] it is reasonable to assume that compounds **4** result from initial addition of alkyl isocyanides to the



1	R
a	*t*-Bu
b	cyclohexyl

2	R'
a	Me
b	Me
c	*t*-Bu
d	*i*-pr

3	R"
a	Me
b	Et

4	R	R'	R"	(%)Yield
a	t-Bu	Me	Me	78
b	cyclohexyl	Me	Me	92
c	t-Bu	Et	Me	73
d	cyclohexyl	Et	Me	80
e	t-Bu	Et	Et	78
f	t-Bu	Me	Et	80
g	cyclohexyl	Me	Et	88
h	cyclohexyl	Et	Et	87
i	cyclohexyl	i-pr	Et	66

Scheme 1.

Keywords: γ-Iminolactones; Isocyanide; Acetylenic esters; Alkyl phenylglyoxylate; α-Ketoesters.
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acetylenic esters and concomitant addition to alkyl phenylglyoxylate leading to iminolactones (Scheme 2). Structures **4** were assigned on the basis of their elemental analyses as well as, their IR, ^{1}H, ^{13}C NMR and mass spectral data. The IR spectrum of **4a** showed strong absorptions at 1765, 1755 and 1710 cm^{-1} due to the ester carbonyl and at 1675 cm^{-1} due to the C=N. The ^{1}H NMR spectrum of **4a** exhibited four singlets arising from the *tert*-butyl (δ 1.35) and methoxy groups (δ 3.73, 3.85 and 3.89). The ^{13}C NMR spectrum showed 16 distinct resonances consistent with the γ-iminolactone structure. Partial assignments of these resonances are given in Section 3.

The characteristic signal due to the C2 carbon was discernible at about δ 91.55. The ^{1}H and ^{13}C NMR spectra of **4b–4i** are similar to those of **4a**, except for *N*-alkyl and esters residues.

In conclusion, a three-component condensation reaction is described. It offers an easy and effective one-pot synthesis of iminolactones, which are potentially amenable to a number of synthetic transformation.[20]

3. Experimental

Melting points were measured on an Electro thermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. IR spectra were measured on a Perkin–Elmer 783 Infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a SHIMADZU GCMS-QP5050 mass spectrometer operating at an ionization potential of 70 eV. Methyl phenylglyoxylate and ethyl phenylglyoxylate were obtained from Merck. Isocyanides and acetylenic esters **1** were obtained from Fluka (Buchs, Switzerland) and all materials were used without further purification.

3.1. General experimental procedure for synthesis of dimethyl-2-(*tert*-butylimino)-5-methoxycarbonyl-5-phenyl-2,5-dihydro-3,4-furandicarboxylate 4a

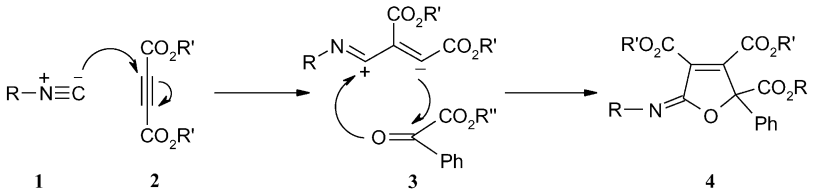
A mixture of alkyl phenylglyoxylate (1 mmol) and dialkyl acetylendicarboxylate (1.1 mmol) in dry benzene was purged with argon at 80 °C. To this mixture, isocyanide (1.1 mmol) was added via a syringe and refluxed for about 4 h. The solvent was removed under vacuum and the product **4** was crystallized out from a CH_2Cl_2–hexane mixture and washed with hexane (4×3 mL) to give crystalline solid.

3.1.1. Selected data for 4a. White crystals, (0.30 g, mp 87 °C, yield 78%); IR (KBr) (ν_{max}, cm^{-1}): 1765, 1755 and 1710 (3C=O), 1675 (C=N); MS (EI), (*m*/*z*, %): 390 (MH^+, 2) 374 (M^+-Me, 78), 342 (M^+-3Me, 19), 274 (M^+-t-Bu-CO_2 Me, 17), 242 (M^+-t-Bu-CO_2Me–2Me, 25), 105 (M^+_{PhCO}, 100), 77 (M^+_{Ph}, 30), 57 ($M_{t\text{-}Bu}$, 59); Anal. Calcd for $C_{20}H_{23}NO_7$ (389.41): C, 61.69; H, 5.95; N, 3.60% Found: C, 61.4; H, 6.0; N, 3.7%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.35 (C*Me*$_3$), 3.73, 3.85 and 3.89 (3O*Me*), 7.36–7.42 (5H, m, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=29.53 (C*Me*$_3$), 52.68, 52.91 and 53.39 (3O*Me*), 55.15 (N–*C*Me$_3$), 91.55 (C2), 126.63, 128.26 and 129.14 (3CH arom.), 134.73 (C_{ipso}), 136.81 (C3), 142.79 (C4), 151, 56, 160.84 and 161.92 (3C=O), 167.24 (C=N).

3.1.2. Selected data for 4b. Bright brown crystals, (0.38 g, mp 132 °C, yield 92%); IR (KBr) (ν_{max}, cm^{-1}): 1737, 1726 and 1720 (3C=O), 1684 (C=N); MS (EI), (*m*/*z*, %): 415 (M^+, 2), 383 (M^+-2Me, 27), 290 ($M^+-C_6H_{11}NCO$, 18) ($M^+-C_6H_{11}NCO$–Me, 15), 258 ($M^+-C_4H_{11}NCO$–2Me, 34), 105 (M^+_{PhCO}, 100); Anal. Calcd for $C_{22}H_{25}O_7N$ (415.44): C, 63.61; H, 4.9; N, 2.72%, Found: C, 63.3; H, 5.0; N, 2.7%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.15–1.77 (10H, m, 5C*H*$_2$), 3,69 (1H, m, N–C*H*), 3.71, 3.84 and 3.86 (9H, 3 s, 3O*Me*), 7.31–7.37 (5H, m, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$); δ=24.60, 24.64, 25.62, 33.24 and 33.27 (5C*H*$_2$), 52.71, 52.99 and 53.50 (3O*Me*), 56.69 (N–*C*H), 91.02 (C_2), 126.59, 128.32 and 129.24 ($3CH_{arom}$), 134.68 (C_{ipso}), 136.57 (C_3), 143.86 (C_4), 153.56, 160.84 and 161.69 (3C=O), 167.16 (C=N).

3.1.3. Selected data for 4c. White crystals, (0.30 g, mp 78 °C, yield 73%); IR (Kerr) (ν_{max}, cm^{-1}): 1764, 1756 and 1730 (3C=O), 1690 (C=N); MS (EI), (*m*/*z*, %): 417 (M^+, 3), 402 (M^+-CH_3, 36), 284 ($M^+-3ET-CO_2$, 58), 256 (M^+-t-BuNCO–C_6H_5, 45) 214 (M^+-t-BuNCO–C_6H_5–Et, 28), 105 (M^+_{PhCO}, 100); 77 (M_{C6H5}), 57 (M_{But}, 78); Anal. Calcd for $C_{22}H_{27}NO_7$ (417.46): C, 63.3; H, 6.52; N, 3.35% Found: C, 63.2; H, 6.50; N, 2.3%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.21 (3H, t, *J*=6.1 Hz, OCH_2*Me*), 1.35 (3H, t, *J*=7 Hz, OCH_2*Me*), 1.35 (9H, s, C*Me*$_3$), 3.86 (O*Me*), 4.19 and 4.37 (4H, 2m, 2OCH_aH_bMe), 7.37–7.43 (5H, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=13.67 and 13.97 (2OCH_2*Me*) 29.55 (C*Me*$_3$), 53.31 (O*Me*), 55.05 (N–*C*Me$_3$), 61.83 and 62.06 97 (2O*C*H$_2$Me), 91.51 (C2), 26.70, 128.17 and 129.05 ($3CH_{arom}$) 134.94 (C_{ipso}), 136.72 (C3), 142.60 (C4), 151.63, 160.46 and 161.53 (3C=O), 167.38 (C=N).

3.1.4. Selected data for 4d. Bright yellow crystals, (0.36 g, mp 74 °C, yield 80%); IR (KBr) (ν_{max}, cm^{-1}): 1760, 1750 and 1732 (3C=O), 1688 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.21 (3H, t, *J*=7 Hz, OCH_2*Me*), 1.34 (3H, t, *J*=7.4 Hz, OCH_2*Me*), 1.25–1.81 (10H, m, 5C*H*$_2$ of cyclohexyl), 3.74 (1H, m, N–C*H*), 3.86 (3H, s, O*Me*),



Scheme 2.

4.19 and 4.37 (4H, 2m, 2OCH_aH_bMe), 7.37–7.41 (5H, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=13.71 and 13.96 (2OCH$_2$*Me*), 24.56, 24.60, 25.69, 33.27 and 33.29 (5*C*H$_2$ of cyclohexyl), 53.43 (O*Me*), 54.53 (N–*C*H), 61,89 and 62.20 (2O*C*H$_2$Me), 91.01 (C2), 126.68, 128.26 and 129.18 (3CH$_{arom}$), 134.90 (C$_{ipso}$), 135.35 (C3), 143.71 (C4), 153.67, 160.45 and 161.31 (3C=O), 167.31 (C=N).

3.1.5. Selected data for 4e. Bright yellow crystals, (0.34 g, mp 82 °C, yield 78%); IR (KBr) (ν_{max}, cm^{-1}): 1750, 1746 and 1730 (3C=O), 1675 (C=N); Ms (EI), (*m*/*z*, %): 431 (M$^+$,), 416 (M$^+$−CH$_3$, 36), 298 (M$^+$−3ET–CO$_2$, 68), 256 (M$^+$−*t*-BuNCO–C$_6$H$_5$, 45), 228 (M$^+$−*t*-BuNCO−C$_6$H$_5$–Et, 28), 213 (M$^+$−3CO$_2$–Et, 12), 105 (M$^+_{PhCO}$, 100); 77 (M$_{C6H5}$), 57 (M$_{But}$, 78); Anal. Calcd for $C_{23}H_{29}O_7N$ (431.49): C, 64.02; H, 6.77; N, 3.25%, Found: C, 64.5; H, 6.4; N, 3.2%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.18 (3H, t, *J*=7 Hz, CH$_2$*Me*), 1.27 (3H, t, *J*=7 Hz), CH$_2$*Me*), 1.32, (3H, t, *J*=7.5 Hz, CH$_2$*Me*), 1.33 (C*Me*$_3$), 4.16 (2H, m, OCH_aH_bMe), 4.32 (4H, m, 2OCH_aH_bMe); 7.33–7.41 (5H, m, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): 13.67, 13.93 and 13.96 (3CH$_2$*Me*), 29.53 (C*Me*$_3$), 54.96 (N–*C*Me$_3$), 61.77, 62.00 and 62.55 (3O*C*H$_2$Me), 91.58 (C$_2$), 126.72, 128.13 and 128.99 (3CH$_{arom}$), 135.00 (C$_{ipso}$), 136.54 (C$_3$), 142.87 (C$_4$), 151.73, 160.50 and 161.55 (3C=0), 166.74 (C=N).

3.1.6. Selected data for 4f. Yellow crystals, (0.33 g, mp 95 °C yield 80%); IR (KBr) (ν_{max}, cm^{-1}): 1745, 1740 and 1735 (3C=O), 1680 (C=N); MS (EI), (*m*/*z*. %): 403 (M$^+$, 2), 388 (M$^+$−CH$_3$,40), 330 (M$^+$−ButN, 15) 284 (M$^+$−ButN–3Me, 58), 274 (M$^+$−*t*-BuNC=O–2Me, 44), 242 (M$^+$−*t*-BuNC=O–2Me, 42), 105 (M$^+_{PhCO}$, 100), 57 (M$_{t\text{-}Bu}$, 73); Anal. Calcd for $C_{21}H_{25}O_7N$ (403.44): C, 62.52; H, 6.25; N, 3.47%. Found: C, 63.O; H, 6.3; N, 3.4%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.25 (3H, t, *J*=6.7 Hz, OCH$_2$*Me*), 1.33 (9H, s, C*Me*$_3$), 3.70 and 3.86 (2O*Me*), 4.31 (2H, q, *J*=6.7 Hz, N–*C*H$_2$Me) 7.34–7.38 (5H, m, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=13.92 (OCH$_2$*Me*), 29.50 (C*Me*$_3$), 52.59 and 52.89 (2O*Me*), 55.10 (N–*C*Me$_3$), 62.64 (O*C*H$_2$Me), 91.02 (C$_2$), 126.65, 128.22 and 129.08 (3CH$_{arom}$), 134.68 (C$_{ipso}$), 136.57 (C$_3$), 143.13 (C$_4$), 151.71, 160.91 and 161.92 (3C=O), 166.60 (C=N).

3.1.7. Selected data for 4g. Yellow crystals, (0.38 g, mp 120 °C, yield 88%); IR (KBr) (ν_{max}, cm^{-1}): 1742, 1733 and 1719 (3C=O), 1681 (C=N); MS (EI), (*m*/*z*, %): 429 (M$^+$, 5), 399 (M$^+$−2Me, 10), 370 (M$^+$−CO$_2$Me, 6), 304 (M$^+$−C$_6$H$_{11}$NCO, 10), 274 (M$^+$−C$_6$H$_{11}$NCO–2Me, 25), 242 (M$^+$−C$_6$H$_{11}$NCO–2Me–Et, 40), 105 (M$^+_{PhCO}$, 100), 77 (M$_{Ph}$, 27); Anal. Calcd for $C_{23}H_{27}NO_7$ (429.47): C, 64.32; H, 6.34; N, 3.26%, Found: C, 64.2; H, 7.4; N, 3.2%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.19 (3H, t, *J*=11.3 Hz, CH$_2$*Me*), 1.26–179 (10H, m, 5C*H*$_2$), 3.70 and 3.87 (2O*Me*), 3.73 (N–C*H*), 4.31 (2H, m, OCH_aH_bMe), 7.32–7.37 (5H, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=13.88 (OCH$_2$*Me*), 24.61, 24.63, 25.63, 33.18 and 33.29, (5*C*H$_2$ of cyclohexyl), 52.61 and 52.97 (2O*Me*), 56.63 (N–*C*H), 62.74 (O–*C*H$_2$Me), 91.06 (C2), 126.63, 128.29 and 129.19 (3CH$_{arom}$), 134.74 (C$_{ipso}$), 135.18 (C3), 144.18 (C4), 153.64, 160.93 and 161.70 (3C=O), 166.56 (C=N).

3.1.8. Selected data for 4h. White crystals, (0.40 g, mp 95 °C, yield 87%); IR (KBr) (ν_{max}, cm^{-1}): 1766, 1754 and 1741 (3C=O), 1690 (C=N); MS (EI), (*m*/*z*, %): 458 (M$^+$, 5), 384 (M−OEt–Et, 20,), 360 (M−C$_6$H$_{11}$NC, 28) 302 (M$^+$−C$_6$H$_{11}$NCO–Et, 34), 105 (M$^+_{PhCO}$, 100), Anal. Calcd for $C_{25}H_{31}NO_7$ (457.52): C, 65.63; H, 6.83; N, 3.04%. Found: C, 65.7; H, 7.3; N, 2.9%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.16, 1.27 and 1.31 (9H, m, 3OCH$_2$*Me*), 1.26–1.79 (10H, m, 5C*H*$_2$ of cylohexyl), 3.71 (1H, m, N–C*H*), 4.16, 4.16 and 4.33 (6H, 3m, 3OCH_aH_bMe), 7.3–7.38 (5H, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=13.68, 13.89 and 13.39 (3OCH$_2$*Me*), 24.55, 24.56, 25.67, 33.18 and 33.30 (5*C*H$_2$ of cyclohexyl) 56.50 (N–*C*H), 61.81, 62.13 and 62.66 (3O*C*H$_2$Me), 91.03 (C2), 126.70, 128.20 and 129.10 (3CH$_{arom}$), 134.93 (C$_{ipso}$), 135.14 (C3), 143.96 (C4), 153.73, 160.50 and 161.31 (3C=O), 166.70 (C=N).

3.1.9. Selected data for 4i. Bright yellow crystals, 0.33 g, mp 98 °C, yield 66%); IR (KBr) (ν_{max}, cm^{-1}): 1750, 1730 and 1717 (3C=O), 1680 (C=N); MS (EI), (*m*/*z*, %): 486 (M$^+$,7), 442 (M$^+$−pr^i, 9.5), 246 (M$^+$−C$_6$H$_{11}$NC–2pr^i-CO$_2$, 56), 105 (M$_{PhCO}$+, 100); Anal. Calcd for $C_{27}H_{35}O_7N$ (485.58): C, 66.78; H, 7.26; N, 2.88% Found: C, 67.1; H, 7.3; N, 2.9%; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.13, 1.61, 1.31 and 1.32 (12H, 4d, *J*=5.2 Hz, 4OCH*Me*$_2$), 1.26–177 (10H, m, 5C*H*$_2$), 1.40 (2H, t, *J*=10.9 Hz, OCH$_2$*Me*), 3.71 (1H, m, N–C*H*), 4.32 (2H, m, OCH_aH_bMe), 5.00 and 5.23 (2H,2septed, 2O*C*HMe$_2$), 7.34–7.38 (5H, m, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=13.91 (OCH$_2$*Me*), 21.33, 21.37, 21.58 and 21.63 (4Me of 2OCH*Me*$_2$), 24.32 24.36, 25.74, 33.19, 33.30 (5*C*H$_2$ of cyclohexyl), 56.07 (N–*C*H), 62.57 (OCH$_2$Me), 62.90 and 70.02 (2O*C*HMe$_2$), 91.03 (C2), 126.78, 128.11 and 129.01 (3CH$_{arom}$) 135.15 (C$_{ipso}$), 135.434 (C3), 143.59 (C4), 153.65, 160.08 and 161.06 (3C=O), 166.82 (C=N).

CAUTION: Acetylenic esters are Lachrymator.

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Palladium(II)-catalyzed heterocyclisation of 8-arylethynyl-1,2,3,4-tetrahydroquinolines: a facile route to 2-aryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives

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Abstract—Dihydropyrroloquinolines have been synthesized reacting 8-arylethynyl-1,2,3,4-tetrahydroquinolines in the presence of palladium(II) chloride catalyst. Heteroannulation has been achieved in good yields and tolerates substituents on the tetrahydroquinoline, including bromo, cyano, and ester.

1. Introduction

The 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline ring constitutes the central core of different series of compounds exerting platelet activating factor production inhibition[1] or acting as 5-hydroxytryptamine (5-HT_{2c}) receptor agonists and exerting antiepileptic or anti-obesity activities[2] (Fig. 1).

During our work in the field of peptidomimetic antagonists of G-protein coupled receptors (GPCRs) we were interested in the synthesis of analogues of the nonpeptidyl luteinizing hormone-releasing hormone (LHRH) receptor antagonist **3** (Fig. 2).[3]

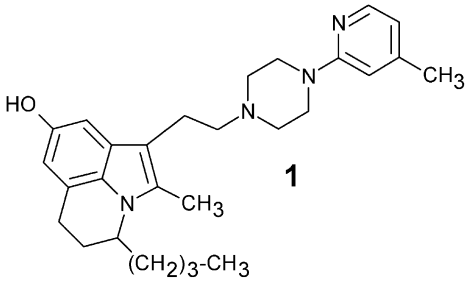
Pharmacomodulation at the level of the central indole core led us to envision the incidence of its replacement by an indole-bridged heterocycle, 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (Fig. 3).

Access to such compounds is regularly described by the well known Fischer indole derivatives synthesis.[1,4]

Herein, we report the strategy for the synthesis of the central scaffold using a palladium(II)-catalyzed intramolecular heterocyclisation.

2. Results and discussion

The 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline is classically



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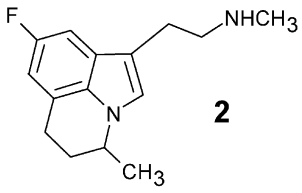

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Figure 1. Structures of a PAF antagonist **1** and a 5HT_{2C} receptor agonist **2**.

Keywords: 5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines; 1,2,3,4-Tetrahydroquinolines; Palladium(II)-catalyzed intramolecular heterocyclisation.
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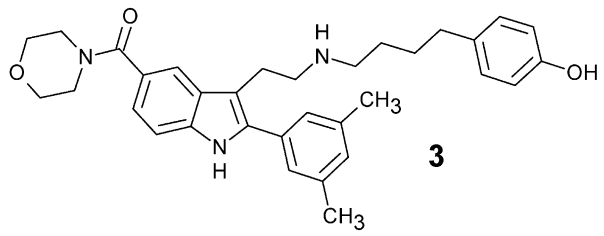


Figure 2. Structure of the nonpeptidyl gonadotropin-releasing hormone (GnRH) receptor antagonist **3**.

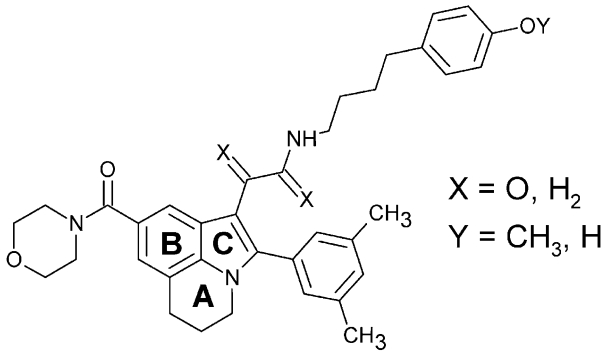
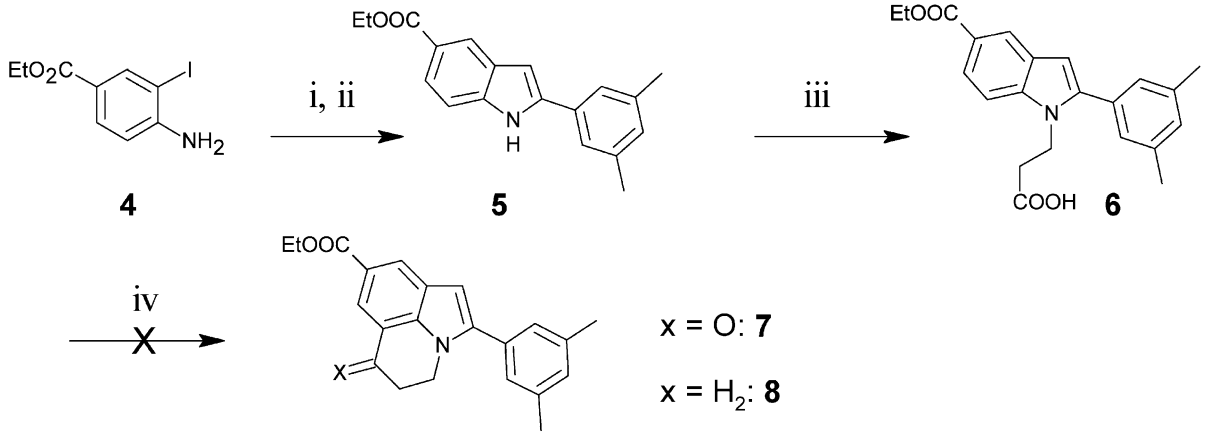


Figure 3. Structure of the novel pyrroloquinolines prepared.

first tried to obtain the tricyclic compound **8** (Scheme 1) by intramolecular acylation of the 1-indolepropionic acid **6** (obtained by reaction of **5** with propiolactone) followed by reduction[5] of the desired 4,5-dihydro-6*H*-pyrroloquinolin-6-one **7**; although the starting 2-xylylindole **5** could be prepared by the Sonogashira[8]/palladium(II)-catalyzed intramolecular cyclisation methods[9] in a 70% overall yield, cyclodehydration of acid **6**, using PPA or $AlCl_3$, failed.

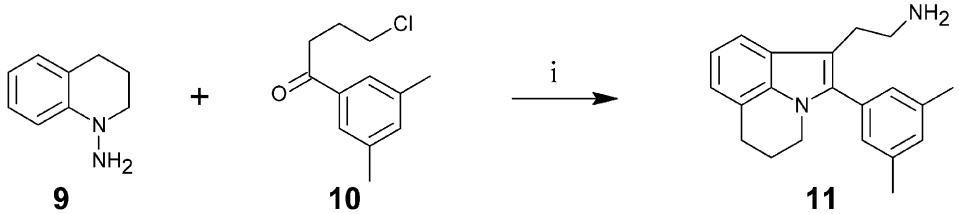
In a second approach, we tried to obtain directly 1-(2-aminoethyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline **11** by the elegant Fischer indole synthesis worked out by Grandberg[10] for tryptamine derivatives. Condensation of 1-amino-1,2,3,4-tetrahydroquinoline[1] **9** with 4-chloro-1-(3,5-dimethylphenyl)butan-1-one **10** afforded the desired azaarylethylamine **11** (Scheme 2), but yield remained poor (15%) and its purification necessitated multiple tedious column chromatography elutions.

We hypothesized that palladium-catalyzed ring closure of alkynylanilines to indoles[11,12] may be directly applicable to the preparation of 2-aryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines (Scheme 3). The synthesis began with the bromination of the commercially available 1,2,3,4-tetrahydroquinoline **12** to give 6-bromo-1,2,3,4-tetrahydroquinoline **13** as major product in 60% yield. The

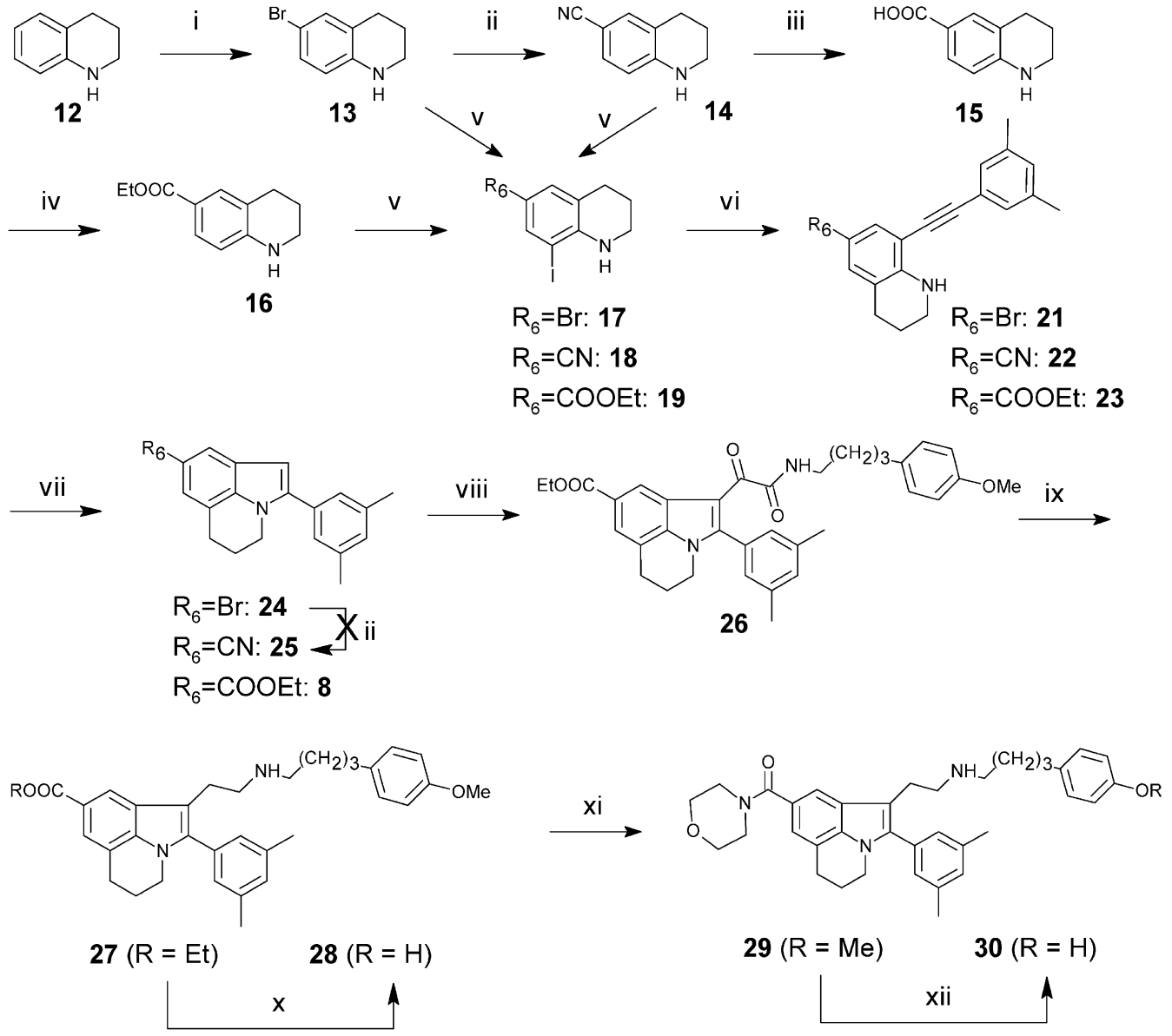


Scheme 1. Synthesis of the 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline **8**: (i) (3,5-dimethylphenyl)acetylene **20**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 10 °C, 89%; (ii) $PdCl_2$, CH_3CN, reflux, 78%; (iii) propiolactone, NaH, DMF, rt, 72%; (iv) PPA or $AlCl_3$, CH_2Cl_2.

elaborated by two strategies (Fig. 3): (i) creation of ring A starting from indole derivative, (ii) creation of ring C using suitably substituted 1,2,3,4-tetrahydroquinoline. In the first case, numerous indole cyclisation reactions have been carried out using N-1 and/or C-7 substituted indoles.[5–7] We temperature must be kept at 0 °C to avoid simultaneous bromination in position 8. Iodination with iodine monochloride gave the 6-bromo-8-iodo-1,2,3,4-tetrahydroquinoline **17**. The Sonogashira palladium-catalyzed cross-coupling reaction[8] of amine **17** with (3,5-



Scheme 2. Grandberg synthesis of azaarylethylamine **11**. (i) EtOH, reflux, 15%.



Scheme 3. Synthesis of 1-aminoethyl-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives. (i) NBS, CCl_4, 0 °C; (ii) CuCN, DMF, reflux; (iii) NaOH, H_2O_2, reflux; (iv) EtOH, HCl, reflux; (v) ICl, $CaCO_3$, MeOH/H_2O, 0 °C; (vi) (3,5-dimethylphenyl)acetylene **20**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 10 °C; (vii) $PdCl_2$, CH_3CN, reflux; (viii) (1) $(COCl)_2$, Et_2O, 0 °C (2) 4-(4-methoxyphenyl)butylamine, THF, rt; (ix) (1) BH_3:THF, reflux (2) *N*,*N*-dimethylethanolamine, MeOH/THF, reflux; (x) NaOH, EtOH, reflux; (xi) morpholine, PyBOP, *N*-methylmorpholine, DMF, rt; (xii) BBr_3, CH_2Cl_2, rt.

dimethylphenyl)acetylene **20**[14] using catalytic amount of the $Pd(PPh_3)_2Cl_2$-CuI system in triethylamine under nitrogen at 0 °C provided access to the key intermediate, the 6-bromo-8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline **21**, in excellent yield.

Palladium dichloride is a well-established catalyst for converting 2-alkynylanilines into 2-substituted indoles through N–C_2 ring closure.[9] We used such reaction conditions with refluxing acetonitrile as solvent to obtain 2-phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline **24** from compound **21**, in 70% yield. The corresponding nitrile **25** could not be obtained by heating the bromo derivative **24** at reflux with copper cyanide in dimethylformamide in a Rosenmund-von Braun reaction.[14] Another attempt using $ZnCN_2$ as cyanation reagent[15] in palladium-catalyzed conditions remained unsuccessful. This problem was solved by carrying out the cyanation with 6-bromo-1,2,3,4-tetrahydroquinoline **13** as starting material in the previous conditions (CuCN/DMF, reflux) to afford 6-cyano-1,2,3,4-tetrahydroquinoline **14** in 60% yield (Scheme 3). Subsequent reactions of iodination (compound **18**), Sonogashira coupling (compound **22**) and palladium-catalyzed cyclisation gave pyrroloquinoline **25** in a 31% overall yield. The cyano derivative **25** was converted to the corresponding carboxylic acid, with aqueous solution of sodium hydroxide in the presence of hydrogen peroxide, only in very poor yield. Since the synthetic route to the ester **8** via the carboxylic acid appeared to be unsuitable, the cyano derivative **14** was first hydrolysed as described above. The synthesis of the 1,2,3,4-tetrahydroquinoline-6-carboxylic acid **15** was achieved easily and in an excellent yield (95%).

Ethyl ester **16** was synthesized by refluxing the compound **15** in an hydrogen chloride ethanolic solution. The ethyl pyrroloquinoline-8-carboxylate **8** was then prepared using a sequence of reactions similar to those described for compounds **24** and **25**, in a satisfactory global yield (39%).

The aminoethyl chain was built in the position 1 of the azaheterocycle **8** via the glyoxamide **26** after reaction with oxalyl chloride and subsequent condensation with 4-(4-methoxyphenyl)butylamine.[1] The glyoxamide **26** was reduced with a borane–THF complex to give ethylamine **27** after treatment with *N*,*N*-dimethylethanolamine to break down the boron–amine complex intermediate. The ester **27** was hydrolyzed under alkaline conditions to afford the corresponding carboxylic acid **28**, which was condensed with morpholine using PyBOP as coupling reagent and *N*-methylmorpholine in dimethylformamide at room temperature to yield the morpholide **29**. Demethylation of **29** with boron tribromide at room temperature gave the corresponding phenol **30** in a 45% yield.

3. Conclusion

Palladium(II)-catalyzed intramolecular heterocyclisation of 8-arylethynyl-1,2,3,4-tetrahydroquinolines provides a simple and high yield method for the preparation of 2-aryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives (**8**, **24**, **25**). They can be modified by substitution to compounds (**26**–**30**), which are of interest as potential antagonists of GPCRs as pharmacological targets.

4. Experimental

4.1. General methods

All common chemicals and solvents utilized were reagent grade and purchased from Sigma-Aldrich (Saint Quentin, France). Melting points were determined on a Electrothermal IA9300 melting point digital apparatus and reported uncorrected. Infrared (IR) spectra were obtained in KBr pellets or neat liquid films with a Perkin–Elmer Paragon FTIR 1000 PC spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance 400 apparatus operating at 400 MHz in d_6-DMSO as solvent. Chemical shifts are expressed as δ values (ppm) relative to Me_4Si as internal standard. Electrospray mass spectrometric analysis was performed on a Esquire-LC Ion Trap System mass spectrometer. All reactions were monitored by TLC, using 0.25 mm-thick precoated silica gel plates (E. Merck) eluted with CH_2Cl_2/EtOH gradients. Compounds were purified by column chromatography using silica gel 60 as stationary phase and eluted with CH_2Cl_2 or CH_2Cl_2/hexane gradients.

4.1.1. 6-Bromo-1,2,3,4-tetrahydroquinoline.[16] (13) To a solution of 1,2,3,4-tetrahydroquinoline **12** (5.00 g, 37.5 mmol) in carbon tetrachloride (10 mL) at 0 °C, was added portion wise *N*-bromosuccinimide (6.68 g, 37.5 mmol). The mixture was stirred at room temperature for 3 h. The succinimide which resulted as a precipitate was filtered off and washed with hexane (4×10 mL). The solvents were removed under reduced pressure, the residue was purified by chromatography (CH_2Cl_2) to give **13** as a yellow oil (4.77 g, 60%). IR (neat) cm^{-1}: 3415 (νNH); 3012 (νCH arom.); 2926, 2836 (νCH alkane); 1598, 1495 (νC=C arom.); 544 (νC–Br). ^{1}H NMR δ 6.98 (d, 1H, J=2.3 Hz, H_5), 6.96 (d, 1H, J=9.2 Hz, H_8), 6.40 (dd, 1H, J=9.2 Hz, J=2.3 Hz, H_7), 5.87 (s, 1H, NH), 3.18 (t, 2H, J=5.5 Hz, H_2), 2.66 (t, 2H, J=6.1 Hz, H_4), 1.89–1.71 (m, 2H, H_3). MS-ES$^+$ (MeOH): *m*/*z* 213 (M+H$^+$, 100%).

4.1.2. 6-Cyano-1,2,3,4-tetrahydroquinoline (14). Compound **13** (3.40 g, 16.0 mmol) was stirred with cuprous cyanide (1.72 g, 19.2 mmol) in dimethylformamide (30 mL) and heated to reflux for 16 h. After the mixture had cooled, 10% ammonium hydroxide solution (50 mL) was added and the resultant mixture was extracted with dichloromethane. The aqueous layer was washed with brine (4×50 mL), water and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography (CH_2Cl_2) to give **14** as a white solid (1.52 g, 60%). Mp 77–79 °C (lit.[16] 78–80 °C). IR (KBr) cm^{-1}: 3382 (νNH); 3052 (νCH arom.); 2931, 2853 (νCH alkane); 2210 (νC≡N); 1608, 1522 (νC=C arom.). ^{1}H NMR δ 7.29–7.21 (m, 2H, H_5, H_7), 6.78 (s, 1H, NH), 6.50 (d, 1H, J=8.0 Hz, H_8), 3.26 (t, 2H, J=5.5 Hz, H_2), 2.67 (t, 2H, J=6.1 Hz, H_4), 1.89–1.71 (m, 2H, H_3). MS-ES$^+$ (MeOH): *m*/*z* 159 (M+H$^+$, 100%).

4.1.3. 1,2,3,4-Tetrahydroquinoline-6-carboxylic acid (15). Thirty-five percent aqueous hydrogen peroxide solution (6 mL) was added to a solution of **14** (1.50 g, 9.5 mmol) in aqueous solution of 2 N NaOH (30 mL) at room temperature. The mixture was refluxed for 24 h, cooled to room temperature and acidified with an aqueous solution of 2 N HCl. The precipitate which resulted was collected by filtration, washed by water and dried over P_2O_5 to give **15** as a white solid (1.60 g, 95%). Mp 169–171 °C (lit.[17] 168–170 °C). IR (KBr) cm^{-1}: 3600–2900 (νOH); 3425 (νNH); 2981, 2928 (νCH alkane); 1703 (νC=O); 1613 (νC=C arom.). ^{1}H NMR δ 7.58–7.41 (m, 2H, H_5, H_7), 6.55 (s, 1H, NH), 6.44 (d, 1H, J=9.1 Hz, H_8), 3.26–3.22 (m, 2H, H_2), 2.69 (t, 2H, J=5.8 Hz, H_4), 1.89–1.71 (m, 2H, H_3). MS-ES$^+$ (MeOH): *m*/*z* 178 (M+H$^+$, 100%).

4.1.4. Ethyl 1,2,3,4-tetrahydroquinoline-6-carboxylate (16). Carboxylic acid **15** (1.00 g, 5.6 mmol) in ethanolic solution of 2 N HCl (50 mL) was refluxed for 3 days. The solution was cooled to room temperature and basified with an aqueous solution of 1 N NaOH. The precipitate which resulted was collected by filtration, washed by ethanol and dried over P_2O_5 to give **16** as a white solid (0.69 g, 60%). Mp 80–81 °C (lit.[17] 82–83 °C, hexane). IR (KBr) cm^{-1}: 3388 (νNH); 2935 (νCH alkane); 1677 (νC=O); 1608, 1525 (νC=C arom.). ^{1}H NMR δ 7.58–7.40 (m, 2H, H_5, H_7), 6.62 (s, 1H, NH), 6.44 (d, 1H, J=8.2 Hz, H_8), 4.21 (q, 2H, J=7.0 Hz, CH_2), 3.28–3.24 (m, 2H, H_2), 2.70 (t, 2H, J=6.1 Hz, H_4), 1.89–1.71 (m, 2H, H_3), 1.28 (t, 3H, J=7.0 Hz, CH_3). MS-ES$^+$ (MeOH): *m*/*z* 206 (M+H$^+$, 100%).

4.2. General procedure for the synthesis of 8-iodo-1,2,3,4-tetrahydroquinolines

A solution of iodine monochloride (21 mmol) in methanol

(25 mL) was added dropwise to a stirred suspension of 1,2,3,4-tetrahydroquinolines **13**, **14** or **16** (20 mmol) and calcium carbonate (30 mmol) in methanol/water (4/1) (100 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h before filtering through a pad of Celite. The filtrate was extracted with dicholoromethane and the organic layer was washed with water. The organic layer was dried over Na_2SO_4 and evaporated in vacuo, and the residue was chromatographed on silica gel, eluting with CH_2Cl_2 to give **17**, **18** or **19**.

4.2.1. 6-Bromo-8-iodo-1,2,3,4-tetrahydroquinoline (17). An orange oil was obtained (69%). IR (neat) cm^{-1}: 3399 (νNH); 3020 (νCH arom.); 2928, 2836 (νCH alkane); 1586, 1494 (νC=C arom.); 546 (νC–Br). ^1H NMR δ 7.54 (s, 1H, H_7), 7.09 (s, 1H, H_5), 5.28 (s, 1H, NH), 3.32–3.26 (m, 2H, H_2), 2.70 (t, 2H, $J=6.2$ Hz, H_4), 1.78–1.72 (m, 2H, H_3). ^{13}C NMR δ 20.5, 27.3, 41.8, 82.0, 97.1, 121.1, 133.1, 140.7, 148.6. MS-ES$^+$ (MeOH): *m/z* 339 ($M+H^+$, 100%).

4.2.2. 6-Cyano-8-iodo-1,2,3,4-tetrahydroquinoline (18). A white solid was obtained (62%). Mp 124–126 °C. IR (KBr) cm^{-1}: 3350 (νNH); 3015 (νCH arom.); 2930, 2842 (νCH alkane); 2212 (νC≡N); 1595, 1512 (νC=C arom.). ^1H NMR δ 7.84 (s, 1H, H_7), 7.31 (s, 1H, H_5), 6.13 (s, 1H, NH), 3.39–3.35 (m, 2H, H_2), 2.72–2.68 (m, 2H, H_4), 1.79–1.74 (m, 2H, H_3). ^{13}C NMR δ 20.3, 27.2, 42.0, 81.8, 97.2, 119.3, 121.4, 132.3, 140.2, 148.4. MS-ES$^+$ (MeOH): *m/z* 285 ($M+H^+$, 100%).

4.2.3. Ethyl 8-iodo-1,2,3,4-tetrahydroquinoline-6-carboxylate (19). An orange oil was obtained (60%). IR (neat) cm^{-1}: 3368 (νNH); 2929, 2843 (νCH arom.); 1700 (νC=O); 1598, 1516 (νC=C arom.). ^1H NMR δ 8.00 (s, 1H, H_7), 7.50 (s, 1H, H_5), 5.97 (s, 1H, NH), 4.23 (q, 2H, $J=7.1$ Hz, CH_2), 3.29–3.25 (m, 2H, H_2), 2.73 (t, 2H, $J=6.1$ Hz, H_4), 1.82–1.78 (m, 2H, H_3), 1.28 (t, 3H, $J=7.1$ Hz, CH_3). ^{13}C NMR δ 14.5, 20.1, 27.1, 41.5, 59.6, 82.6, 96.8, 120.9, 131.6, 140.5, 147.9, 168.1. MS-ES$^+$ (MeOH): *m/z* 332 ($M+H^+$, 100%).

4.3. General procedure for the synthesis of 8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinolines

4.3.1. (3,5-Dimethylphenyl)acetylene.[13] (20) To a mixture of trimethylsilylacetylene (2.64 g, 26.9 mmol) and 3,5-dimethyliodobenzene 6.17 g, 26.6 mmol) in triethylamine (30 mL) was added bis(triphenylphosphine)palladium dichloride (360 mg, 0.52 mmol) and copper(I) iodide (49 mg, 0.26 mmol). The reaction mixture was stirred at room temperature for 4 h under nitrogen and a crystalline grey-green solid of triethylamine hydroiodide was isolated by filtration and washed with toluene. The filtrate was concentrated under reduced pressure and the crude product was purified by chromatography on neutral alumina using CH_2Cl_2/hexane (1/1) as an eluent to afford the 3,5-dimethyl-1-trimethylsilylethynylbenzene as a yellow oil (5.27 g, 98%). ^1H NMR δ 7.09 (s, 2H, $H_{2,6}$), 7.04 (s, 1H, H_4), 2.54 (s, 6H, CH_3), 0.25 (s, 9H, $Si(CH_3)_3$).

A solution of TBAF 1 M in tetrahydrofuran (12 mL, 12 mmol) was added dropwise to a stirred solution of 3,5-dimethyl-1-trimethylsilylethynylbenzene (2.21 g, 10.9 mmol) in tetrahydrofuran (50 mL) at −15 °C. The mixture was stirred for 30 min and the solvent was evaporated in vacuo. The residue was purified by chromatography on neutral alumina using hexane as an eluent to afford **20** as a light yellow liquid (1.13 g, 80%). IR (neat) cm^{-1}: 3248 (ν≡C–H); 3105, 3002 (νCH arom.); 2100 (νC≡C); 1510, 1482 (νC=C arom.). ^1H NMR δ 7.12 (s, 2H, $H_{2,6}$), 7.07 (s, 1H, H_4), 4.13 (s, 1H, C≡C–H), 2.28 (s, 6H, CH_3).

4.4. Sonogashira coupling

8-Iodo-1,2,3,4-tetrahydroquinolines **17**, **18** or **19** (16.5 mmol), (3,5-dimethylphenyl)acetylene **20** (17.3 mmol), bis(triphenylphosphine)palladium dichloride (0.38 mmol) and copper(I) iodide (0.82 mmol) were dissolved in triethylamine (100 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 h. The precipitate was filtered off and washed with triethylamine. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel, eluting with CH_2Cl_2 to give **21**, **22** or **23**.

4.4.1. 6-Bromo-8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline (21). A white solid was obtained (97%). Mp 145–147 °C. IR (KBr) cm^{-1}: 3410 (νNH); 3008 (νCH arom.); 2945, 2912 (νCH alkane); 1596, 1494 (νC=C arom.); 548 (νC–Br). ^1H NMR δ 7.28 (s, 2H, H_{ar}), 7.22 (d, 1H, $J=2.4$ Hz, H_7), 7.07 (d, 1H, $J=2.4$ Hz, H_5), 7.05 (s, 1H, H_{ar}), 6.49 (s, 1H, NH), 3.37–3.33 (m, 2H, H_2), 2.74–2.70 (m, 2H, H_4), 2.31 (s, 6H, CH_3), 1.82–1.78 (m, 2H, H_3). ^{13}C NMR δ 20.3, 20.6, 26.4, 41.2, 84.5, 95.3, 95.7, 105.4, 121.7, 122.4, 129.3, 130.5, 132.4, 134.3, 137.4, 148.5. MS-ES$^+$ (MeOH): *m/z* 341 ($M+H^+$, 100%).

4.4.2. 6-Cyano-8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline (22). A white solid was obtained (96%). Mp 131–133 °C. IR (KBr) cm^{-1}: 3375 (νNH); 3002 (νCH arom.); 2932, 2847 (νCH alkane); 2213 (νC≡N); 1599, 1524 (νC=C arom.). ^1H NMR δ 7.51 (s, 1H, H_7), 7.41–7.38 (m, 3H, $2H_{ar}$, H_5), 7.07 (s, 1H, H_{ar}), 6.64 (s, 1H, NH), 3.37–3.33 (m, 2H, H_2), 2.74–2.70 (m, 2H, H_4), 2.32 (s, 6H, CH_3), 1.82–1.78 (m, 2H, H_3). ^{13}C NMR δ 20.1, 20.8, 26.7, 41.3, 84.1, 95.2, 95.5, 105.3, 120.1, 121.2, 122.3, 129.2, 130.4, 132.2, 134.1, 137.8, 149.0. MS-ES$^+$ (MeOH): *m/z* 287 ($M+H^+$, 100%).

4.4.3. Ethyl 8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinoline-6-carboxylate (23). An orange solid was obtained (92%). Mp 84–86 °C. IR (KBr) cm^{-1}: 3403 (νNH); 2926, 2843 (νCH arom.); 1694 (νC=O); 1598, 1514 (νC=C arom.). ^1H NMR δ 7.71 (s, 1H, H_7), 7.50 (s, 1H, H_5), 7.32 (s, 2H, H_{ar}), 7.06 (s, 1H, H_{ar}), 6.49 (s, 1H, NH), 4.24 (q, 2H, $J=7.1$ Hz, CH_2), 3.44–3.40 (m, 2H, H_2), 2.78–2.74 (m, 2H, H_4), 2.31 (s, 6H, CH_3), 1.78–1.88 (m, 2H, H_3), 1.31 (t, 3H, $J=7.1$ Hz, CH_3). ^{13}C NMR δ 14.5, 20.5, 20.8, 27.0, 41.4, 59.9, 85.1, 94.8, 104.4, 115.4, 119.9, 122.6, 129.2, 130.2, 130.4, 131.9, 137.7, 149.5, 165.5. MS-ES$^+$ (MeOH): *m/z* 334 ($M+H^+$, 100%).

4.5. General procedure for the synthesis of 2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines

8-(3,5-Dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinolines **21**, **22** or **23** (5 mmol) and palladium dichloride (0.5 mmol) were dissolved in acetonitrile (35 mL) and the reaction mixture was refluxed for 16 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel, eluting with CH_2Cl_2 to give **24**, **25** or **8**.

4.5.1. 8-Bromo-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (24). A white solid was obtained (70%). Mp 136–138 °C. IR (KBr) cm^{-1}: 2971 (νCH alkane); 1582, 1464 (νC=C arom.); 545 (νC–Br). ^{1}H NMR δ 7.56 (s, 1H, H_9), 7.26 (s, 2H, H_{ar}), 7.09 (s, 1H, H_{ar}), 7.04 (s, 1H, H_7), 6.52 (s, 1H, H_1), 4.24–4.20 (m, 2H, H_4), 2.99–2.95 (m, 2H, H_6), 2.37 (s, 6H, CH_3), 2.14–2.10 (m, 2H, H_5). ^{13}C NMR δ 21.1, 22.6, 24.2, 43.6, 99.6, 112.3, 119.7, 120.9, 124.8, 126.3, 127.2, 129.7, 131.5, 133.7, 138.1, 141.1. MS-ES$^+$ (MeOH): *m/z* 341 (M+H$^+$, 100%).

4.5.2. 8-Cyano-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline (25). A white solid was obtained (87%). Mp 124–126 °C. IR (KBr) cm^{-1}: 2951 (νCH alkane); 2211 (νC≡N); 1596, 1486 (νC=C arom.). ^{1}H NMR δ 7.92 (s, 1H, H_9), 7.29 (s, 2H, H_{ar}), 7.26 (s, 1H, H_7), 7.12 (s, 1H, H_{ar}), 6.69 (s, 1H, H_1), 4.28–4.24 (m, 2H, H_4), 3.03–2.98 (m, 2H, H), 2.39 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5). ^{13}C NMR δ 21.1, 22.4, 24.4, 43.7, 100.8, 101.6, 120.7, 121.2, 123.5, 123.9, 125.2, 126.4, 130.0, 131.1, 136.7, 138.1, 142.4. MS-ES$^+$ (MeOH): *m/z* 287 (M+H$^+$, 100%).

4.5.3. Ethyl 2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-8-carboxylate (8). A white solid was obtained (70%). Mp 87–88 °C. IR (KBr) cm^{-1}: 2939 (νCH alkane); 1701 (νC=O); 1594 (νC=C arom.). ^{1}H NMR δ 8.14 (s, 1H, H_9), 7.56 (s, 1H, H_7), 7.28 (s, 2H, H_{ar}), 7.10 (s, 1H, H_{ar}), 6.70 (s, 1H, H_1), 4.37 (q, 2H, J=7.1 Hz, CH_2), 4.25 (t, 2H, J=5.5 Hz, H_4), 3.02 (t, 2H, J=5.8 Hz, H_6), 2.38 (s, 6H, CH_3), 2.28–2.15 (m, 2H, H_5), 1.37 (t, 3H, J=7.1 Hz, CH_3). ^{13}C NMR δ 14.5, 21.1, 22.7, 24.3, 43.7, 60.2, 101,4, 119.1, 120.5, 121.5, 122.3, 125.0, 126.3, 129.7, 131.5, 137.6, 138.1, 141.6, 167.2. MS-ES$^+$ (MeOH): *m/z* 334 (M+H$^+$, 100%).

4.6. Procedure for the synthesis of 2-[2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]-2-oxoacetamide (26) and ethylamines (27–30)

4.6.1. *N*-[4-(4-Methoxyphenyl)but-1-yl]-2-[8-ethoxycarbonyl-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]-2-oxoacetamide (26). A solution of ethyl 2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-8-carboxylate **8** (0.80 g, 2.3 mmol) in diethyl ether (10 mL) was added dropwise to a solution of oxalyl chloride (0.62 mL, 7.0 mmol) in diethyl ether (5 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and the solvent was removed with nitrogen flow. The residue was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C. 4-(4-Methoxyphenyl)butylamine (1.26 g, 7.1 mmol) was added portionwise and the mixture was stirred at room temperature overnight. The precipitate which resulted was filtered off and the filtrate was concentrated in vacuo. The crude mixture was purified by silica gel column chromatography eluting with hexane/ethyl acetate (1/1) to give oxoacetamide **26** as a white solid (1.24 g, 95%). Mp 128–130 °C. IR (KBr) cm^{-1}: 3303 (νNH); 2928, 2857 (νCH); 1705, 1651 (νC=O); 1511 (νC=C arom.). ^{1}H NMR δ 8.60 (s, 1H, H_9), 8.49–8.45 (m, 1H, NH), 7.72 (s, 1H, H_7), 7.19–7.02 (m, 5H, 2H'$_{ar}$, 3H$_{ar}$), 6.86 (d, 2H, J=8.5 Hz, 2H'$_{ar}$), 4.37 (q, 2H, J=7.0 Hz, CH_2), 4.04–3.98 (m, 2H, H_4), 3.74 (s, 3H, OCH_3), 3.06–3.02 (m, 2H, H_6), 2.76–2.72 (m, 2H, CH_2), 2.52–2.48 (m, 2H, CH_2), 2.38 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.59–1.21 (m, 4H, CH_2), 1.38 (t, 3H, J=7.0 Hz, CH_3). ^{13}C NMR δ 14.5, 21.0, 22.2, 24.1, 28.1, 28.8, 34.0, 38.3, 43.3, 55.1, 60.6, 110.8, 113.8, 121.1, 121.5, 123.3, 124.4, 128.3, 128.8, 129.3, 129.4, 131.1, 134.0, 136.4, 137.2, 148.9, 157.5, 166.5, 166.8, 187.8. MS-ES$^+$ (MeOH): *m/z* 568 (M+H$^+$, 100%).

4.6.2. Ethyl 1-{*N*-[4-(4-methoxyphenyl)but-1-yl]aminoethyl}-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo-[3,2,1-*ij*]quinoline-8-carboxylate (27). Borane–tetrahydrofuran complex (4.4 mL, 4.4 mmol) was added to a solution of *N*-[4-(4-methoxyphenyl)but-1-yl]-2-[8-ethoxycarbonyl-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl]-2-oxoacetamide **26** (0.50 g, 0.87 mmol) in dry tetrahydrofuran (20 mL) under nitrogen at room temperature. The reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure and the residue was dissolved in methanol (30 mL). *N*,*N*-Dimethylethanolamine (5 mL) was added and the solution was refluxed for 3 h. The solvent was removed in vacuo and the residue was chromatographed on silica gel, eluting with hexane/ethyl acetate (1/1), to afford ester **27** as a white solid (197 mg, 42%). Mp 87–89 °C. IR (KBr) cm^{-1}: 3449 (νNH); 2928 (νCH); 1703 (νC=O); 1607, 1512 (νC=C arom.). ^{1}H NMR δ 8.15 (s, 1H, H_9), 7.55 (s, 1H, H_7), 7.16–7.12 (m, 5H, 2H'$_{ar}$, 3H$_{ar}$), 6.87 (d, 2H, J=8.3 Hz, 2H'$_{ar}$), 4.34 (q, 2H, J=8.3 Hz, CH_2), 4.01–3.97 (m, 2H, H_4), 3.74 (s, 3H, OCH_3), 3.02–2.98 (m, 2H, H_6), 2.91–2.72 (m, 4H, CH_2), 2.57–2.53 (m, 2H, CH_2), 2.47–2.43 (m, 2H, CH_2), 2.38 (s, 6H, CH_3), 2.14–2.10 (m, 2H, H_5), 1.59–1.21 (m, 4H, CH_2), 1.37 (t, 3H, J=8.3 Hz, CH_3). ^{13}C NMR δ 14.6, 21.1, 21.4, 22.3, 24.2, 25.4, 28.4, 33.7, 42.8, 46.1, 47.3, 55.1, 60.1, 108.3, 113.6, 119.1, 119.4, 121.4, 122.9, 123.4, 127.9, 128.5, 129.0, 129.3, 130.9, 134.4, 136.3, 137.1, 157.2, 185.3. MS-ES$^+$ (MeOH): *m/z* 540 (M+H$^+$, 100%).

4.6.3. 1-[*N*-[4-(4-Methoxyphenyl)but-1-yl]aminoethyl]-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-8-carboxylic acid 28. An aqueous solution of 2 N NaOH (10 mL) was added to ester **27** (180 mg, 0.33 mmol) in ethanol (20 mL) at room temperature. The reaction mixture was refluxed for 2 h, cooled to room temperature and neutralised with a 6 N solution of HCl. The precipitate which resulted was collected by filtration, washed by water and dried over P_2O_5 to give carboxylic acid **28** as a white solid (102 mg, 72%). Mp 315 °C (degradation). IR (KBr) cm^{-1}: 3600–2400 (νOH); 3425 (νNH); 2927, 2856 (νCH); 1701 (νC=O); 1600, 1512 (νC=C arom.). ^{1}H NMR δ 8.25 (s, 1H, H_9), 7.58 (s, 1H, H_7), 7.16–7.12 (m, 5H, 2H'$_{ar}$, 3H$_{ar}$), 6.87 (d, 2H, J=8.3 Hz, 2H'$_{ar}$), 4.01–3.97 (m, 2H, H_4), 3.74 (s, 3H, OCH_3),

3.02–2.98 (m, 2H, H_6), 2.97–2.91 (m, 4H, CH_2), 2.74–2.70 (m, 2H, CH_2), 2.50–2.46 (m, 2H, CH_2), 2.40 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.56–1.52 (m, 4H, CH_2), 12.46 (s, 1H, OH). ^{13}C NMR δ 21.2, 21.6, 22.5, 24.4, 25.4, 28.3, 33.8, 42.9, 46.5, 47.4, 55.1, 108.3, 113.9, 119.4, 119.9, 121.8, 122.4, 124.5, 127.8, 129.4, 130.1, 133.7, 136.3, 137.8, 138.1, 138.5, 157.6, 169.0. MS-ES$^+$ (MeOH): *m/z* 512 ($M+H^+$, 100%).

4.6.4. 4-{1-[*N*-[4-(4-Methoxyphenyl)but-1-yl]aminoethyl]-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-8-oyl}morpholine 29. Morpholine (0.17 mL, 0.58 mmol) and PyBOP (0.56 g, 0.32 mmol) were added to the solution of *N*-methylmorpholine (0.22 mL, 0.58 mmol) and carboxylic acid **28** (0.50 g, 0.29 mmol) in dimethylformamide (5 mL). The mixture was stirred at room temperature for 3 days. The mixture was quenched with water and the aqueous solution was extracted with dichloromethane. The organic layer was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography eluting with dichloromethane/ethanol (9/1) to give morpholide **29** as a white solid (109 mg, 65%). Mp 92–94 °C. IR (KBr) cm^{-1}: 3448 (νNH); 2926, 2855 (νCH); 1604 (νC=O); 1512, 1435 (νC=C arom.). ^{1}H NMR δ 7.56 (s, 1H, H_9), 6.99 (s, 1H, H_7), 7.16–7.12 (m, 3H, $3H_{ar}$), 7.11 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 6.87 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 4.01–3.97 (m, 2H, H_4), 3.74 (s, 3H, OCH_3), 3.65–3.61 (m, 2H, CH_2 morph.), 3.60–3.57 (m, 2H, CH_2 morph.), 3.00–2.96 (m, 2H, H_6), 2.88–2.84 (m, 4H, CH_2), 2.68–2.66 (m, 2H, CH_2), 2.50–2.46 (m, 2H, CH_2), 2.39 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.52–1.48 (m, 4H, CH_2). ^{13}C NMR δ 21.2, 21.9, 22.6, 24.4, 25.5, 28.2, 33.8, 42.8, 46.7, 47.1, 48.3, 55.2, 66.4, 108.1, 113.9, 118.1, 122.1, 124.3, 126.8, 127.7, 129.4, 130.1, 130.3, 133.6, 134.4, 136.6, 138.1, 138.2, 157.6, 173.4. MS-ES$^+$ (MeOH): *m/z* 581 ($M+H^+$, 100%).

4.6.5. 4-{1-[*N*-[4-(4-Hydroxyphenyl)but-1-yl]aminoethyl]-2-(3,5-dimethylphenyl)-5,6-dihydro-4*H*-pyrrolo-[3,2,1-*ij*]quinolin-8-oyl}morpholine 30. A solution of amide **29** (0.28 g, 0.48 mmol) in dry dichloromethane was stirred at room temperature during dropwise addition of boron tribromide (1 mL, 1 mmol) under nitrogen atmosphere. The reaction mixture was stirred for 2 h. Saturated aqueous solution of $NaHCO_3$ was added and the mixture was extracted by dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the waited phenol **30** as a white solid (122 mg, 45%). Mp 120–122 °C. IR (KBr) cm^{-1}: 3600–2400 (νOH); 3426 (νNH); 2926, 2856 (νCH); 1600 (νC=O); 1514, 1438 (νC=C arom.). ^{1}H NMR δ 7.56 (s, 1H, H_9), 6.99 (s, 1H, H_7), 7.14–7.10 (m, 3H, $3H_{ar}$), 7.11 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 6.86 (d, 2H, $J=8.5$ Hz, $2H'_{ar}$), 4.01–3.97 (m, 2H, H_4), 3.65–3.61 (m, 2H, CH_2 morph.), 3.60–3.57 (m, 2H, CH_2 morph.), 3.00–2.96 (m, 2H, H_6), 2.88–2.84 (m, 4H, CH_2), 2.62–2.58 (m, 2H, CH_2), 2.50–2.46 (m, 2H, CH_2), 2.39 (s, 6H, CH_3), 2.16–2.12 (m, 2H, H_5), 1.52–1.48 (m, 4H, CH_2). ^{13}C NMR δ 21.1, 21.7, 22.6, 24.4, 25.1, 28.6, 34.0, 42.4, 46.1, 47.3, 48.6, 66.4, 115.2, 116.2, 118.0, 122.0, 124.4, 126.1, 127.7, 129.2, 130.4, 131.9, 133.1, 134.4, 135.9, 138.0, 138.1, 155.6, 171.1. MS-ES$^+$ (MeOH): *m/z* 567 ($M+H^+$, 100%).

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Synthesis of (*Z*)-1-bromo-1-alkenes and terminal alkynes from *anti*-2,3-dibromoalkanoic acids by microwave-induced reaction

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Abstract—(*Z*)-1-Bromo-1-alkenes were stereoselectively prepared in high yields in a short reaction time by microwave irradiation of the corresponding *anti*-2,3-dibromoalkanoic acids in a Et_3N/DMF system. A one-pot synthesis of terminal alkynes and enynes from 2,3-dibromoalkanoic acids were also developed by microwave-induced reaction.

1. Introduction

(*Z*)-1-Bromo-1-alkenes are an important synthetic intermediate for stereospecific synthesis of substituted alkenes. A variety of methods have been reported for the stereocontrolled preparation of (*Z*)-1-bromo-1-alkenes, including Wittig-type condensation,[1] metal–halogen exchange of metalloalkenes,[2] hydroboration–protonolysis of haloalkynes,[3] palladium catalyzed hydrogenolysis of 1,1-dibromo-1-alkenes by tributyltin hydride,[4] transformation of ketones using an appropriate acetyl halide in a strongly acidic solvent,[5] SmI_2-mediated β-elimination of *O*-acetyl dihalo alcohols,[6] and debrominative decarboxylation of cinnamic and acrylic acids dibromides.[7] Debrominative decarboxylation of brominated α,β-unsaturated carboxylic acids might be one of the most useful methods for a synthesis of (*Z*)-1-bromo-1-alkenes since the starting α,β-unsaturated acids are readily available and the procedure is very simple, especially, the reaction is easy to be operated in a large scale. However, the yields are low in the case of aliphatic (*Z*)-1-bromoalkenes and (*Z*)-β-bromostyrene carrying *ortho*- and *para*-nitro-substituents even if an improved procedure using triethylamine and DMF solvent was used in these reactions.

Recently, the method of microwave irradiation to effect organic transformation has been used by organic chemists. Remarkable reductions in reaction times, clean conditions and better yields have been reported in microwave-induced reactions.[8] In a preliminary paper,[9] we reported a rapid and convenient method for a stereoselective synthesis of (*Z*)-1-bromoalkenes from the corresponding 2,3-dibromoalkanoic acids using a Et_3N/DMF system under microwave irradiation. In this paper, we describe the details of debrominative decarboxylation of 2,3-dibromoalkanoic acids, including its mechanism and its uses for the preparation of terminal alkynes and enynes in a one-pot reaction (Scheme 1).

2. Results and discussion

2.1. Stereoselective synthesis of (*Z*)-1-bromo-1-alkenes

Microwave irradiation of *anti*-2,3-dibromoalkanoic acids (**2**), in DMF solution containing 1.05 equiv of triethylamine for 0.2–1.0 min, gave the corresponding (*Z*)-1-bromo-1-alkenes (**3**) in excellent yields and high (*Z*)-selectivities (Scheme 1). *anti*-2,3-Dibromoalkanoic acids (**2**) were readily obtained by bromination of the corresponding *trans*-α,β-unsaturated carboxylic acids (**1**). The yields of (*Z*)-**3** and the ratios of (*Z*) and (*E*) are summarized in Table 1. These results indicate that present reaction can be used for the synthesis of both aromatic and aliphatic (*Z*)-1-bromo-1-alkenes. Unsubstituted cinnamic acid dibromides (**2a** and **2q**) and those with electron-withdrawing group (entries 3 and 4) were converted to the corresponding (*Z*)-β-bromostyrenes (**3a**, **3q**, **3g–i**, **3k–l** and **3m–p**)in excellent

Keywords: (*Z*)-1-Bromo-1-alkenes; *anti*-2,3-Dibromoalkanoic acids; Terminal alkynes; Enynes; Microwave irradiation.
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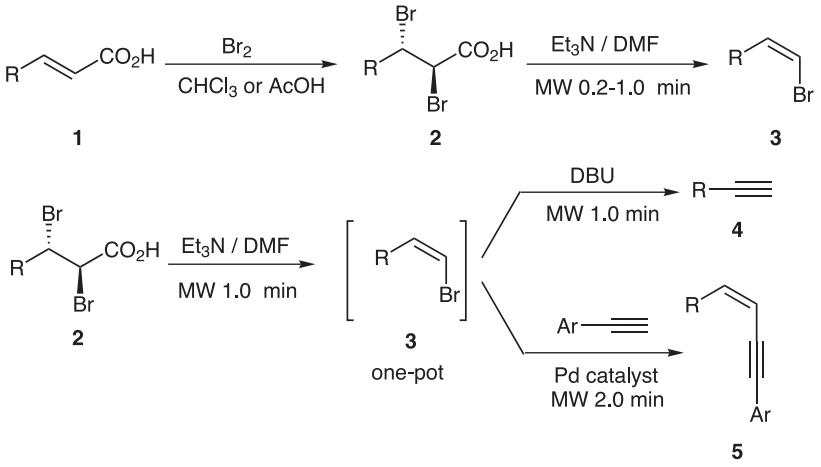
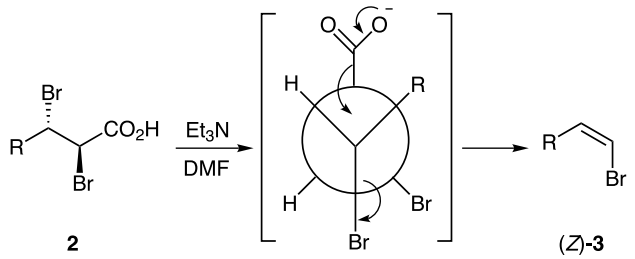


Scheme 1.

Table 1. Stereoselective synthesis of (*Z*)-1-bromo-1-alkenes

Entry	Dibromide (**2**)	Product (**3**)		MW (min)	Yield (%)[a]	*Z*/*E*[b]
1	**2a**	**3a**		0.5	95	>98/2
			EDG			
	2b	**3b**	4-CH_3	0.5	98	98/2
	2c	**3c**	4-CH_3O	0.5	95	75/25
2	**2d**	**3d**	4-*n*-$C_7H_{15}O$	0.5	96	90/10
	2e	**3e**	3,4-OCH_2O	0.5	99	95/5
	2f	**3f**	3,4,5-$(CH_3O)_3$	0.5	97	82/18
			X			
	2g	**3g**	4-Br	1.0	96	>98/2
	2h	**3h**	4-Cl	1.0	96	>98/2
	2i	**3i**	2-Cl	1.0	94	98/2
3	**2j**	**3j**	2,6-Cl_2	1.0	92	85/15
	2k	**3k**	4-F	1.0	98	>98/2
	2l	**3l**	3-F	1.0	98	>98/2
			EWG			
	2m	**3m**	4-CO_2CH_3	1.0	99	>98/2
	2n	**3n**	4-NO_2	1.0	98	>98/2
4	**2o**	**3o**	3-NO_2	1.0	99	>98/2
	2p	**3p**	2-NO_2	1.0	96	>98/2
5	**2q**	**3q**		0.5	96	>98/2
6	**2r**	**3r**		0.5	98	65/35
7	**2s**	**3s**		1.0	73	>98/2
8	**2t**	**3t**		0.2	82	>98/2
9	**2u**	**3u**		0.2	91	>98/2

[a] Isolated yields of (*Z*)- and (*E*)-1-bromo-1-alkenes.
[b] Determined by ^{1}H NMR.

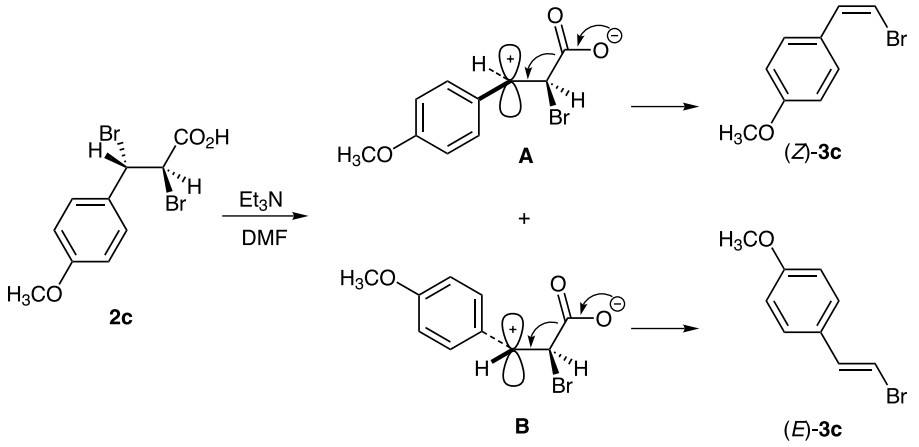


Scheme 2.

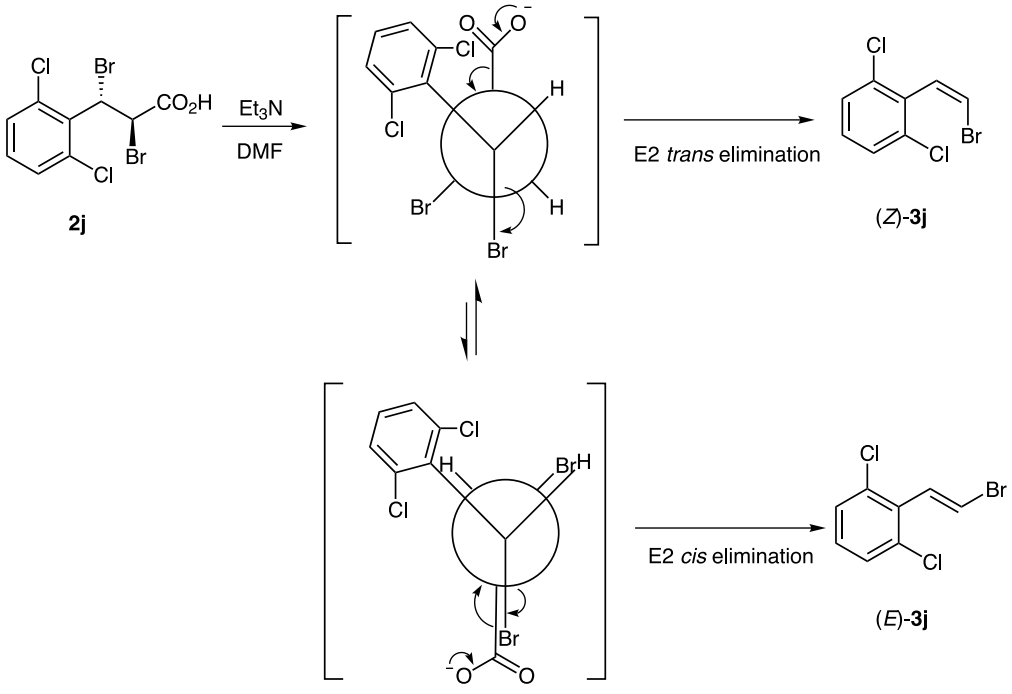
yields with high stereoselectivies. Even if weak electron-donating group such as methyl and methyenedioxy were contained in the molecules, the reaction stereoselectively proceeded in high yields (**3b** and **3e**). However, the *Z*/*E* stereoselectivity was reduced to 65–90% when the benzene ring (**3c**–**f**) was substituted with strong electron-donating group (entry 2) or there was a large steric hindrance in the *ortho* position of the benzene ring (**3j** and **3r**). The reaction of pyridyl-substituted and aliphatic *anti*-2,3-dibromoalkanoic acids gave the corresponding (*Z*)-1-bromo-1-alkenes (**3s**–**u**) with the complete *Z* selectivity and excellent yields. All of these results indicate that the yields by the present method are quite higher than those of previous procedures.

Three proposed reaction pathways for the present debrominative decarboxylations are shown in Schemes 2–4. Most of the reactions probably proceed via *trans*-elimination involving simultaneous loss of carbon dioxide and bromide ion to give (*Z*)-vinyl bromides (Scheme 2).

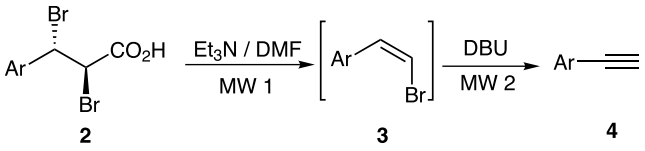
On the other hand, in the case of cinnamic acid dibromides carrying strong electron-donating group such as alkyloxyl



Scheme 3.



Scheme 4.



Scheme 5.

(**2c–f**), a unimolecular elimination process of bromide ion to give relatively stable carbocations **A** and **B** would give (*Z*)- and (*E*)-vinyl bromide, respectively, with a preferential formation of (*Z*)-isomer (Scheme 3).

When a large steric hindrance is present at the *ortho* position of the aryl ring, anion of *anti*-2,3-dibromoalkanoic acids (**2j** and **2r**) might undergo both *cis* and *trans* elimination to give *cis* and *trans* isomer, respectively (Scheme 4).

2.2. A one-pot synthesis of terminal alkynes

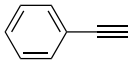
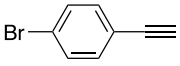
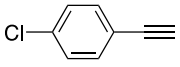
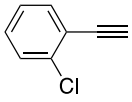
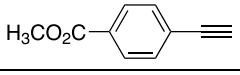
Terminal alkynes are useful and versatile intermediates in organic synthesis. In our continuous study, we have developed a new procedure for one-pot conversion of *anti*-3-aryl-2,3-dibromopropanoic acids (**2**) into terminal alkynes (**4**) in excellent yields within a few minutes under microwave irradiation (Scheme 5).

Various conditions were examined to optimize the yields of terminal alkynes. In the first step (MW1), treatment of *anti*-3-aryl-2,3-dibromopropanoic acids with triethylamine in DMF under microwave irradiation within 0.5–1.0 min resulted in (*Z*)-1-bromo-1-alkenes with high *Z*/*E* selectivity and excellent yields. No remarkable improvement of the yields and stereoselectivities of (*Z*)-1-bromo-1-alkenes was observed when the microwave irradiation was lasted for a longer time (2 min) or an excess base (3 equiv of Et_3N) was used. As to the second step (MW2), it was found that bases such as Et_3N, pyridine, DABCO, NaOH, K_2CO_3 or *t*-BuOK were not effective in this one-pot reaction. 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) was found to be the best base in this one-pot system. It would be very convenient for this one-pot reaction to use same base in two successive steps. Unfortunately, when DBU instead of Et_3N was used in the first step, a mixture of (*Z*)- and (*E*)-vinyl bromide (approximate to 92/8) was formed, and this stereoselectivity was much lower than those using Et_3N. Since DBU did only cause an elimination of (*Z*)-vinyl bromides under these conditions, a mixture of terminal alkynes and unreacted (*E*)-vinyl bromides was obtained. Under microwave irradiation the reaction of *anti*-3-aryl-2,3-dibromopropanoic acids and triethylamine in DMF followed by addition of DBU proceeded smoothly to afford the corresponding terminal alkynes in high yields. As shown in Table 2, these terminal alkynes were obtained in high yields and in short reaction time by the microwave irradiation method. The proposed reaction pathway of the present elimination was shown in Scheme 6. However, microwave irradiation of alkyl-substituted 2,3-dibromoalkanoic acids by the same way gave the corresponding aliphatic alkynes in low yields.

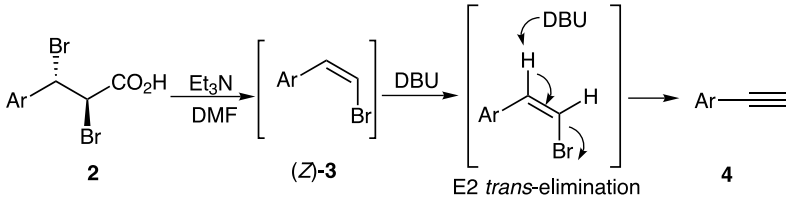
2.3. A one-pot synthesis of enynes

Furthermore, we applied this transformation to a one-pot synthesis of enynes from *anti*-2,3-dibromoalkanoic acids. Microwave irradiation of a mixture of *anti*-2,3-dibromo-3-phenylpropanoic acid (**2a**), Et_3N and DMF for 1 min and subsequent microwave irradiation of the mixture in the presence of ethynylbenzene, $Pd(PPh_3)_4$, CuI and Et_3N for

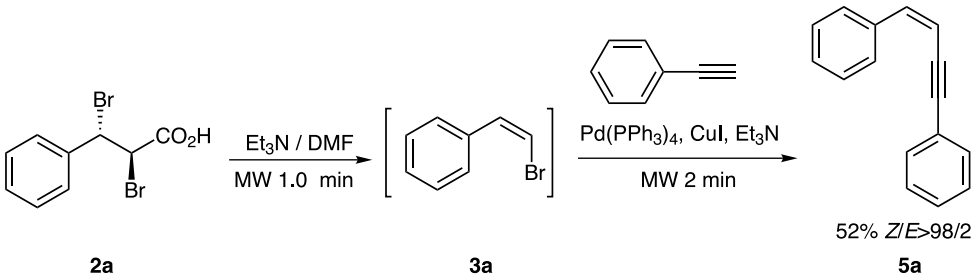
Table 2. One-pot synthesis of terminal alkynes by microwave irradiation of anti-3-aryl-2,3-dibromopropanoic acids

Entry	Dibromide (**2**)	Product (**4**)		MW1/MW2 (min)	Yield (%)[a]
1	**2a**		**4a**	0.5/1.0	88
2	**2g**		**4g**	1.0/1.0	95
3	**2h**		**4h**	1.0/1.0	93
4	**2i**		**4i**	1.0/1.0	90
5	**2m**		**4**m	1.0/1.0	99

[a] Isolated yields.



Scheme 6.



Scheme 7.

2 min gave the desired product **5a** in 52% yield (Scheme 7). The one-pot synthetic method is convenient for operation in comparison with a two-step strategy. The enynes could be obtained directly from *anti*-2,3-dibromo-3-arylpropanoic acid (**2**) without the isolation of (*Z*)-1-bromo-1-alkenes (**3**) which is an unstable intermediate. Furthermore, the two-step method does not have any advantage in yield over the one-pot method. By a two-step synthetic method, **3a** was obtained with a 95% isolated yield in the first step then subjected to the next coupling step. The enyne **5a** was obtained in 55% yield in the second step under the same condition as that of the one-pot method. Thus, the total yield of a two-step reaction was almost same as that of the one-pot reaction. Conjugated enynes are of great interest in organic synthesis.

3. Conclusions

In summary, we have developed a facile method for stereoselective synthesis of (*Z*)-1-bromo-1-alkenes from the corresponding *anti*-2,3-dibromoalkanoic acids using a Et_3N/DMF system, in which the use of microwave irradiation enables the preparation of (*Z*)-1-bromo-1-alkenes in high yields and high stereoselectivities within 0.2–1.0 min of reaction time. Additionally, we applied this transformation to a one-pot synthesis of terminal alkynes and enynes under microwave irradiation.

4. Experimental

Melting points were recorded using a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were recorded using a JASCO IR-810 infrared spectrometer (between NaCl plates). ^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-EX270 FT NMR spectrometer at 270 MHz (^{1}H) and at 67.8 MHz (^{13}C) in $CDCl_3$. Chemical shifts are reported in ppm (δ) using $SiMe_4$ as an internal standard. High- and low- resolution mass spectra were determined using a JEOL JMS-FABmate or JEOL JMS-700TZ spectrometer. Column chromatography was carried out on a Silica Gel 60 N (100–210 μm, Kanto Chemical Co. Ltd).

4.1. General procedure for the preparation of *trans*-α,β-unsaturated carboxylic acids (1)

Acids (**1a–c**, **1e–l**, **1n–s**) were commercially available. Acids (**1d**, **1m**, **1t** and **1u**) were prepared according to the procedure reported in the literature.[10–12] The physical data of **1d**, **1m**, **1t** and **1u** are shown below.

4.1.1. 4-Heptyloxy-*trans*-cinnamic acid (1d). Mp 148 °C (AcOH) (lit.[10] 148 °C); IR (nujol) 1795, 1573, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 0.89 (3H, t, J=6.6 Hz), 1.30–1.47 (8H, m), 1.78 (2H, tq, J=6.6 Hz), 3.96 (2H, t, J=6.6 Hz), 6.29 (1H, d, J=15.8 Hz), 6.88 (2H, d, J=8.6 Hz), 7.46 (2H, d, J=8.6 Hz), 7.64 (1H, d, J=15.8 Hz); ^{13}C NMR δ 13.89, 22.39, 25.75, 28.82, 28.93, 31.55, 67.92, 114.61, 115.65, 126.75, 129.52, 144.54, 160.73, 169.45.

4.1.2. 4-Methoxycarbonylcinnamic acid (1m). Mp 246–247 °C (H_2O–MeOH); IR (nujol) 1717, 1687, 1282 cm^{-1}; ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 3.92 (3H, s), 6.51 (1H, d, J=16.1 Hz), 7.60 (2H, d, J=8.2 Hz), 7.65 (1H, d, J=16.1 Hz), 8.03 (2H, d, J=8.2 Hz); ^{13}C NMR δ 51.39, 120.71, 127.04, 129.16, 130.24, 138.00, 142.01, 165.44, 167.16; EIMS *m/z* 206 (M^+, 38), 191 (20), 175 (100), 147 (32); HRMS calcd for $C_{11}H_{10}O_4$. *m/z* 206.0579. Found *m/z* 206.0579.

4.1.3. *trans*-3-Cyclohexylacrylic acid (1t). Mp 57–58 °C (hexane) (lit.[11] 58–59 °C); IR (nujol) 1774, 1695, 985 cm^{-1}; ^{1}H NMR δ 1.07–1.48 (5H, m), 1.66–1.96 (5H, m), 2.10–2.21 (1H, m), 5.77 (1H, d, J=15.8 Hz), 7.03 (1H, dd, J=15.8, J=6.6 Hz); EIMS *m/z* 154 (M^+, 26), 82 (88), 67 (100); ^{13}C NMR δ 25.60, 25.84, 31.48, 40.48, 118.27, 157.16, 172.83.

4.1.4. *trans*-Dec-2-enoic acid (1u). Bp 98 °C/0.07 mm Hg (lit.[12] 98 °C/0.07 mm Hg); IR (neat) 1774, 1695, 981 cm^{-1}; ^{1}H NMR δ 0.88 (3H, t, J=6.9 Hz), 1.28–1.64 (10H, m), 2.18–2.26 (2H, m), 5.82 (1H, d, J=15.8 Hz), 7.03–7.14 (1H, m); ^{13}C NMR δ 13.98, 22.57, 27.83, 29.00, 29.05, 31.68, 32.57, 120.61, 152.45, 172.41.

4.2. General procedure for the preparation of *anti*-2,3-dibromoalkanoic acids (2)

anti-2,3-Dibromoalkanoic acids (**2a–u**) were prepared according to the previous described procedure.[7i,7j]

4.2.1. *anti*-2,3-Dibromo-3-phenylpropanoic acid (2a). Mp 197–198 °C ($CHCl_3$) (lit.[13] 196–198 °C); ^{1}H NMR δ 4.88 (1H, d, J=11.5 Hz), 5.33 (1H, d, J=11.5 Hz), 7.38–7.43 (5H, m).

4.2.2. *anti*-2,3-Dibromo-3-(4-methylphenyl)propanoic acid (2b). Mp 191–192 °C ($CHCl_3$) (lit.[7i] 192 °C); ^{1}H NMR δ 2.35 (3H, s) 4.88 (1H, d, J=11.5 Hz), 5.32 (1H, d,

J=11.5 Hz), 7.20 (2H, d, J=8.0 Hz), 7.30 (2H, d, J=8.0 Hz).

4.2.3. *anti*-2,3-Dibromo-3-(4-methoxyphenyl)propanoic acid (2c). Mp 155–156 °C ($CHCl_3$) (lit.[7i] 155–156 °C); ^{1}H NMR δ 3.83 (3H, s), 4.86 (1H, d, J=11.9 Hz), 5.34 (1H, d, J=11.9 Hz), 6.92 (2H, d, J=8.6 Hz), 7.34 (2H, d, J=8.6 Hz).

4.2.4. *anti*-2,3-Dibromo-3-(4-heptyloxyphenyl)propanoic acid (2d). Mp 83–84 °C (hexane); IR (film) 1717, 1609, 1514 cm^{-1}; ^{1}H NMR δ 0.89 (3H, t), 1.31–1.48 (8H, m), 1.77 (2H, dd, J=6.6 Hz), 3.97 (2H, t, J=6.6 Hz), 4.88 (1H, d, J=11.5 Hz), 5.34 (1H, d, J=11.5 Hz), 6.90 (2H, d, J=8.6 Hz), 7.33 (2H, d, J=8.6 Hz); ^{13}C NMR δ 14.07, 22.59, 25.96, 29.02, 29.16, 31.75, 46.74, 50.46, 68.10, 114.79, 128.91, 129.32, 159.91, 173.35; EIMS m/z 422 (($M+2)^+$, 3), 420 (M^+, 5), 198 (50), 107 (100); HRMS calcd for $C_{16}H_{22}^{79}Br_2O_3$. m/z 419.9936. Found m/z 419.9919. Anal. Calcd for $C_{16}H_{22}Br_2O_3$: C, 45.52, H, 5.25, Br, 37.86. Found: C, 45.50, H, 5.21, Br, 37.88.

4.2.5. *anti*-2,3-Dibromo-3-(3,4-methylenedioxyphenyl)-propanoic acid (2e).[14] Mp 143–144 °C ($CHCl_3$); ^{1}H NMR δ 4.81 (1H, d, J=11.8 Hz), 5.28 (1H, d, J=11.8 Hz), 6.01 (2H, s), 6.77–6.90 (3H, m).

4.2.6. *anti*-2,3-Dibromo-3-(3,4,5-trimethoxyphenyl)propanoic acid (2f). Mp 154–155 °C (benzene–hexane) (lit.[15] 153–155 °C); ^{1}H NMR δ 3.86 (3H, s), 3.88 (3H×2, s), 4.78 (1H, d, J=11.5 Hz), 5.29 (1H, d, J=11.5 Hz), 6.63 (2H, s).

4.2.7. *anti*-2,3-Dibromo-3-(4-bromophenyl)propanoic acid (2g). Mp 191–192 °C (EtOH) (lit.[7i] 192 °C); ^{1}H NMR δ 4.84 (1H, d, J=11.5 Hz), 5.28 (1H, d, J=11.5 Hz), 7.29 (2H, d, J=8.6 Hz), 7.54 (2H, d, J=8.6 Hz).

4.2.8. *anti*-2,3-Dibromo-3-(4-chlorophenyl)propanoic acid (2h). Mp 194–195 °C (acetone–hexane) (lit.[16] 194–195 °C); IR (nujol) 1719, 721 cm^{-1}; ^{1}H NMR δ 4.82 (1H, d, J=11.5 Hz), 5.30 (1H, d, J=11.5 Hz), 7.20–7.40 (4H, m).

4.2.9. *anti*-2,3-Dibromo-3-(2-chlorophenyl)propanoic acid (2i). Mp 175–176 °C (acetone–hexane) (lit.[17] 175–176 °C); ^{1}H NMR δ 4.98 (1H, d, J=11.5 Hz), 5.92 (1H, d, J=11.5 Hz), 7.28–7.51 (4H, m); ^{13}C NMR δ 44.68, 45.01, 127.68, 130.25, 130.47, 134.05, 134.84, 173.06.

4.2.10. *anti*-2,3-Dibromo-3-(2,6-dichlorophenyl)propanoic acid (2j). Mp 193–194 °C (acetone–hexane) (lit.[17] 193–194 °C); ^{1}H NMR δ 5.69 (1H, d, J=11.8 Hz), 6.37 (1H, d, J=11.8 Hz), 7.25–7.28 (1H, m), 7.35–7.41 (2H, m); EIMS m/z 376 (($M+2)^+$, 8), 374 (M^+, 5), 297 (62), 181 (64), 171 (100); HRMS calcd for $C_9H_6^{79}Br_2^{35}Cl_2O_2$. m/z 373.8111. Found m/z 373.8124.

4.2.11. *anti*-2,3-Dibromo-3-(4-fluorophenyl)propanoic acid (2k).[7i] Mp 191–192 °C ($CHCl_3$); IR (nujol) 1718, 1600, 1591, 1509 cm^{-1}; ^{1}H NMR δ 4.83 (1H, d, J=11.5 Hz), 5.32 (1H, d, J=11.5 Hz), 7.10 (2H, m), 7.40 (2H, m); ^{13}C NMR δ 47.17, 49.68, 115.11 (d, J=22.0 Hz), 129.37 (d, J=8.6 Hz), 133.39 (d, J=3.7 Hz), 161.95 (d, J=249.1 Hz), 168.64; EIMS m/z 328 (($M+2)^+$, 8), 326 (M^+, 17), 245 (43), 121 (100); HRMS calcd for $C_9H_7^{79}Br^{81}Br FO_2$. m/z 325.8777. Found m/z 325.8768.

4.2.12. *anti*-2,3-Dibromo-3-(3-fluorophenyl)propanoic acid (2l).[7i] Mp 196–197 °C ($CHCl_3$); IR (nujol) 1716, 1591, 1146 cm^{-1}; ^{1}H NMR δ 4.92 (1H, d, J=11.5 Hz), 5.38 (1H, d, J=11.5 Hz), 7.06–7.75 (4H, m); ^{13}C NMR δ 46.86, 49.32, 113.98 (d, J=22.0 Hz), 114.92 (d, J=20.7 Hz), 123.02 (d, J=3.6 Hz), 129.32 (d, J=7.3 Hz), 139.60 (d, J=7.1 Hz), 161.25 (d, J=246.5 Hz), 168.20; EIMS m/z 326 (($M+2)^+$, 35), 324 (M^+, 20), 245 (42), 121 (100); HRMS calcd for $C_9H_7^{79}Br^{81}Br FO_2$. m/z 323.8796. Found m/z 323.8796.

4.2.13. *anti*-2,3-Dibromo-3-(4-methoxycarbonylphenyl)-propanoic acid (2m). Mp 208–209 °C (acetone–hexane); IR (film) 1718, 1508, 1436 cm^{-1}; ^{1}H NMR δ 3.92 (3H, s), 4.79 (1H, d, J=11.5 Hz), 5.37 (1H, d, J=11.5 Hz), 7.48 (2H, d, J=8.2 Hz), 8.06 (2H, d, J=8.2 Hz); ^{13}C NMR δ 46.92, 49.63, 52.20, 128.10, 130.00, 130.71, 130.71, 142.64, 166.25, 169.30; EIMS m/z 366 (($M+2)^+$, 13), 364 (M^+, 10), 285 (45), 175 (100); HRMS calcd for $C_{11}H_{10}^{79}Br_2O_4$. m/z 363.8946. Found m/z 363.8942. Anal. Calcd for $C_{11}H_{10}Br_2O_4$: C, 36.10, H, 2.75, Br, 43.66. Found: C, 36.05, H, 2.78, Br, 43.70.

4.2.14. *anti*-2,3-Dibromo-3-(4-nitrophenyl)propanoic acid (2n). Mp 216–217 °C (AcOH) (lit.,[18] 216–217 °C); IR (nujol) 1715, 1515, 1366 cm^{-1}; ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 4.85 (1H, d, J=11.8 Hz), 5.43 (1H, d, J=11.8 Hz), 7.65 (2H, d, J=8.9 Hz), 8.25 (2H, d, J=8.9 Hz).

4.2.15. *anti*-2,3-Dibromo-3-(3-nitrophenyl)propanoic acid (2o). Mp 172–173 °C (AcOH) (lit.[7i] 172 °C); IR (film) 1709, 1680, 1541, 1356 cm^{-1}; ^{1}H NMR δ 4.86 (1H, d, J=11.8 Hz), 5.39 (1H, d, J=11.8 Hz), 7.61 (1H, t, J=7.9 Hz), 7.75 (1H, d, J=8.9 Hz), 8.26 (2H, dt, J=8.9, 7.9 Hz).

4.2.16. *anti*-2,3-Dibromo-3-(2-nitrophenyl)propanoic acid (2p). Mp 179–180 °C (benzene) (lit.[7i] 180 °C); IR (nujol) 1711, 1540, 1351 cm^{-1}; ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 4.89 (1H, d, J=11.8 Hz), 6.10 (1H, d, J=11.8 Hz), 7.51–7.58 (1H, m), 7.73–7.79 (2H, m), 7.91 (1H, d, J=7.9 Hz).

4.2.17. *anti*-2,3-Dibromo-3-(2-naphthyl)propanoic acid (2q). Mp 178–180 °C (EtOH) (lit.[19] 177–180 °C); ^{1}H NMR ($CDCl_3$+d_6-DMSO) δ 4.98 (1H, d, J=11.8 Hz), 5.56 (1H, d, J=11.8 Hz), 7.50–7.56 (3H, m), 7.83–7.91 (4H, m); ^{13}C NMR δ 47.06, 51.23, 123.95, 126.02, 126.28, 126.99, 127.13, 127.43, 128.28, 132.00, 132.61, 134.46, 168.98.

4.2.18. *anti*-2,3-Dibromo-3-(1-naphthyl)propanoic acid (2r). Mp 181–182 °C (CCl_4) (lit.[20] 181–182 °C); ^{1}H NMR δ 5.14 (1H, d, J=11.5 Hz), 6.29 (1H, d, J=11.5 Hz), 7.44–7.93 (6H, m), 8.16 (1H, d, J=8.6 Hz).

4.2.19. *anti*-2,3-Dibromo-3-pyridin-3-yl-propanoic acid (2s).[7j] Mp 169–170 °C ($CHCl_3$); ^{1}H NMR (d_6-DMSO+$CDCl_3$) δ 5.35 (1H, d, J=11.5 Hz), 5.82 (1H, d, J=11.5 Hz), 7.36 (1H, m), 8.48 (1H, m), 8.76 (1H, d, J=3.9 Hz), 9.06 (1H, s); ^{13}C NMR δ 44.61, 45.83, 127.49, 130.51, 141.93, 142.15, 145.44, 168.31.

4.2.20. *anti*-2,3-Dibromo-3-cyclohexylpropanoic acid (2t).[21] Mp 158–159 °C (hexane); ^{1}H NMR δ 1.14–1.84 (10H, m), 1.94–2.03 (1H, m), 4.36 (1H, dd, J=11.8, J=2.3 Hz), 4.53 (1H, d, J=11.8 Hz); ^{13}C NMR δ 25.39, 25.51, 25.91, 25.95, 32.05, 38.95, 45.14, 59.01, 173.78.

4.2.21. *anti*-2,3-Dibromodecanoic acid (2u). Mp 44–45 °C (hexane) (lit.[7i] 45 °C); IR (nujol) 1728, 1285 cm^{-1}; ^{1}H NMR δ 0.89 (3H, t, J=3.9 Hz), 1.22–1.48 (10H, m), 1.50–1.64 (2H, m), 4.31–4.47 (2H, m).

4.3. General procedure for the preparation of (*Z*)-1-bromo-1-alkene (3)

A mixture of *anti*-2,3-dibromoalkanoic acid (1 mmol) and triethylamine (1.05 mmol) was added to 2 ml DMF. The mixture was kept inside a microwave oven operated at 2450 MHz (TOSHIBA, ER-V11, 200 W) and was irradiated for 0.2–1.0 min without any stirring. The reaction mixture was then removed from the oven and cooled to room temperature. Water and ether were added to the reaction mixture and the organic layer was separated. Aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with EtOAc–hexane to give (*Z*)-1-bromo-1-alkene (**3**). Large scale reaction using 20 mmol of *anti*-2,3-dibromoalkanoic acid was also operated in the same way.

4.3.1. (*Z*)-β-Bromostyrene (3a).[4c] Colorless oil; IR (neat) 1616, 1491, 925, 771 cm^{-1}; ^{1}H NMR δ 6.43 (1H, d, J=8.2 Hz), 7.07 (1H, d, J=8.2 Hz), 731–7.40 (3H, m), 7.66–7.69 (2H, m); ^{13}C NMR δ 106.31, 128.17, 128.26, 128.93, 132.29, 134.83; EIMS *m/z* 184((M+2)$^+$, 92), 182 (M$^+$, 97), 103 (100), 77 (42); HRMS calcd for $C_8H_7^{79}Br$. *m/z* 181.9731. Found *m/z* 181.9734.

4.3.2. (*Z*)-β-Bromo-4-methylstyrene (3b).[4c] Colorless oil; IR (neat) 1606, 1510, 947 cm^{-1}; ^{1}H NMR δ 2.36 (3H, s), 6.36 (1H, d, J=7.9 Hz), 7.02 (1H, d, J=7.9 Hz), 7.17 (2H, d, J=7.9 Hz), 7.58 (2H, d, J=7.9 Hz); ^{13}C NMR δ 21.33, 105.40, 128.89, 132.14, 138.26; EIMS *m/z* 198 ((M+2)$^+$, 8),196 (M$^+$, 8), 121 (100), 91 (44); HRMS calcd for $C_9H_9^{79}Br$. *m/z* 195.9887. Found *m/z* 195.9890.

4.3.3. (*Z*/*E*)-β-Bromo-4-methoxystyrene (3c).[22] Colorless oil; IR (neat) 1608, 1574, 1511, 927 cm^{-1}; ^{1}H NMR δ 3.80 (0.75H, s. *E*), 3.82 (2.25H, s, *Z*), 6.30 (0.75H, d, J=8.2 Hz, *Z*), 6.60 (0.25H, d, J=13.9 Hz, *E*), 6.84 (0.5H, d, J=8.9 Hz, *E*), 6.88 (0.25H, d, J=13.9 Hz, *E*), 6.90 (1.50H, d, J=8.9 Hz, *Z*), 6.99 (0.75H, d, J=8.2 Hz, *Z*), 7.22 (0.50H, d, J=8.9 Hz, *E*), 7.67 (1.50H, d, J=8.9 Hz, *Z*); ^{13}C NMR δ 55.18, 104.09, 113.54, 114.12, 127.31, 130.44, 131.59, 159.44; EIMS *m/z* 214 ((M+2)$^+$, 99), 212 (M$^+$, 100), 197 (85), 133 (68); HRMS calcd for $C_9H_9^{79}BrO$. *m/z* 211.9837. Found *m/z* 211.9835.

4.3.4. (*Z*/*E*)-β-Bromo-4-heptyloxystyrene (3d). Colorless oil; IR (neat) 1607, 1510, 924 cm^{-1}; ^{1}H NMR δ 0.89 (3H, t, J=6.9 Hz), 1.20–1.47 (8H, m), 1.78 (2H, q, J=6.9 Hz), 3.96 (2H, t, J=6.6 Hz), 6.28 (0.90H, d, J=7.9 Hz, *Z*), 6.59 (0.10H, d, J=13.9 Hz, *E*), 6.86 (0.10H, d, J=13.9 Hz, *E*),6.88 (2H, d, J=8.6 Hz), 6.98 (0.90H, d, J=7.9 Hz, *Z*), 7.65 (2H, d, J=8.6 Hz); ^{13}C NMR δ 14.05, 22.57, 25.95, 29.02, 29.16, 31.73, 67.89, 103.81, 114.03, 114.61, 127.20, 130.37, 131.59, 159.03; EIMS *m/z* 298 ((M+2)$^+$, 99), 296 (M$^+$, 100), 200 (100), 198 (98), 119 (65); HRMS calcd for $C_{15}H_{21}^{79}BrO$. *m/z* 296.0776. Found *m/z* 296.0757. Anal. Calcd for $C_{15}H_{21}BrO$: C, 60.61, H, 7.12, Br, 26.88. Found: C, 60.52, H, 7.08, Br, 26.93.

4.3.5. (*Z*)-β-Bromo-3,4-methylenedioxystyrene (3e).[14] Colorless oil; IR (neat) 1611, 1503, 1489, 965, 940 cm^{-1}; ^{1}H NMR δ 5.98 (2H, s), 6.29 (1H, d, J=7.9 Hz), 6.81 (1H, d, J=7.9 Hz), 6.95 (1H, d, J=8.2 Hz), 7.02–7.10 (1H, m), 7.38 (1H, d, J=1.3 Hz); ^{13}C NMR δ 101.16, 104.50, 108.05, 108.66, 123.78, 128.87, 131.64, 147.34, 147.45; EIMS *m/z* 228 ((M+2)$^+$, 99), 226 (M$^+$, 100), 149 (97); HRMS calcd for $C_9H_7^{79}BrO_2$. *m/z* 225.9630. Found *m/z* 225.9627.

4.3.6. (*Z*/*E*)-β-Bromo-3,4,5-trimethoxystyrene (3f).[23] Colorless oil; IR (neat) 1615, 1581, 970 cm^{-1}; ^{1}H NMR δ 3.84 (0.54H, s, *E*), 3.86 (1.08H, s, *E*), 3.87 (2.46H, s, *Z*), 3.88 (4.92H, s, *Z*), 6.37 (0.82H, d, J=8.2 Hz, *Z*), 6.51 (0.36H, s, *E*), 6.69 (0.18H, d, J=13.9 Hz, *E*), 6.97–7.05 (2.64H, m); ^{13}C NMR δ 55.99, 60.72, 103.12, 105.44, 106.20, 130.15, 131.89, 152.74; EIMS *m/z* 274 ((M+2)$^+$, 100), 272 (M$^+$, 100), 259 (96), 229 (75); HRMS calcd for $C_{11}H_{13}^{79}BrO_3$. *m/z* 272.0048. Found *m/z* 272.0044.

4.3.7. (*Z*)-β-Bromo-4-bromostyrene (3g).[7i] Colorless oil; IR (neat) 1612, 1587, 1486, 1010 cm^{-1}; ^{1}H NMR δ 6.45 (1H, d, J=8.2 Hz), 6.98 (1H, d, J=8.2 Hz), 7.48 (2H, d, J=8.6 Hz), 7.54 (2H, d, J=8.6 Hz); ^{13}C NMR δ 107.26, 122.24, 130.44, 131.21, 131.35, 133.71; EIMS *m/z* 264 ((M+4)$^+$, 8), 262 ((M+2)$^+$, 100), 260 (M$^+$, 51), 181 (31), 102 (55); HRMS calcd for $C_8H_6^{79}Br_2$. *m/z* 259.8836. Found *m/z* 259.8839.

4.3.8. (*Z*)-β-Bromo-4-chlorostyrene (3h).[16] Colorless oil; IR (neat) 1614, 1589, 1490, 1014, 946, 720 cm^{-1}; ^{1}H NMR δ 6.45 (1H, d, J=7.9 Hz), 7.12 (1H, d, J=7.9 Hz), 7.34 (2H, d, J=8.2 Hz), 7.62 (2H, d, J=8.2 Hz); ^{13}C NMR δ 107.17, 128.44, 130.22, 131.20, 133.31, 134.01; EIMS *m/z* 220 ((M+4)$^+$, 43), 218 ((M+2)$^+$, 43), 216 (M$^+$, 30), 195 (100), 139 (28), 137 (60), 102 (40), 101 (45), 75 (31); HRMS calcd for $C_8H_6^{79}Br^{35}Cl$. *m/z* 215.9341. Found *m/z* 215.9335.

4.3.9. (*Z*)-β-Bromo-2-chlorostyrene (3i). Colorless oil; IR (neat) 1619, 1593, 1468, 1435, 946 cm^{-1}; ^{1}H NMR δ 6.59 (1H, d, J=8.2 Hz), 7.23–7.31 (3H, m), 7.37–7.44 (1H, m), 7.80–7.84 (1H, m); ^{13}C NMR δ 109.34, 126.20, 129.38, 129.90, 130.22, 133.24, 133.46; EIMS *m/z* 220 ((M+4)$^+$, 11), 218 ((M+2)$^+$, 42), 216 (M$^+$, 32), 137 (100), 101 (52); HRMS calcd for $C_8H_6^{79}Br^{35}Cl$. *m/z* 215.9341. Found *m/z* 215.9322. Anal. Calcd for C_8H_6BrCl: C, 44.18, H, 2.78, Br, 36.74, Cl, 16.30. Found: C, 44.42, H, 2.90, Br, 36.11, Cl, 16.02.

4.3.10. (*Z*/*E*)-β-Bromo-2,6-dichlorostyrene (3j). Colorless oil; IR (film) 1698, 1558, 1429, 978 cm^{-1}; ^{1}H NMR δ 6.64 (0.15H, d, J=14.5 Hz, *E*), 6.74 (0.85H, d, J=7.6 Hz, *Z*), 6.97 (0.85H, d, J=7.6 Hz, *Z*), 7.05 (0.15H, d, J=14.5 Hz,

E); 7.15–7.30 (1H, m), 7.31–7.39 (2H, m); ^{13}C NMR δ 114.09, 127.85, 129.38, 129.47, 133.65, 134.28; EIMS *m/z* 254 ($(M+4)^+$, 18), 252 ($(M+2)^+$, 35), 250 (M^+, 24), 181 (100), 137 (52); HRMS calcd for $C_8H_5^{79}Br^{35}Cl_2$. *m/z* 249.8952. Found *m/z* 249.8954. Anal. Calcd for $C_8H_5BrCl_2$: C, 38.14, H, 2.00, Br, 31.72, Cl, 28.14. Found: C, 38.10, H, 2.02, Br, 31.75, Cl, 28.18.

4.3.11. (*Z*)-β-Bromo-4-fluorostyrene (3k).[24] Colorless oil; IR (neat) 1602, 1506, 1327, 1237 cm^{-1}; ^{1}H NMR δ 6.38 (1H, d, J=8.2 Hz), 6.97–7.07 (3H, m), 7.61–7.67 (2H, m); ^{13}C NMR δ 106.12, 115.16 (d, J=21.9 Hz), 130.75 (d, J=8.6 Hz), 130.93 (d, J=3.6 Hz), 131.14, 162.30 (d, J=249.1 Hz); EIMS *m/z* 202 ($(M+2)^+$, 92), 200 (M^+, 95), 121 (100), 101 (65); HRMS calcd for $C_8H_6^{79}BrF$. *m/z* 199.9637. Found *m/z* 199.9637.

4.3.12. (*Z*)-β-Bromo-3-fluorostyrene (3l).[24] Colorless oil; IR (neat) 1609, 1582, 950 cm^{-1}; ^{1}H NMR δ 6.47 (1H, d, J=8.2 Hz), 6.98–7.03 (2H, m), 7.27–7.49 (3H, m); ^{13}C NMR δ 107.70, 115.19 (d, J=20.8 Hz), 115.50 (d, J=21.9 Hz), 148.89 (d, J=3.7 Hz), 129.67 (d, J=8.5 Hz), 131.24 (d, J=2.4 Hz), 136.89 (d, J=7.3 Hz), 162.45 (d, J=245.4 Hz); EIMS *m/z* 202 ($(M+2)^+$, 77), 200 (M^+, 80), 121 (100), 101 (62); HRMS calcd for $C_8H_6^{79}BrF$. *m/z* 199.9637. Found *m/z* 199.9643.

4.3.13. (*Z*)-Methyl-4-(β-bromovinyl)benzoate (3m). Mp 43–44 °C (hexane); IR (film) 1722, 1609, 1565, 967 cm^{-1}; ^{1}H NMR δ 3.93 (3H, m), 7.56 (1H, d, J=8.2 Hz), 7.12 (1H, d, J=8.2 Hz), 7.74 (2H, d, J=8.6 Hz), 8.04 (2H, d, J=8.6 Hz); ^{13}C NMR δ 52.167, 108.73, 128.84, 129.47, 129.59, 131.61, 139.30, 166.68; EIMS *m/z* 242 ($(M+2)^+$, 47), 240 (M^+, 48), 209 (37), 211 (98), 209 (99), 183 (73), 181 (85), 102 (68); HRMS calcd for $C_{10}H_9^{79}BrO_2$. *m/z* 239.9786. Found *m/z* 239.9790. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82, H, 3.76, Br, 33.14. Found: C, 49.73, H, 3.85, Br, 33.17.

4.3.14. (*Z*)-β-Bromo-4-nitrostyrene (3n).[7i] Colorless oil; IR (film) 1594, 1509, 1341, 856 cm^{-1}; ^{1}H NMR δ 6.68 (1H, d, J=8.2 Hz), 7.15 (1H, d, J=8.2 Hz), 7.83 (2H, d, J=8.9 Hz), 8.24 (2H, d, J=8.9 Hz); ^{13}C NMR δ 110.75, 123.52, 129.66, 130.65, 141.25; EIMS *m/z* 229 ($(M+2)^+$, 100), 227 (M^+, 100), 182 (60), 181 (61), 102 (81); HRMS calcd for $C_8H_6^{79}BrNO_2$. *m/z* 226.9582. Found *m/z* 226.9584.

4.3.15. (*Z*)-β-Bromo-3-nitrostyrene (3o).[7i] Colorless oil; IR (neat) 1611, 1592, 1574, 1532, 1351, 924 cm^{-1}; ^{1}H NMR δ 6.64 (1H, d, J=8.2 Hz), 7.14 (1H, d, J=8.2 Hz), 7.56 (1H, t, J=7.9 Hz), 7.98 (1H, d, J=7.9 Hz), 8.17 (1H, m), 8.55 (1H, s); ^{13}C NMR δ 109.77, 122.87, 123.59, 129.20, 130.27, 134.71, 136.42, 148.07; EIMS *m/z* 229 ($(M+2)^+$, 100), 227 (M^+, 100), 182 (80), 181 (80), 102 (71); HRMS calcd for $C_8H_6^{79}BrNO_2$. *m/z* 226.9582. Found *m/z* 226.9594.

4.3.16. (*Z*)-β-Bromo-2-nitrostyrene (3p).[7i] Colorless oil; IR (film) 1604, 1571, 1524, 1345, 960 cm^{-1}; ^{1}H NMR δ 6.62 (1H, d, J=7.9 Hz), 7.45–7.60 (2H, m), 7.62–7.71 (2H, m), 8.09–8.12 (1H, m); ^{13}C NMR δ 110.19, 124.71, 129.00, 130.19, 130.80, 131.75, 133.15, 147.38; EIMS *m/z* 148 (M^+ − Br, 46), 102 (32), 92 (100).

4.3.17. (*Z*)-2-(β-Bromovinyl)naphthalene (3q).[4c] Colorless oil; IR (film) 1615, 1592, 929 cm^{-1}; ^{1}H NMR δ 6.52 (1H, d, J=7.9 Hz), 7.23 (1H, d, J=7.9 Hz), 7.47–7.51 (2H, m), 7.80–7.85 (4H, m), 8.15 (1H, s); ^{13}C NMR δ 106.66, 126.27, 126.41, 126.47, 127.64, 127.71, 128.28, 128.57, 132.38, 132.99, 133.04, 136.90; EIMS *m/z* 234 ($(M+2)^+$, 100), 232 (M^+, 98), 153 (88), 127 (58); HRMS calcd for $C_{12}H_9^{79}Br$. *m/z* 231.9888. Found *m/z* 231.9884.

4.3.18. (*Z*/*E*)-1-(β-Bromovinyl)naphthalene (3r).[4c] Colorless oil; IR (neat) 1605, 1590, 935 cm^{-1}; ^{1}H NMR δ 6.73 (0.65H, d, J=7.9 Hz, *Z*), 6.76 (0.35H, d, J=13.5 Hz, *E*), 7.39–7.59 (4H, m), 7.70 (0.65H, d, J=7.2 Hz, *Z*), 7.79–7.92 (3H, m), 8.01–8.04 (0.35H, m, *E*); ^{13}C NMR δ 108.46 (*E*), 109.95 (*Z*), 123.61 (*E*+*Z*), 124.11 (*Z*), 124.15 (*E*), 125.08 (*Z*), 125.46 (*E*), 125.89 (*Z*), 126.03 (*E*), 126.18 (*Z*+*E*), 126.39 (*E*), 126.72 (*Z*), 128.44 (*Z*), 128.50 (*E*), 128.69 (*E*), 130.45 (*E*), 131.01 (*Z*), 131.30 (*Z*), 132.11 (*Z*), 133.42 (*Z*), 133.50 (*E*), 134.91 (*E*); EIMS *m/z* 234 ($(M+2)^+$, 92), 232 (M^+, 93), 153 (100), 126 (75); HRMS calcd for $C_{12}H_9^{79}Br$. *m/z* 231.9894. Found *m/z* 231.9893.

4.3.19. (*Z*)-3-(β-Bromovinyl)pyridine (3s).[4c] Colorless oil; IR (neat) 1617, 1567, 954 cm^{-1}; ^{1}H NMR δ 6.57 (1H, d, J=8.2 Hz), 7.05 (1H, d, J=8.2 Hz), 7.28 (1H, dd, J=7.9, 4.3 Hz), 8.13 (1H, d, J=7.9 Hz), 8.53 (1H, d, J=4.3 Hz), 8.76 (1H, s); ^{13}C NMR δ 109.21, 123.07, 129.14, 130.96, 135.50, 149.07, 150.27; EIMS *m/z* 185 ($(M+2)^+$, 96), 183 (M^+, 94), 104 (100), 77 (41); HRMS calcd for $C_7H_6^{79}BrN$. *m/z* 182.9684. Found *m/z* 182.9682.

4.3.20. (*Z*)-1-Bromo-2-cyclohexylethene (3t).[4c] Colorless oil; IR (neat) 1412, 1261, 929, 701 cm^{-1}; ^{1}H NMR δ 1.05–1.43 (5H, m), 1.61–1.73 (5H, m), 5.92 (1H, dd, J=6.9, 8.9 Hz), 6.04 (1H, dd, J=1.0 Hz, 6.9 Hz); ^{13}C NMR δ 25.55, 25.91, 31.57, 38.82, 105.42, 140.16; EIMS *m/z* 190 ($(M+2)^+$, 7), 188 (M^+, 8), 109 (100), 67 (94); HRMS calcd for $C_8H_{13}^{79}Br$. *m/z* 188.0201. Found *m/z* 188.0190.

4.3.21. (*Z*)-1-Bromonon-1-ene (3u).[7i] Colorless oil; IR (neat) 1623, 939 cm^{-1}; ^{1}H NMR δ 0.88 (3H, t, J=6.6 Hz), 1.21–1.44 (10H, m), 2.18 (2H, q, J=6.9 Hz), 6.04–6.15 (2H, m); ^{13}C NMR δ 14.09, 22.64, 28.14, 29.09, 29.68, 31.79, 107.49, 135.04; EIMS *m/z* 206 ($(M+2)^+$, 30), 204 (M^+, 31), 119 (20), 69 (82), 43 (100); HRMS calcd for $C_9H_{17}^{79}Br$. *m/z* 204.0514. Found *m/z* 204.0522.

4.4. General procedure for the one-pot synthesis of terminal alkynes (4)

A mixture of *anti*-3-aryl-2,3-dibromopropanoic acids (**2**, 1.0 mmol) and triethylamine (1.05 mmol) was added to 2 ml DMF. The mixture was kept inside a microwave oven operated at 2450 MHz (TOSHIBA, ER-V11, 200 W) and was irradiated for 0.5–1.0 min without any stirring. The reaction mixture was then removed from the oven and cooled to room temperature. DBU (2.0 mmol) was added to the reaction mixture and the mixture was also irradiated for 1.0 min without any stirring. Water and ether were added to the reaction mixture and the organic layer was separated. Aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, and dried over anhydrous magnesium sulfate. After evaporation of the

solvent, the crude product was purified by column chromatography on silica gel with EtOAc–hexane to give terminal alkynes (**4**).

4.4.1. Ethynylbenzene (4a).[25] Colorless oil; IR (neat) 3290, 2108, 1599, 1575, 1489, 1445, 1071, 1026 cm^{-1}; ^1H NMR δ 3.05 (1H, s), 7.27–7.31 (3H, m), 7.46–7.49 (2H, m); ^{13}C NMR δ 77.18, 83.59, 122.06, 128.24, 128.71, 132.05.

4.4.2. 4-Bromo-1-ethynylbenzene (4g).[26] Mp 63.5–64.5 °C (hexane); IR (nujol) 3312, 2110, 1485, 1071, 825 cm^{-1}; ^1H NMR δ 3.12 (1H, s), 7.35 (2H, d, $J=8.5$ Hz), 7.46 (2H, d, $J=8.5$ Hz); ^{13}C NMR δ 78.33, 82.55, 121.04, 123.12, 131.59, 133.54; EIMS *m/z* 182 ($(M+2)^+$, 90), 180 (M^+, 100), 101 (92), 75 (52); HRMS calcd for $C_8H_5^{79}Br$. *m/z* 179.9575. Found *m/z* 179.9575.

4.4.3. 4-Chloro-1-ethynylbenzene (4h).[27] Mp 45–46 °C (hexane); IR (nujol) 3272, 2110 cm^{-1}; ^1H NMR δ 3.10 (1H, s), 7.29 (2H, d, $J=8.5$ Hz), 7.41 (2H, d, $J=8.5$ Hz); ^{13}C NMR δ 78.15, 82.49, 120.57, 128.65, 133.33, 134.90; EIMS *m/z* 138 ($(M+2)^+$, 38), 136 (M^+, 100), 101 (40), 75 (37); HRMS calcd for C_8H_5Cl. *m/z* 136.0080. Found *m/z* 136.0077.

4.4.4. 2-Chloro-1-ethynylbenzene (4i).[28] Colorless oil; IR (neat) 3312, 2114, 1485, 1071, 825 cm^{-1}; ^1H NMR δ 3.12 (1H, s), 7.35 (2H, d, $J=8.5$ Hz), 7.46 (2H, d, $J=8.5$ Hz); ^{13}C NMR δ 78.33, 82.55, 121.04, 123.12, 131.59, 133.54; EIMS *m/z* 138 ($(M+2)^+$, 35), 136 (M^+, 100), 101 (38), 75 (34); HRMS calcd for C_8H_5Cl. *m/z* 136.0080. Found *m/z* 136.0078.

4.4.5. Methyl 4-ethynylbenzoate (4m).[29] Mp 94–95 °C (hexane–EtOAc); IR (nujol) 2106, 1733, 1275 cm^{-1}; ^1H NMR δ 3.23 (1H, s), 3.92 (3H, s), 7.55 (2H, d, $J=8.5$ Hz), 7.98 (2H, d, $J=8.5$ Hz); ^{13}C NMR δ 52.25, 80.00, 82.77, 126.73, 129.43, 130.11, 132.05, 166.39; EIMS *m/z* 160 (M^+, 53), 129 (100), 101 (52); HRMS calcd for $C_{10}H_8O_2$. *m/z* 160.0524. Found *m/z* 160.0508.

4.5. General procedure for the one-pot synthesis of enyne (5a)

A mixture of *anti*-2,3-dibromo-3-phenylpropanoic acid (**2a**, 1.0 mmol) and triethylamine (1.05 mmol) was added to 2 ml DMF. The mixture was kept inside a microwave oven operated at 2450 MHz (TOSHIBA, ER-V11, 200 W) and was irradiated for 1.0 min without any stirring. The reaction mixture was then removed from the oven and cooled to room temperature. A mixture of ethynylbenzene (1.2 mmol), $Pd(PPh_3)_4$ (0.05 mmol), CuI (1.2 mmol) and Et_3N (2.0 mmol) was added to the reaction mixture and the mixture was kept inside a microwave oven and was irradiated for 2.0 min. Water and ether were added to the reaction mixture and the organic layer was separated. Aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with EtOAc–hexane to give (*Z*)-1,4-diphenyl-1-buten-3-yne (**5a**).

4.5.1. (*Z*)-1,4-diphenyl-1-buten-3-yne (5a).[30] Colorless oil; IR (neat) 3061, 3022, 2185, 1595, 1449 cm^{-1}; ^1H NMR δ 5.91 (1H, d, $J=12.0$ Hz), 6.69 (1H, d, $J=12.0$ Hz), 7.28–7.43 (10H, m); ^{13}C NMR δ 138.65, 136.53, 131.48, 128.75, 128.48, 128.38, 128.32, 128.28, 123.43, 107.36, 95.83, 88.23; EIMS *m/z* 204 (M^+, 31), 119 (20), 69 (82), 43 (100); HRMS calcd for $C_{16}H_{12}$. *m/z* 204.0939. Found *m/z* 204.0938.

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A formal total synthesis of Lycopodium alkaloid, (±)-magellanine, by using the intramolecular Pauson Khand reaction

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Abstract—A formal total synthesis of magellanine was accomplished by using the stereoselective Ireland–Claisen rearrangement and the intramolecular Pauson–Khand reaction of exocyclic enynes as key steps.

1. Introduction

The magellanine family, as represented by magellanine (**1**), magellaninone (**2**), and paniculatine (**3**) is one group of the alkaloids isolated from the Lycopodium species (Fig. 1).[1] Because of their intriguing tetracyclic structure bearing 5–7 stereogenic centers, several synthetic efforts to date have resulted in the total synthesis of magellanine (**1**),[2a–d] magellaninone (**2**),[2a–d] and paniculatine (**3**).[2e,3] Thus, Overman and co-workers[2a] reported the total synthesis of (−)-**1** and (+)-**2** by using pinacol-terminated cationic cyclization as the key step. Paquette et al.[2b,c] synthesized racemic **1** and **2** by the Michael–Michael ring annulation of α,β-unsaturated ketone followed by the construction of a piperidine ring. Using a magnificent masked Diels–Alder protocol, Yen and Liao[2d] recently successfully achieved the total synthesis of racemic **1**. The tandem radical cyclization approach to (+)-**3** was reported by Sha et al.[2e]

Recent work in our laboratory[4] concerning the intramolecular Pauson–Khand reaction of exocyclic enynes has revealed methods for the facile construction of bi- and tricyclic skeletons, which can be considered promising for the stereoselective construction of ABC rings in magellanine (**1**).[5] In this paper, we describe the formal total synthesis of magellanine (**1**) based on the intramolecular Pauson–Khand reaction of exocyclic enynes and stereoselective Ireland–Claisen rearrangement as key steps.[6]

Keywords: Magellanine; Total synthesis; Intramolecular Pauson–Khand reaction; Exocyclic enynes.
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2. Results and discussion

The synthetic plan for magellanine (**1**) is shown in Scheme 1. Tricycle (**A**) was thought to be a suitable intermediate for the attachment of the D ring. The angular tricyclic enone (**A**) could be obtained by the intramolecular Pauson–Khand reaction of the exocyclic enyne (**B**). The enyne (**B**) could be obtained from carboxylic acid (**C**) by the stereoselective Ireland–Claisen rearrangement of **D**. Furthermore, the allyl acetate (**D**) could be synthesized from the known keto alcohol (**E**).[7]

The first object in the synthesis was access to the Pauson–Khand reaction precursors. As shown in Scheme 2, synthesis was begun from the known alcohol (**4**)[7] by acetylation and subsequent stereoselective Luche reduction to give an allyl alcohol (**6**). The stereochemistry of **6** was determined by an NOE experiment between the C1 and C5 hydrogens. Silylation of **6** afforded a TIPS ether (**7**) in 74% yield. The Ireland–Claisen rearrangement of **7** followed by reduction with $LiAlH_4$ furnished an alcohol (**8**) in 70% yield as a single isomer, as expected.[5] Dess–Martin oxidation of **8** produced an aldehyde (**9**) in quantitative yield. To introduce an alkynyl moiety, **9** was reacted with ethynylmagnesium bromide to provide a propargyl alcohol (**10**) as an inseparable 1:1 mixture of diastereomers. After protection of **10** with the MOM group, the reaction of **11** with Me_2AlCl and β-propiolactone[8] was carried out. However, even after several conditions were investigated, the expected carboxylic acid (**12**) could not be obtained in good yield.

Next, we turned our attention to introducing the

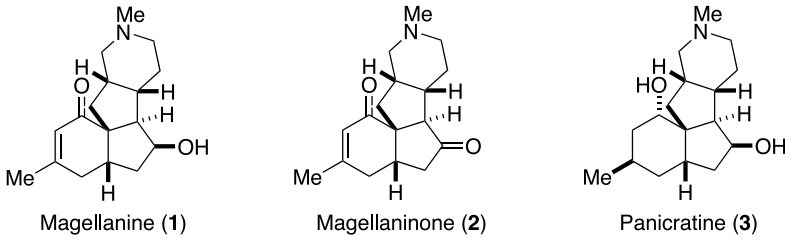
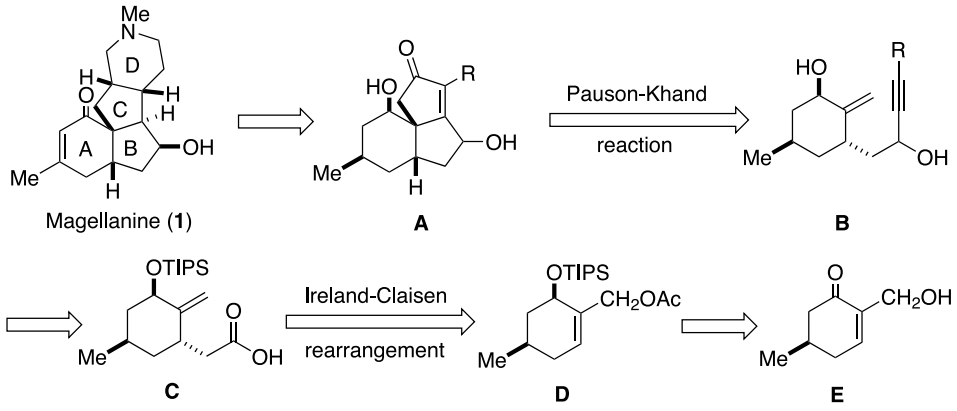
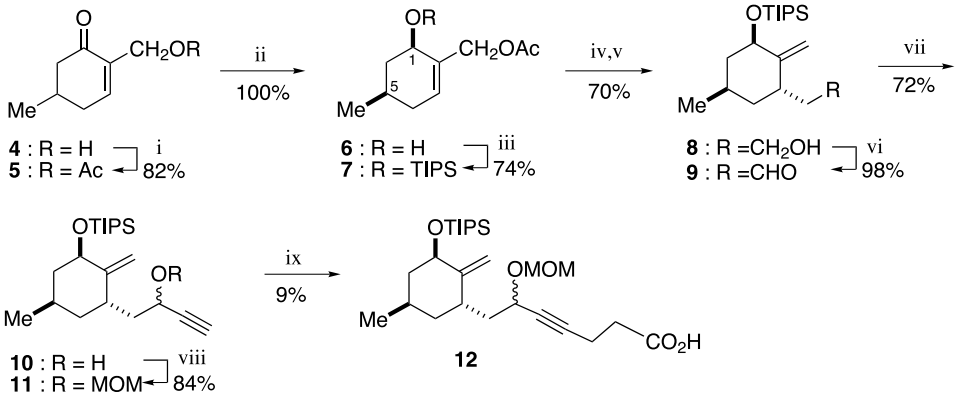


Figure 1.



Scheme 1.



Scheme 2. Reagents and conditions: (i) Ac_2O, Et_3N, CH_2Cl_2, rt, 24 h; (ii) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 1.5 h; (iii) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; (iv) LDA, HMPA, TBSCl, THF, −78 °C→rt, 1d then rt, 2 days; (v) $LiAlH_4$, THF, reflux, 0.5 h; (vi) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h; (vii) HC≡CMgBr, THF, 0 °C, 1 h; (viii) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt, 22 h; (ix) BuLi then Me_2AlCl, β-lactone, −30 °C, 3 days then rt, 3 days.

aminoalkynyl moiety, directly. Thus, the reaction of **9** with *N*-Boc-protected lithium butynylamide successfully gave an inseparable 1:1 diastereomeric mixture of alkynyl alcohols (**13**), which could be separated after desilylation with TBAF into alcohols (**15a**,**b**). In a similar manner, *N*-Cbz-protected derivatives (**16a**,**b**) were obtained via **14**. The stereochemistry of the Pauson–Khand reaction precursors (**15a**,**b** and **16a**,**b**) were determined by an after cyclization reaction to the tricyclic compounds (**17** and **18**).

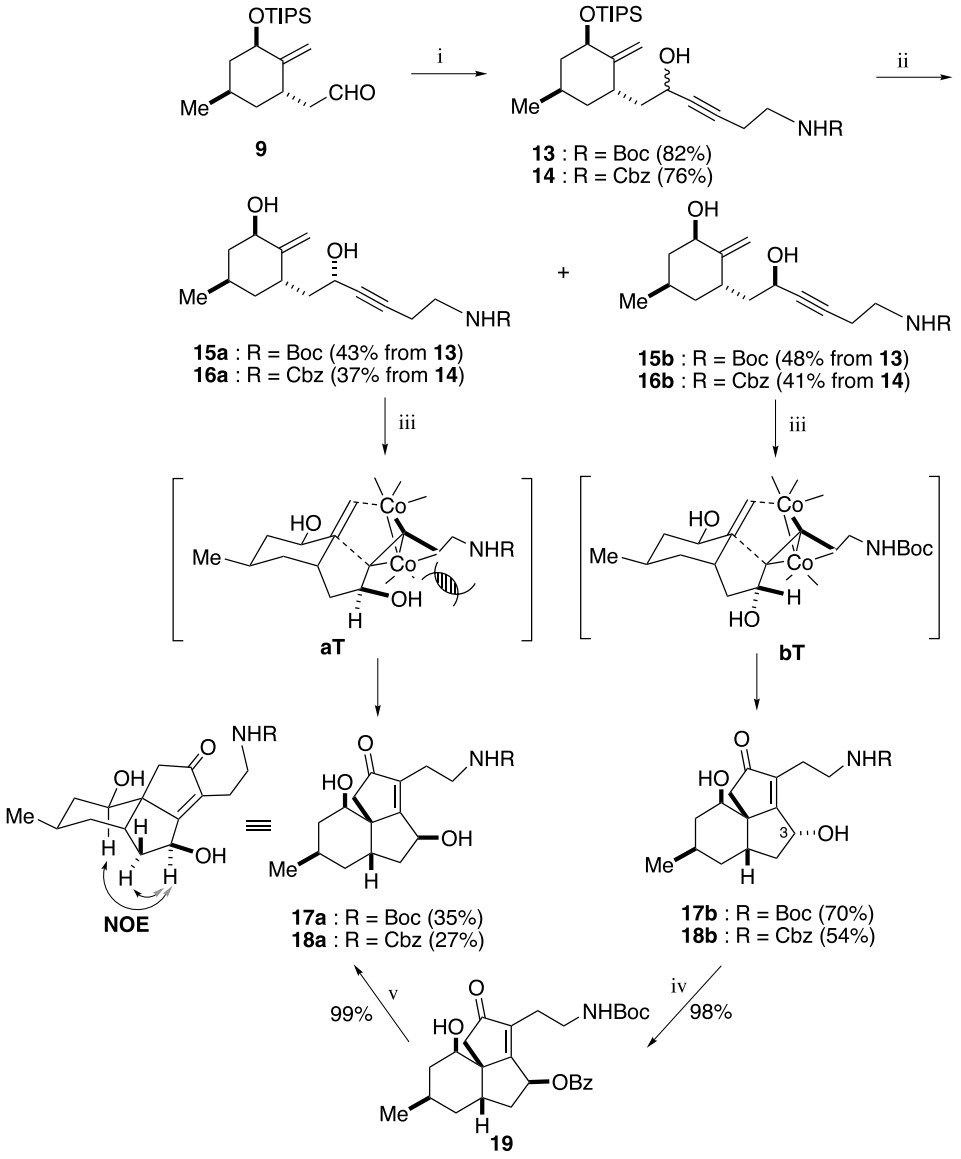
With enynes (**15a**,**b** and **16a**,**b**) in hand, the Pauson–Khand reaction was investigated under thermal or oxidative conditions (Table 1). Unfortunately, the reaction of the alkyne–cobalt complex of **15a** in boiling toluene resulted in the formation of an intractable mixture and did not give the desired compound (**17a**) (entry 1). However, the reaction with *N*-methylmorpholine *N*-oxide (NMO)[9a] produced **17a** in 18% yield along with the starting enyne (**15a**) (55%) (entry 2). Interestingly, employment of trimethylamine *N*-oxide (TMANO)[9b] instead of NMO markedly improved the yield of cyclization to furnish **17a** in 35% yield (entry 3). A similar reaction of **15b** using TMANO afforded **17b** and **15b** in 70% and 18% yields, respectively (entry 6). A similar tendency was observed in the reaction of *N*-Cbz-enynes (**16a**,**b**) with the amine *N*-oxide to give tricycles (**18a**,**b**). Although the reason for the influence on the yields of the cyclization by each amine *N*-oxide was not clear,[10] the difference in the cyclization yields by the stereoisomers (**15a**,**16a** and **15b**,**16b**) could be explained as follows. Inspection with the Dreiding model suggested that the

Table 1. Pauson–Khand reaction of exocyclic enynes (**15a**, **15b**, **16a**, **16b**)

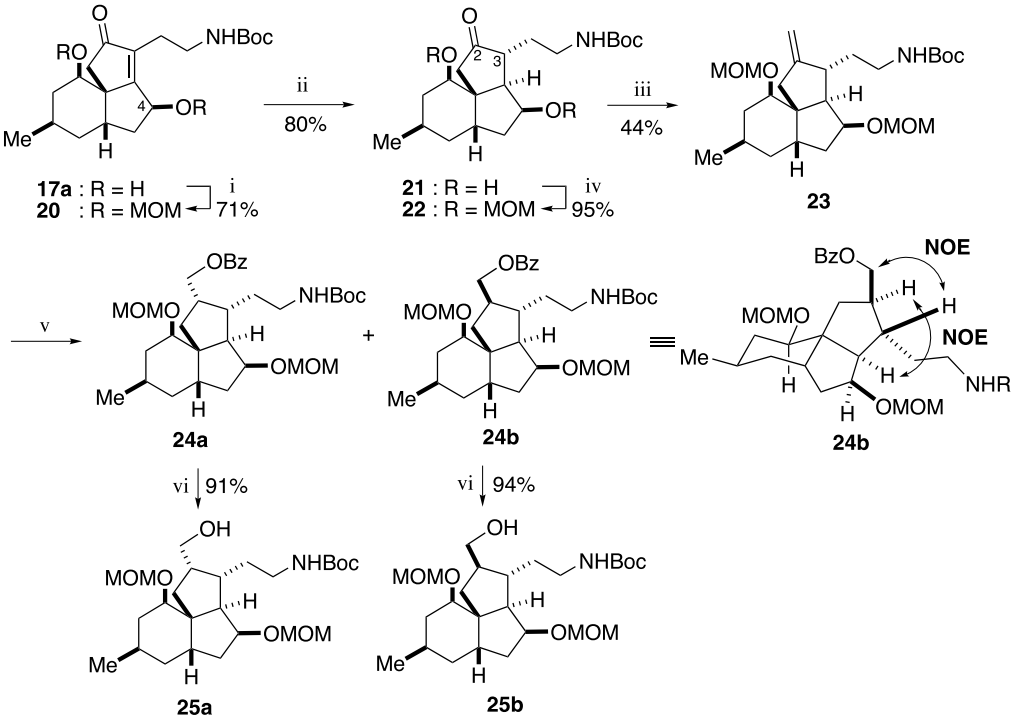
Entry	Substrate	Solvent	Additive[a]	Temperature	Time (h)	Product	Yield (%)[b]
1	**15a**	Toluene	None	Reflux	1	**17a**	0
2	**15a**	CH_2Cl_2	NMO	rt	1	**17a**	18 (55)
3	**15a**	THF	TMANO	rt	1	**17a**	35 (37)
4	**15b**	Toluene	None	Reflux	1	**17b**	0
5	**15b**	CH_2Cl_2	NMO	rt	1	**17b**	50 (28)
6	**15b**	THF	TMANO	rt	2	**17b**	70 (18)
7	**16a**	Toluene	None	Reflux	1	**18a**	0
8	**16a**	CH_2Cl_2	NMO	rt	1	**18a**	9 (62)
9	**16a**	THF	TMANO	rt	3	**18a**	30 (45)
10	**16b**	Toluene	None	Reflux	1	**18b**	0
11	**16b**	CH_2Cl_2	NMO	rt	1	**18b**	27 (33)
12	**16b**	THF	TMANO	rt	3	**18b**	65 (26)

[a] Nine to twelve equivalents of *N*-oxide were used.
[b] Isolated yield. Value in parenthesis is recovery of starting enyne.

interaction between a hydroxyl group and a side chain in the transition state (**aT**) would be more severe than that in **bT**, as depicted in Scheme 3. Therefore, the yields of **17a** and **18a** were low compared to those of **17b** and **18b**, respectively. The stereochemistry of **17a** and **18a** was confirmed by NOE experiments and was found to be the same as that of **1**. Although a considerable amount of starting enynes was recovered by decomplexation during



Scheme 3. Reagents and conditions: (i) BuLi, $HC{\equiv}CCH_2CH_2NHR$, THF, HMPA, 0 °C, 1 h; (ii) TBAF, THF, reflux, 2 h; (iii) Pauson–Khand reaction (Table 1); (iv) $PhCO_2H$, PPh_3, DEAD, THF, rt, 4 h; (v) 1 M NaOH, THF–MeOH, rt, 1 h.



Scheme 4. Reagents and conditions: (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 3 days; (ii) H_2, 10% Pd/C, MeOH–H_2O, rt, 38.5 h; (iii) Tebbe reagent, THF, 0 °C, 1 h; (iv) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 18 h; (v) Hydroboration then PhCOCl, Et_3N, DMAP, CH_2Cl_2, rt, 18 h (Table 2); (vi) 1 M NaOH, MeOH, rt, 4 h.

the reaction, the enynes could be reused for the Pauson–Khand reaction to give **17a**,**b** and **18a**,**b**. Consequently, from the standpoint of yield, we chose Boc-protected substrates (**17a**,**b**) for further synthesis. Moreover, **17b**, which had an undesired stereochemistry at C3, could be converted into **17a** via benzoate (**19**) in 98% overall yield by the Mitsunobu reaction and subsequent hydrolysis.

Next, attention was focused on the functionalization of the C ring in the angular tricyclic compound (**17a**) for the construction of the tetracyclic skeleton (Scheme 4). Catalytic hydrogenation of enone (**17a**) in MeOH gave **21** in 70% yield, which may have formed by isomerization at the C3 position in the reaction due to steric repulsion between the side chain and hydroxyl group. Moreover, reduction of **17a** in MeOH containing 5% water cleanly afforded **21** in 80% yield. This may be due to the small amount of water deactivating Pd/C, because appreciable amounts of unidentified products were formed without water. Interestingly, when catalytic hydrogenation of the benzoate (**19**) and MOM ether (**20**), which were derived from **17a**, was carried out, none of the desired product was formed and most of the starting material was recovered. These results suggested that the steric environment around the C3–C3a double bond was markedly affected by the C4 substituent. Then, the two hydroxyl groups in **21** were protected as MOM ethers (**22**), because the reaction of **21** with benzoyl chloride, PMBCl, or BOMCl under standard conditions was very sluggish and a mixture of mono- and di-protected compounds were formed along with the unchanged starting material.

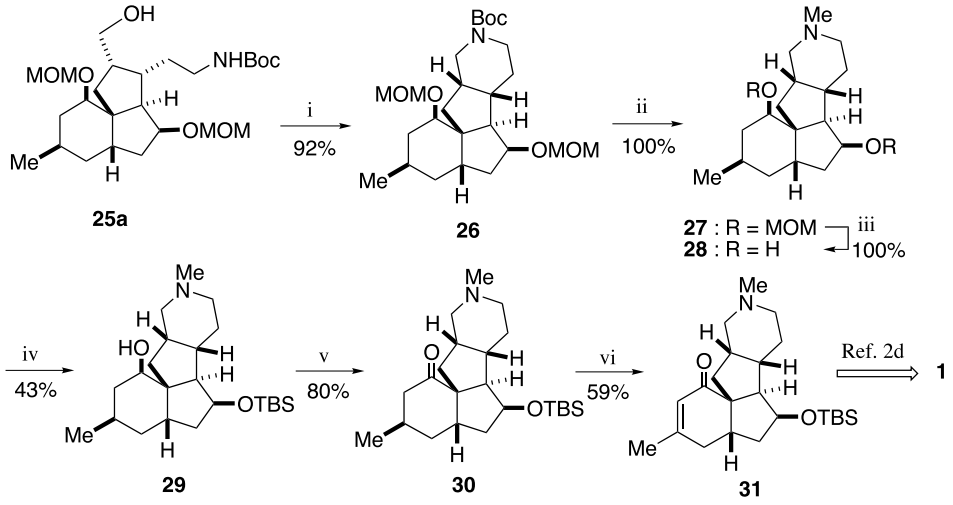
Next, homologation at the C2 moiety was examined. However, the Wittig reaction of **22** with $MeBr\cdot PPh_3$, $MeOCH_2Cl\cdot PPh_3$[11] or Ph_2POCH_2OMe[12] in the presence of a base failed and **22** was recovered quantitatively. Also, the Takai method ($Zn/TiCl_4/CH_2Br_2$)[13] was not effective. The reaction using other nucleophilic reagents such as $CH_2{=}CHMgBr$, $HC{\equiv}CMgBr$, TMSCN/ZnI_2, and MeSOI/NaH[14] resulted in the formation of intractable mixtures. After further investigation, the reaction with the Tebbe reagent[15] was found to give an *exo*-alkene (**23**) in 44% yield together with unchanged **22** (38%).

Then, hydroboration–oxidation of **23** was performed. When the reaction was carried out, inseparable alcohols (**25a**,**b**)

Table 2. Hydroboration of olefin (**23**)

Entry	Borane (equiv)	Time (h)	**24a** (%)[a]	**24b** (%)[a]
1	$BH_3\cdot Me_2S$ (3)	2	16	55
2	$BH_3\cdot THF$ (3)	1	14	55
3	9-BBN (8)	19	10	29
4	Thexylborane (4)	3	15	48
5	Dicyclohexylborane (12)	72	0[b]	0[b]
6	Disiamylborane (12)	24	0[b]	0[b]
7	Catecholborane (16)	24	0[b]	0[b]

[a] Isolated yield.
[b] No reaction.

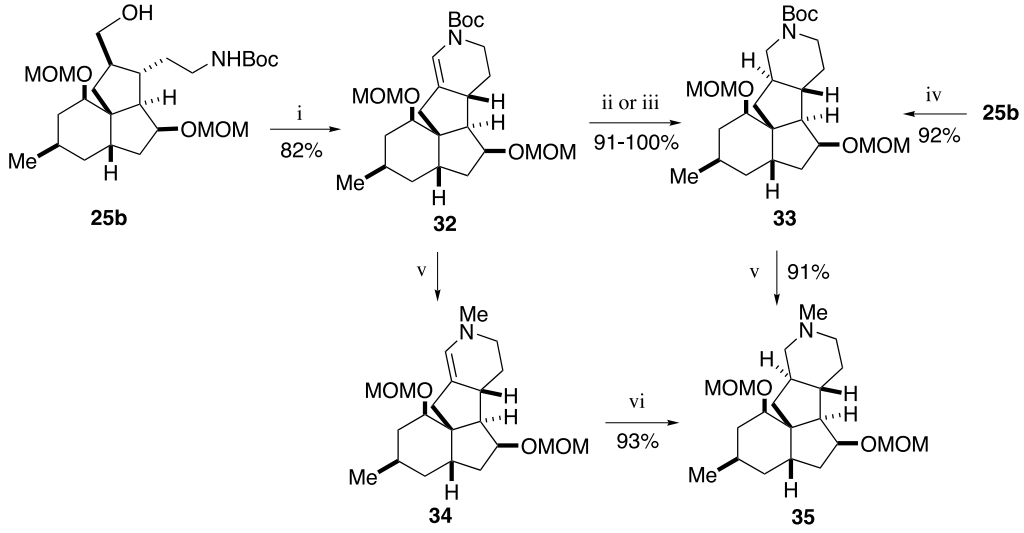


Scheme 5. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h; *t*-BuOK, THF, 0 °C, 0.5 h; (ii) $LiAlH_4$, THF, reflux, 4 h; (iii) 6 M HCl, THF, rt, 24 h; (iv) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h; (v) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 0.5 h then rt, 0.5 h; (vi) LDA, THF, −78 °C then Ph(Cl)S=NO*t*-Bu, 0 °C, 1 h.

were formed. After benzoylation of the crude products, each isomer (**24a**,**b**) was separated. Unfortunately, when BH_3·THF was employed, the major product (**24b**) had the undesired stereochemistry (Table 2, entry 1). The stereochemistry of the benzoates (**24a**,**b**) was determined by NOE experiments. To improve the stereoselectivity, reactions with other borane reagents were examined. However, an undesired alcohol (**25b**) was formed as the major product.

The final stage to magellanine is shown in Scheme 5. Mesylation of the alcohol (**25a**) followed by treatment with *t*-BuOK readily constructed a piperidine ring to afford a tetracyclic compound (**26**) in 92% yield. Reduction of **26** with $LiAlH_4$ and subsequent deprotection of MOM ethers with 6 M HCl furnished a diol (**28**) in quantitative yield. Selective silylation of **28** produced mono-TBS ether (**29**), the Dess–Martin oxidation of which gave a silyl ketone (**30**). Although conversion of the ketone (**30**) to an enone (**31**) by $(PhSeO)_2O$[16a] or IBX[16b] failed, the Mukaiyama method[17] succeeded in the conversion to the enone (**31**), the ^1H and ^{13}C NMR spectra of which were identical with those reported in the literature.[2d] Thus, a formal total synthesis of (±)-magellanine (**1**) was accomplished.

Finally, we briefly carried out alternative attempts for the synthesis of magellanine from the epimeric alcohol (**25b**) as shown in (Scheme 6). The Dess–Martin oxidation of **25b** smoothly afforded an enamide (**32**) in 74% yield. Unfortunately, catalytic hydrogenation of **32** produced stereoselectively a C11a epi-compound (**33**), of which the ^1H NMR spectrum was identical with that obtained from **25b** by mesylation followed by base treatment. We also carried out reduction[18] of an enamine derivative (**34**), which was obtained by $LiAlH_4$ reduction of **32**. However, only **35** was obtained and the desired product (**27**) was not produced. For the stereochemistry of **35**, it was confirmed that the ^1H NMR spectrum of **35** was identical with that obtained by $LiAlH_4$ reduction of **33**. The unexpected high stereoselectivity in the reduction prevented the use of the epimeric alcohol (**25b**).



Scheme 6. Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h; (ii) PtO_2, H_2, MeOH, rt, 29 h; (iii) Pd/C, H_2, MeOH, rt, 9 h; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h; *t*-BuOK, THF, 0 °C, 1 h; (v) $LiAlH_4$, THF, 2–5 h; (vi) Pd/C, H_2, MeOH, rt, 3 h.

3. Conclusion

In summary, we have accomplished the formal total synthesis of (±)-magellanine (**1**) by using the stereoselective Ireland–Claisen rearrangement and the intramolecular Pauson–Khand reaction of exocyclic enynes as key steps. Although some conversions in the synthesis lacked stereoselectivity, we believe the facile construction of tricycles by the intramolecular Pauson–Khand reaction of exocyclic enynes is applicable for the total synthesis of other polycyclic natural products.

4. Experimental

4.1. General

All melting and boiling points were measured on a Büchi or a Yanagimoto (hot plate) melting point apparatus and by a bulb-to-bulb distillation apparatus, respectively, and are uncorrected. ^{1}H NMR spectra were taken with a JEOL JNM AL-300 (300 MHz) or JEOL A-500 spectrometer using $CDCl_3$ solutions with tetramethylsilane as the internal standard. Mass spectra were measured on a Hitachi M-80 or a JEOL JMS D-300 spectrometer. Column chromatography was performed with silica gel (Merck Kieselgel 60). Preparative TLCs were run on Merck 5744, or Merck 5715 plates. Organic extracts were dried over $MgSO_4$. TBAF was purchased from Aldrich Chemical Co. as a 1 M THF solution. $BH_3\cdot$THF was purchased from Aldrich Chemical Co. as a 1 M THF solution. *n*-BuLi was purchased from Kanto Chemical Co. as a 1.56 M hexane solution.

4.1.1. 2-Acetoxymethyl-5-methyl-2-cyclohexenone (5). A mixture of **4** (32.6 g, 232 mmol), Et_3N (48.1 mL, 345 mmol), and Ac_2O (32.6 mL, 345 mmol) in CH_2Cl_2 (500 mL) was stirred at rt for 24 h. Then, the mixture was washed with brine and dried. The solvent was evaporated under reduced pressure to give a residue, which was distilled under reduced pressure (119.5–122 °C/4 mmHg) to afford **5** (34.4 g, 81.5%) as a colorless oil; ^{1}H NMR δ 6.95–6.98 (1H, m), 4.74 (2H, s), 2.04–2.56 (5H, m), 2.07 (3H, s), 1.11 (3H, t, J=6.3 Hz); ^{13}C NMR δ 198.2, 170.7, 148.0, 134.1, 61.2, 46.2, 34.1, 30.3, 21.1, 20.9; IR (neat) 1742, 1672, 1457 cm^{-1}; EI MS *m*/*z* 182 (M^+); high-resolution mass *m*/*z* calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943. Found: 182.0947.

4.1.2. (1*R,5*R**)-2-Acetoxymethyl-5-methyl-2-cyclohexenol (6).** To a stirred solution of **5** (17.1 g, 93.7 mmol) and $CeCl_3\cdot 7H_2O$ (34.9 g, 93.7 mmol) in MeOH (460 mL) at 0 °C was added $NaBH_4$ (3.19 g, 84.3 mmol) in small portions. After stirring for 1.5 h, the reaction was quenched with 3 M HCl. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried and evaporated in vacuo to give **6** (17.2 g, 100%) as a colorless oil; ^{1}H NMR δ 5.82 (1H, d, J=5.3 Hz), 4.96 (1H, dd, J=1, 12.1 Hz), 4.39 (1H, d, J=12.1 Hz), 4.25–4.30 (1H, m), 2.37 (1H, br s), 2.05–2.14 (2H, m), 2.09 (3H, s), 1.64–1.85 (2H, m), 1.18–1.31 (1H, m), 0.99 (3H, d, J=6.3 Hz); ^{13}C NMR δ 135.8, 130.1, 67.3, 65.7, 40.7, 30.1, 28.1, 21.8, 21.1; IR (neat) 3424, 1737, 1456 cm^{-1}; EI MS *m*/*z* 184 (M^+); high-resolution mass *m*/*z* calcd for $C_{10}H_{16}O_3$ (M^+) 184.1099. Found: 184.1083.

4.1.3. (4*R,6*R**)-1-Acetoxymethyl-6-triisopropylsilyloxy-4-methylcyclohexene (7).** To a stirred solution of **6** (17.2 g, 93.7 mmol) and 2,6-lutidine (28.2 g, 263 mmol) in CH_2Cl_2 (350 mL) at 0 °C was added TIPSOTf (40.3 g, 132 mmol) over a period of 10 min. After stirring for 1 h, the reaction was quenched with water. The mixture was extracted with CH_2Cl_2. The organic extracts were washed with 1 M HCl and brine, then dried and evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:50) to afford **7** (30.2 g, 74.2%) as a colorless oil; ^{1}H NMR δ 5.75–5.76 (1H, m), 4.77 (1H, d, J=12.2 Hz), 4.49–4.53 (2H, m), 2.05 (3H, s), 2.05–2.09 (2H, m), 1.60–1.80 (2H, m), 1.26–1.39 (1H, m), 1.08 (21H, s), 0.98 (3H, d, J=6.3 Hz); ^{13}C NMR δ 170.8, 136.3, 128.0, 69.0, 65.5, 42.0, 33.9, 28.1, 22.0, 21.1, 18.3, 12.9; IR (neat) 1744, 1462 cm^{-1}; EI MS *m*/*z* 339 (M^+-1); high-resolution mass *m*/*z* calcd for $C_{19}H_{35}O_3Si$ (M^+-1) 339.2355. Found: 339.2364.

4.1.4. (1*S,3*R**,5*R**)-1-(2′-Hydroxyethyl)-3-triisopropylsilyloxy-5-methyl-2-methylenecyclohexane (8).** To a stirred solution of diisopropylamine (17.2 mL, 123 mmol) in THF (400 mL) at 0 °C was added *n*-BuLi (75 mL, 117 mmol) dropwise and the mixture was stirred for 10 min. Then, the mixture was cooled to −78 °C and HMPA (21.2 mL, 122 mmol) was added. After stirring for 10 min, a solution of **7** (28.0 g, 82.2 mmol) and TBSCl (18.3 g, 122 mmol) in THF (120 mL) was added over a period of 1 h. The mixture was warmed up to rt over a period of 1 day and stirring was continued for an additional 2 days. The reaction was quenched with 3 M HCl and extracted with Et_2O. The organic extracts were washed with brine, then dried and evaporated under reduced pressure to furnish a crude silyl ester (28.2 g), which was dissolved in THF (400 mL). $LiAlH_4$ (3.80 g, 100 mmol) was added to the solution and the mixture was refluxed for 30 min. The reaction was quenched with a saturated Na_2SO_4 solution. The precipitate was filtered with suction and the filtrate was evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:6 then 1:3) to afford **8** (18.8 g, 70.1%) as a pale yellow oil; ^{1}H NMR δ 5.15, 4.83 (each 1H, each t, J=2.3 Hz), 4.33 (1H, dt, J=2.3, 11.4 Hz), 3.63 (2H, dt, J=1.7, 6.5 Hz), 2.64–2.68 (1H, m), 2.26 (1H, br s), 1.97–2.06 (1H, m), 1.70–1.88 (2H, m), 1.52–1.65 (3H, m), 1.16–1.32 (1H, m), 1.06 (18H, s), 0.94–1.14 (3H, m), 0.92 (3H, d, J=6.3 Hz); ^{13}C NMR δ 153.2, 106.6, 69.7, 61.2, 47.0, 41.0, 40.9, 35.7, 27.1, 22.1, 18.2, 12.5; IR (neat) 3336, 1650, 1462 cm^{-1}; EI MS *m*/*z* 326 (M^+); high-resolution mass *m*/*z* calcd for $C_{19}H_{38}O_2Si$ (M^+) 326.2623. Found: 326.2643.

4.1.5. (1*S,3*R**,5*R**)-1-Formylmethyl-3-triisopropylsilyloxy-5-methyl-2-methylenecyclohexane (9).** A mixture of **8** (16.3 g, 50.0 mmol) and Dess–Martin periodinane (26.5 g, 62.5 mmol) in CH_2Cl_2 (400 mL) was stirred at rt for 2 h. The reaction was quenched with a 10% $Na_2S_2O_3$ solution and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$ and brine, then dried and evaporated under reduced pressure to give a crude residue (28.2 g), which was purified by column chromatography (AcOEt/hexane=1:10) to give **9** (15.9 g, 98.1%) as a colorless oil; ^{1}H NMR δ 9.69 (1H, t, J=2.3 Hz), 5.16, 4.88 (each 1H, each d, J=2 Hz), 4.26–4.32 (1H, m),

3.16–3.24 (1H, m), 2.49 (2H, ddd, J=2.3, 3.9, 7.7 Hz), 1.97–2.03 (1H, m), 1.72–1.88 (1H, m), 1.55–1.62 (2H, m), 1.24–1.35 (1H, m), 1.07 (18H, s), 0.97–1.17 (3H, m), 0.94 (3H, d, J=6.6 Hz); ^{13}C NMR δ 201.9, 151.7, 107.3, 69.9, 46.7, 46.4, 40.1, 38.1, 26.9, 21.9, 18.1, 12.4; IR (neat) 1729, 1651, 1463 cm^{-1}; EI MS m/z 324 (M^+); high-resolution mass m/z calcd for $C_{19}H_{36}O_2Si$ (M^+) 324.2484. Found: 324.2475.

4.1.6. (1*S,2′*RS**,3*R**,5*R**)-1-(2′-Hydroxy-3′-butynyl)-3-triisopropylsilyloxy-5-methyl-2-methylene cyclohexane (10).** To a stirred solution of **9** (10.8 g, 33.3 mmol) in THF (400 mL) was added 0.5 M ethynylmagnesium bromide (100 mL, 50 mmol) over a period of 15 min. After stirring for 1 h, the reaction was quenched with 1 M HCl and the mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried and evaporated under reduced pressure to give a crude residue, which was purified by column chromatography (AcOEt/hexane=1:30) to afford **10** (8.34 g, 71.5%) as a colorless oil; ^{1}H NMR δ 5.22, 5.17 (together 1H, each t, J=2.3 Hz), 4.92, 4.88 (together 1H, each t, J=2.3 Hz), 4.27–4.36 (2H, m), 2.76–2.95 (1H, m), 2.50, 2.46 (together 1H, each d, J=2 Hz), 1.55–2.04 (7H, m), 1.20–1.55 (1H, m), 1.08 (18H, s), 0.98–1.17 (3H, m), 0.91 (3H, d, J=6.6 Hz); ^{13}C NMR δ 152.6, 107.8, 107.3, 85.0, 84.5, 73.3, 72.8, 69.7, 61.6, 60.5, 46.9, 40.9, 40.7, 39.9, 29.1, 22.0, 18.1, 12.5; IR (neat) 3359, 3311, 1652, 1457 cm^{-1}; EI MS m/z 350 (M^+); high-resolution mass m/z calcd for $C_{21}H_{38}O_2Si$ (M^+) 350.2641. Found: 350.2638.

4.1.7. (1*S,2′*RS**,3*R**,5*R**)-1-(2′-Methoxymethoxy-3′-butynyl)-3-triisopropylsilyloxy-5-methyl-2-methylene-cyclohexane (11).** To a stirred solution of **10** (1.753 g, 5.0 mmol) and *N*,*N*-diisopropylethylamine (2.587 g, 20.0 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added MOMCl (1.208 g, 15.0 mmol) over a period of 10 min. After stirring at rt for 22 h, the reaction was quenched with water. The mixture was extracted with $CHCl_3$. The organic extracts were washed with 1 M HCl and brine, then dried and evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:30) to afford **11** (1.655 g, 84.0%) as a colorless oil; ^{1}H NMR δ 5.20, 5.17 (together 1H, each t, J=2.3 Hz), 4.96, 4.93 (together 1H, each d, J=6.9 Hz), 4.87, 4.84 (together 1H, each t, J=2.3 Hz), 4.62, 4.58 (together 1H, each d, J=6.9 Hz), 4.20–4.35 (2H, m), 3.42, 3.36 (together 3 H, each s), 2.81–2.88 (1H, m), 2.45, 2.40 (together 1H, each d, J=2 Hz), 1.60–2.03 (6H, m), 1.20–1.31 (1H, m), 1.08 (18H, s), 0.98–1.17 (3H, m), 0.92 (3H, d, J=6.3 Hz); IR (neat) 3310, 1653, 1541, 1457 cm^{-1}; EI MS m/z 394 (M^+); high-resolution mass m/z calcd for $C_{23}H_{42}O_3Si$ (M^+) 394.2903. Found: 394.2900.

4.1.8. (1′*S,3′*R**,5′*R**,6*RS**)-7-(5′-Methyl-2′-methylene-3′-triisopropylsilyloxy-cyclohexyl)-6-methoxymethoxy-4-heptynoic acid (12).** To a stirred solution of **11** (0.394 g, 1.0 mmol) in toluene (5 mL) at −30 °C was added *n*-BuLi (2.6 mL, 4.1 mmol). After stirring for 30 min, 1 M Me_2AlCl in hexane (4.1 mL, 4.0 mmol) was added. After further stirring for 30 min, β-propiolactone (0.38 mL, 6.0 mmol) was added and stirring was continued at −30 °C for 3 days and also at rt for 3 days. The reaction was quenched with MeOH. Then, 3 M HCl was added and the mixture was extracted with Et_2O. The organic extracts were washed with brine, then dried and evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:10) to afford **12** (0.043 g, 9.3%) as a colorless oil and **11** (0.137 g, 34.6%); ^{1}H NMR δ 5.17, 5.13 (together 1H, each br s), 4.92, 4.58 (together 1H, each d, J=6.6 Hz), 4.82 (1H, m), 4.91, 4.54 (together 1H, each d, J=6.9 Hz), 4.12–4.40 (2H, m), 3.40, 3.34 (together 3H, each s), 2.78 (1H, br s), 2.56–2.67 (4H, m), 1.62–2.05 (5H, m), 1.26–1.39 (2H, m), 1.08 (18H, s), 0.94–1.08 (3H, m), 0.91 (3H, d, J=6.3 Hz); ^{13}C NMR δ 200.4, 152.3, 107.6, 107.3, 107.2, 94.5, 94.0, 83.6, 79.8, 69.7, 65.4, 64.5, 56.0, 55.7, 46.9, 40.8, 40.7, 40.2, 40.1, 39.7, 38.9, 33.3, 27.2, 27.1, 22.1, 18.2, 17.8, 14.5, 12.5; IR (neat) 3000–3600, 1741, 1716, 1652, 1457 cm^{-1}; EI MS m/z 466 (M^+); high-resolution mass m/z calcd for $C_{26}H_{46}O_5Si$ (M^+) 466.3115. Found: 466.3107.

4.1.9. (1*S,2′*RS**,3*R**,5*R**)-1-(6′-*tert*-Butyloxycarbonyl-amino-2′-hydroxy-3′-hexynyl)-3-triisopropylsilyloxy-5-methyl-2-methylenecyclohexane (13).** To a stirred solution of *tert*- butyl 3-butynylcarbamate (5.49 g, 32.5 mmol) in THF (200 mL) at 0 °C was added *n*-BuLi (40 mL, 62.4 mmol) over a period of 10 min. After stirring for 10 min, HMPA (13.5 mL) was added and the mixture was stirred for another 10 min. A solution of **9** (8.10 g, 25.0 mmol) in THF (60 mL) was added over a period of 30 min and stirring was continued for an additional 1 h. The reaction was quenched with water. The mixture was extracted with Et_2O. The organic extracts were washed with brine, then dried and evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:5 then 1:2) to afford **13** (10.11 g, 82.0%) as a colorless oil; ^{1}H NMR δ 5.18, 5.12 (together 1H, each s), 4.87 (1H, br s), 4.82, 4.87 (together 1H, each s), 4.22–4.32 (2H, m), 3.23–3.33 (3H, m), 2.70–2.85 (1H, m), 2.54–2.64 (1H, m), 2.36–2.42 (2H, m), 1.51–2.06 (5H, m), 1.43 (9H, s), 1.12–1.28 (1H, m), 1.06 (18H, s), 0.96–1.08 (3H, m), 0.91, 0.89 (together 3H, each d, J=6.6 Hz); ^{13}C NMR δ 184.1, 155.5, 152.8, 107.4, 107.1, 79.5, 69.7, 61.9, 60.9, 46.9, 40.8, 40.0, 39.5, 28.4, 27.1, 22.0, 20.3, 18.2, 12.5; IR (neat) 3367, 2215, 1717, 1698, 1680, 1507, 1457 cm^{-1}; EI MS m/z 493 (M^+); high-resolution mass m/z calcd for $C_{28}H_{51}NO_4Si$ (M^+) 493.3587. Found: 493.3593.

4.1.10. (1*S,2′*RS**,3*R**,5*R**)-1-(6′-Benzyloxycarbonyl-amino-2′-hydroxy-3′-hexynyl)-3-triisopropylsilyloxyl-5-methyl-2-methylenecyclohexane (14).** To a stirred solution of benzyl 3-butynylcarbamate (0.305 g, 1.50 mmol) in THF (8 mL) at 0 °C was added *n*-BuLi (1.8 mL, 2.80 mmol) over a period of 5 min. After stirring for 10 min, HMPA (0.52 mL, 3.0 mmol) was added and the mixture was stirred for 20 min. A solution of **9** (0.325 g, 1.0 mmol) in THF (2 mL) was added over a period of 5 min and stirring was continued for an additional 1 h. A work-up similar to that described above gave an oily residue, which was purified by column chromatography (AcOEt/hexane=1:5) to give **14** (0.403 g, 76.4%) as a colorless oil; ^{1}H NMR δ 7.28–7.53 (5H, m), 5.19, 5.15 (together 1H, each t, J=2.3 Hz), 5.10 (2H, s), 5.10 (1H, br s), 4.88, 4.84 (together 1H, each t, J=2.3 Hz), 4.23–4.35 (2H, m), 3.30–3.36 (2H, m), 2.72–2.89 (1H, m), 2.43–2.47 (2H, m), 1.54–2.01 (7H,

m), 1.17–1.44 (1H, m), 1.07 (18H, s), 0.94–1.14 (3H, m), 0.91 (3H, d, $J=6.6$ Hz); ^{13}C NMR δ 156.3, 152.6, 152.4, 138.6, 136.2, 128.5, 128.1, 107.4, 69.6, 66.7, 61.7, 60.6, 46.8, 41.0, 40.8, 40.7, 39.8, 27.0, 22.0, 20.2, 18.1, 12.4; IR (neat) 3347, 3303, 2216, 1705, 1529, 1456 cm^{-1}; EI MS *m/z* 527 (M^+); high-resolution mass *m/z* calcd for $C_{31}H_{49}NO_4Si$ (M^+) 527.3431. Found: 527.3410.

4.1.11. (1*R,2′*S**,3*S**,5*R**)-3-(6′-*tert*-Butyloxycarbonylamino-2′-hydroxy-3′-hexynyl-5-methyl-2-methylenecyclohexanol (15a) and (1*R**,2′*S**,3*R**,5*R**)-3-(6′-*tert*-butyloxycarbonylamino-2′-hydroxy-3′-hexynyl)-5-methyl-2-methylenecyclohexanol (15b).** A solution of **13** (9.86 g, 20.0 mmol) and TBAF (10.0 mL, 10.0 mmol) in THF (30 mL) was refluxed for 2 h. The solvent was evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=4:5) to afford **15a** (2.88 g, 42.7%) and **15b** (3.24 g, 48.1%) as colorless oils; **15a**; ^{1}H NMR δ 5.09 (1H, br s), 5.02, 4.87 (each 1H, each d, $J=1.6$ Hz), 4.26 (2H, br s), 3.25–3.27 (3H, m), 2.74–2.78 (1H, m), 2.51 (1H, br s), 2.41 (2H, t, $J=6.4$ Hz), 2.05–2.10 (1H, m), 1.90–2.01 (2H, m), 1.58–1.68 (2H, m), 1.45 (9H, s), 1.15–1.34 (1H, m), 0.99–1.06 (1H, m), 0.93 (3H, dd, $J=1.3$, 6.6 Hz); ^{13}C NMR δ 156.0, 152.5, 105.9, 82.7, 79.5, 68.7, 61.4, 45.9, 40.9, 40.8, 39.5, 28.4, 27.1, 22.0, 20.3; IR (neat) 3364, 2143, 1698, 1652, 1541, 1507, 1457 cm^{-1}; FAB MS *m/z* 338 ($M^+ +1$); high-resolution FAB mass *m/z* calcd for $C_{19}H_{32}NO_4$ ($M^+ +1$) 338.2331. Found: 338.2327.

Compound **15b**. ^{1}H NMR δ 5.07 (2H, br s), 4.90 (1H, s), 4.22–4.39 (2H, m), 3.24 (2H, br s), 2.84 (1H, m), 2.75 (2H, br s), 2.39 (2H, t, $J=6.3$ Hz), 2.04–2.10 (1H, m), 1.83–1.94 (2H, m), 1.64–1.74 (1H, m), 1.58–1.62 (1H, m), 1.45 (9H, s), 1.19–1.36 (1H, m), 0.95–1.14 (1H, m), 0.92 (3H, d, $J=6.3$ Hz); ^{13}C NMR δ 156.0, 152.6, 106.4, 83.1, 82.1, 79.5, 68.8, 60.5, 45.9, 41.1, 40.9, 40.1, 39.5, 28.4, 27.0, 22.0, 20.3; IR (neat) 3396, 2143, 1698, 1538, 1520, 1508, 1457 cm^{-1}; FAB MS *m/z* 338 ($M^+ +1$); high-resolution FAB mass *m/z* calcd for $C_{19}H_{32}NO_4$ ($M^+ +1$) 338.2331. Found: 338.2338.

4.1.12. (1*R,2′*S**,3*S**,5*R**)-3-(6′-Benzyloxycarbonylamino-2′-hydroxy-3′-hexynyl)-5-methyl 2-methylenecyclohexanol (16a) and (1*R**,2′*S**,3*R**,5*R**)-3-(6′-benzyloxycarbonylamino-2′-hydroxy-3′-hexynyl)-5-methyl 2-methylenecyclohexanol (16b).** A solution of **14** (0.360 g, 0.68 mmol) and TBAF (0.34 mL, 0.34 mmol) in THF (10 mL) was refluxed for 2 h. The solvent was evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:1) to afford **16a** (0.093 g, 36.7%) and **16b** (0.104 g, 41.0%) as colorless oils; **16a**; ^{1}H NMR δ 7.30–7.35 (5H, m), 5.28 (1H, br s), 5.10 (2H, s), 5.00, 4.85 (each 1H, each s), 4.26 (2H, br s), 3.33 (2H, dd, $J=5.8$, 12.0 Hz), 2.73–2.77 (1H, m), 2.43 (2H, t, $J=5.9$ Hz), 1.84–2.08 (2H, m), 1.59–1.67 (2H, m), 1.16–1.27 (2H, m), 0.87–1.05 (1H, m), 0.91 (3H, d, $J=6.6$ Hz); ^{13}C NMR δ 156.5, 152.6, 136.3, 128.4, 128.1, 128.0, 105.8, 82.8, 82.4, 68.7, 66.7, 61.5, 45.8, 40.9, 40.8, 40.7, 39.9, 27.0, 21.8, 20.1; IR (neat) 3357, 2229, 1698, 1540, 1456 cm^{-1}; EI MS *m/z* 371 (M^+); high-resolution mass *m/z* calcd for $C_{22}H_{29}NO_4$ (M^+) 371.2097. Found: 371.2091.

Compound **16b**; ^{1}H NMR δ 7.31–7.36 (5H, m), 5.29 (1H, br s), 5.10 (2H, s), 5.04, 4.89 (each 1H, each s), 4.19–4.32 (2H, m), 3.31 (2H, dd, $J=6.0$, 12.4 Hz), 2.82–2.86 (1H, m), 2.41 (2H, t, $J=6.0$ Hz), 1.55–1.94 (4H, m), 1.18–1.30 (2H, m), 0.97–1.01 (1H, m), 0.91 (3H, d, $J=6.3$ Hz); ^{13}C NMR δ 156.4, 152.6, 136.3, 128.4, 128.0, 127.9, 106.2, 83.1, 82.0, 68.7, 66.7, 60.6, 45.9, 41.0, 40.8, 40.1, 39.8, 26.9, 21.8, 20.1; IR (neat) 3364, 2229, 1698, 1541, 1520, 1456 cm^{-1}; EI MS *m/z* 371 (M^+); high-resolution mass *m/z* calcd for $C_{22}H_{29}NO_4$ (M^+) 371.2097. Found: 371.2093.

4.2. General procedure for the Pauson–Khand reaction of enynes (15a,b and 16a,b).

(a) With NMO. A mixture of the enyne (1 equiv) and $Co_2(CO)_8$ (1.1 equiv) in CH_2Cl_2 was stirred at rt for 1 h. Then, NMO (3 equiv) was added to the mixture four times at intervals of 15 min. The solvent was removed under reduced pressure to give a residue, which was diluted with Et_2O. The precipitate was removed by suction filtration through a short pad of Celite 545. The filtrate was evaporated under reduced pressure to furnish a residue, which was purified by column chromatography (AcOEt/hexane=1:1 then 10:1) to afford the cyclized product (**17a**, **17b**, **18a** or **18b**) and the starting material.

(b) With TMANO. A mixture of the enyne (1 equiv) and $Co_2(CO)_8$ (1.1 equiv) in THF was stirred at rt for 1 h. Then, TMANO (3 equiv) was added to the mixture four times at intervals of 15 min. A work-up similar to that described above furnished the cyclized product (**17a**, **17b**, **18a** or **18b**) as colorless crystals and the starting material.

4.2.1. (4*S,5a*S**,7*R**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-1,4,5,5a,6,7,8,9-octahydro-4,9-dihydroxy-7-methyl-1*H*-cyclopenta[*c*]inden-2-one (17a).** Mp 62–63 °C (AcOEt–hexane); ^{1}H NMR δ 5.21 (1H, d, $J=8.9$ Hz), 5.02 (1H, br s), 3.57 (1H, dd, $J=3.6$, 12 Hz), 3.20–3.34 (2H, m), 2.69, 1.86 (each 1H, each d, $J=17.2$ Hz), 2.43–2.58 (3H, m), 2.28 (1H, br s), 1.80–1.89 (3H, m), 1.62–1.67 (1H, m), 1.40 (9H, s), 1.10–1.29 (2H, m), 0.95 (3H, d, $J=6.3$ Hz); ^{13}C NMR δ 210.3, 184.1, 157.3, 136.5, 79.8, 69.6, 68.9, 57.1, 43.0, 42.7, 40.5, 39.9, 39.5, 33.4, 28.4, 26.9, 23.8, 22.1; IR (KBr) 3377, 1692, 1656, 1525, 1457 cm^{-1}; EI MS *m/z* 365 (M^+); high-resolution mass *m/z* calcd for $C_{20}H_{31}NO_5$ (M^+) 365.2202. Found: 365.2196.

4.2.2. (4*R,5a*S**,7*R**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-1,4,5,5a,6,7,8,9-octahydro-4,9-dihydroxy-7-methyl-1*H*-cyclopenta[*c*]inden-2-one (17b).** Mp 54–55 °C (AcOEt–hexane); ^{1}H NMR δ 5.38 (1H, br s), 4.85 (1H, t, $J=6.9$ Hz), 4.09 (1H, dd, $J=6.9$, 14.9 Hz), 3.20–3.31 (2H, m), 2.74, 1.77 (each 1H, each d, $J=17.2$ Hz), 2.30–2.51 (3H, m), 1.63–2.05 (5H, m), 1.42 (9H, s), 1.03–1.29 (2H, m), 0.96 (3H, d, $J=6.3$ Hz); ^{13}C NMR δ 211.2, 180.8, 157.1, 137.0, 80.1, 68.0, 66.7, 55.9, 42.8, 40.6, 39.6, 39.2, 33.2, 28.3, 27.0, 24.6, 22.2; IR (KBr) 3373, 1697, 1524, 1456 cm^{-1}; EI MS *m/z* 365 (M^+); high-resolution mass *m/z* calcd for $C_{20}H_{31}NO_5$ (M^+) 365.2202. Found: 365.2204.

4.2.3. (4*S,5a*S**,7*R**,9*R**,9a*S**)-3-Benzyloxycarbonylaminoethyl-1,4,5,5a,6,7,8,9-octahydro-4,9-dihydroxy-7-methyl-1*H*-cyclopenta[*c*]inden-2-one (18a).** Mp 47 °C

(AcOEt–hexane); ^{1}H NMR δ 7.33 (5H, s), 5.70 (1H, br s), 5.08 (2H, d, J=12.2 Hz), 4.92 (2H, d, J=12.2 Hz), 3.21–3.34 (2H, m), 2.97 (1H, brd, J=9.9 Hz), 2.59, 1.72 (each 1H, each d, J=17.2 Hz), 2.43–2.62 (2H, m), 2.02–2.31 (2H, m), 1.51–1.75 (5H, m), 0.83–1.19 (2H, m), 0.91 (3H, d, J=5.9 Hz); ^{13}C NMR δ 210.7, 184.6, 157.8, 136.6, 136.0, 128.5, 128.2, 128.1, 69.5, 68.5, 66.7, 57.0, 42.9, 42.6, 40.2, 39.4, 39.3, 33.4, 26.9, 24.5, 22.1; IR (KBr) 3395, 1700, 1686, 1655, 1542, 1457 cm^{-1}; EI MS m/z 399 (M^+); high-resolution mass m/z calcd for $C_{23}H_{29}NO_5$ (M^+) 399.2046. Found: 399.2037.

4.2.4. (4*R,5a*S**,7*R**,9*R**,9a*S**)-3-Benzyloxycarbonylaminoethyl-1,4,5,5a,6,7,8,9-octahydro-4,9-dihydroxy-7-methyl-1*H*-cyclopenta[*c*]inden-2-one (18b).** Mp 50–51 °C (AcOEt–hexane); ^{1}H NMR δ 7.30 (5H, s), 5.87 (1H, br s), 5.00 (2H, s), 4.81 (1H, br s), 3.98 (1H, brd, J=10.9 Hz), 3.68 (2H, br s), 3.25–3.30 (2H, m), 2.70, 1.72 (each 1H, each d, J=17.2 Hz), 2.26–2.47 (3H, m), 1.58–2.00 (5H, m), 0.98–1.17 (2H, m), 0.93 (3H, d, J=5.6 Hz); ^{13}C NMR δ 211.5, 181.2, 157.5, 136.9, 136.2, 128.4, 128.2, 128.0, 68.0, 66.8, 66.7, 55.9, 42.9, 42.6, 40.5, 39.7, 39.2, 33.1, 26.9, 24.5, 22.1; IR (KBr) 3366, 1700, 1656, 1542, 1456 cm^{-1}; EI MS m/z 399 (M^+); high-resolution mass m/z calcd for $C_{23}H_{29}NO_5$ (M^+) 399.2046. Found: 399.2041.

4.2.5. (4*S,5a*S**,7*R**,9*R**,9a*S**)-4-Benzoyloxy-3-*tert*-butyloxycarbonylaminoethyl-1,4,5,5a,6,7,8,9-octahydro-9-hydroxy-7- methyl-1*H*-cyclopenta[*c*]inden-2-one (19).** To a stirred solution of **17b** (0.704 g, 1.93 mmol), $PhCO_2H$ (0.262 g, 2.14 mmol), and PPh_3 (0.556 g, 2.12 mmol) in THF (10 mL) at rt was added a solution of DEAD (0.924 g, 2.12 mmol) in THF (1 mL) dropwise. After stirring for 4 h, the solvent was removed in vacuo. The residue was taken up in Et_2O and the precipitate was filtered. The filtrate was evaporated under reduced pressure to give a residue, which was purified by column chromatography (AcOEt/hexane=1:3 then 1:2) to afford **19** (0.885 g, 97.9%) as colorless crystals; mp 70–72 °C (AcOEt–hexane); ^{1}H NMR δ 8.04 (2H, d, J=7.6 Hz), 7.61 (1H, t, J=7.6 Hz), 7.47 (2H, t, J=7.6 Hz), 6.63 (1H, d, J=8.9 Hz), 4.05 (1H, t, J=6.6 Hz), 3.64 (1H, dd, J=3.5, 12 Hz), 3.08–3.34 (2H, m), 2.82, 1.90 (each 1H, each d, J=16.8 Hz), 2.49–2.74 (3H, m), 2.22–2.39 (1H, m), 1.80–2.04 (3H, m), 1.64–1.70 (1H, m), 1.41 (9H, s), 1.16–1.36 (2H, m), 0.98 (3H, d, J=6.6 Hz); ^{13}C NMR δ 209.5, 178.0, 165.9, 157.2, 137.7, 133.5, 129.7, 128.7, 79.8, 71.7, 68.6, 57.4, 43.0, 42.9, 40.2, 39.9, 37.6, 33.3, 28.4, 26.9, 24.8, 22.2; IR (KBr) 3401, 1713, 1602, 1523, 1452 cm^{-1}; EI MS m/z 469 (M^+); high-resolution mass m/z calcd for $C_{27}H_{35}NO_6$ (M^+) 469.2465. Found: 469.2459.

4.3. Hydrolysis of 19 to 17a

A solution of **19** (0.619 g, 1.32 mmol) and 1 M NaOH (4 mL) in THF (5 mL) and MeOH (5 mL) was stirred at rt for 1 h. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried and evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:1 then AcOEt) to afford **17a** (0.476 g, 98.7%) as colorless crystals. The ^{1}H NMR spectrum of **17a** was identical with that obtained by the Pauson–Khand reaction of **15a**.

4.3.1. (4*S,5a*S**,7*R**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-1,4,5,5a,6,7,8,9-octahydro-4,9-bis(methoxymethoxy)-7-methyl-1*H*-cyclopenta[*c*]inden-2-one (20).** To a stirred solution of **17a** (0.189 g, 0.52 mmol) and *N*,*N*-diisopropylethylamine (0.269 g, 2.08 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added MOMCl (0.167 g, 2.07 mmol). After stirring at rt for 3 h, *N*,*N*-diisopropylethylamine (0.136 g, 1.06 mmol) and MOMCl (0.0800 g, 0.99 mmol) were added and stirring was continued for an additional 3 days. The reaction was quenched with water. The mixture was extracted with $CHCl_3$. The organic extracts were washed with 1 M HCl and brine, then dried and evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:1) to afford **20** (0.167 g, 71.2%) as a colorless oil; ^{1}H NMR δ 5.34 (1H, br s), 5.12 (1H, brd, J=8.6 Hz), 4.73–4.80 (2H, m), 4.52, 4.35 (each 1H, each d, J=6.9 Hz), 3.44, 3.22 (each 3H, each s), 3.22–3.49 (3H, m), 2.69, 1.92 (each 1H, each d, J=17.1 Hz), 2.27–2.64 (3H, m), 2.17–2.23 (1H, m), 1.50–2.04 (4H, m), 1.50 (9H, s), 1.13–1.28 (1H, m), 0.96 (3H, d, J=6.3 Hz), 0.90–1.03 (1H, m); ^{13}C NMR δ 207.2, 180.2, 155.9, 137.0, 96.1, 95.2, 78.7, 74.6, 73.8, 56.2, 55.3, 55.0, 43.4, 43.2, 39.3, 38.6, 35.9, 33.2, 28.5, 26.7, 23.6, 22.1; IR (neat) 3365, 1714, 1705, 1674, 1519, 1455 cm^{-1}; FAB MS m/z 454 ($M^+ + 1$); high-resolution FAB mass m/z calcd for $C_{24}H_{40}NO_7$ ($M^+ + 1$) 454.2805. Found: 454.2804.

4.3.2. (3*R,3a*R**,4*S**,5a*S**,7*R**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-4,9-dihydroxy-7-methyl-perhydrocyclopenta[*c*]inden-2-one (21).** A suspension of **17a** (0.257 g, 0.70 mmol) and 10% Pd/C (0.026 g) in MeOH (7 mL) and H_2O (0.35 mL) under an H_2 atmosphere was stirred at rt for 14.5 h. Then, 10% Pd/C (0.013 g) was added and the mixture was stirred for an additional 24 h. The catalyst was removed by suction filtration and the filtrate was evaporated under reduced pressure to give a residue, which was purified by column chromatography (AcOEt/hexane=1:1) to afford **21** (0.210 g, 80.0%) as colorless crystals; mp 58–60 °C (AcOEt–hexane); ^{1}H NMR δ 4.51 (1H, t, J=5.9 Hz), 3.52 (1H, dd, J=3.3, 11.9 Hz), 3.19 (4H, br s), 2.74–3.19 (1H, m), 2.61, 2.07 (each 1H, each d, J=18.5 Hz), 2.51 (1H, m), 2.23–2.31 (1H, m), 1.89–2.11 (2H, m), 1.42–1.76 (5H, m), 1.42 (9H, s), 1.09–1.26 (1H, m), 0.92 (3H, d, J=6.3 Hz), 0.91–0.98 (1H, m); ^{13}C NMR δ 157.0, 79.6, 72.9, 71.1, 56.4, 51.5, 45.5, 43.9, 42.9, 41.4, 40.3, 38.5, 32.7, 31.5, 28.3, 27.0, 22.1; IR (KBr) 3400, 1722, 1686, 1523, 1456 cm^{-1}; EI MS m/z 367 (M^+); high-resolution mass m/z calcd for $C_{20}H_{33}NO_5$ (M^+) 367.2359. Found: 367.2368.

4.3.3. (3*R,3a*R**,4*S**,5a*S**,7*R**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-4,9-bis(methoxymethoxy)-7-methylperhydrocyclopenta[*c*]inden-2-one (22).** To a stirred solution of **21** (0.189 g, 0.52 mmol) and *N*,*N*-diisopropylethylamine (0.556 g, 4.30 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added a solution of MOMCl (0.335 g, 4.16 mmol) in CH_2Cl_2 (2 mL). After stirring at rt for 18 h, the reaction was quenched with water. The mixture was extracted with $CHCl_3$. The organic extracts were washed with 1 M HCl and brine, then dried and evaporated in vacuo to give an oily residue, which was purified by column chromatography (AcOEt/hexane=1:3 then 1:1) to afford **22** (0.225 g, 95.0%) as a colorless oil; ^{1}H NMR (500 MHz) δ

5.10 (1H, br s), 4.72, 4.55 (each 1H, each d, $J=7$ Hz), 4.68, 4.61 (each 1H, each d, $J=6.4$ Hz), 4.35 (1H, t, $J=6.7$ Hz), 3.36, 3.34 (each 3H, each s), 3.34–3.40 (1H, m), 3.22–3.33 (1H, m), 3.11–3.20 (1H, m), 2.71 (1H, ddd, $J=1.5$, 6.7, 15.2 Hz), 2.65 (1H, d, $J=18.3$ Hz), 2.56 (1H, t, $J=8.1$ Hz), 2.16–2.21 (1H, m), 2.09 (1H, dd, $J=1.5$, 18.3 Hz), 1.81–1.99 (5H, m), 1.60–1.65 (2H, m), 1.43 (9H, s), 1.13–1.20 (1H, m), 0.92 (3H, d, $J=6.4$ Hz), 0.80–0.88 (1H, m); ^{13}C NMR (125 MHz) δ 220.4, 155.9, 95.9, 95.3, 78.8, 78.6, 76.9, 55.8, 55.7, 54.7, 50.9, 46.2, 43.8, 43.0, 38.6, 38.0, 37.1, 32.5, 31.0, 28.5, 26.7, 22.1; IR (neat) 3365, 1715, 1518, 1455 cm^{-1}; EI MS *m/z* 455 (M^+); high-resolution mass *m/z* calcd for $C_{24}H_{41}NO_7$ (M^+) 455.2883. Found: 455.2888.

4.3.4. (3*R,3a*R**,4*S**,5a*S**,7*S**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-4,9-bis(methoxymethoxy)-7-methyl-2-methyleneperhydrocyclopenta[*c*]indene (23).** To a stirred solution of **22** (0.046 g, 0.10 mmol) in THF (1 mL) at 0 °C was added 0.5 M Tebbe reagent in toluene (1.2 mL, 0.60 mmol) over a period of 10 min. After stirring for 1 h, the mixture was diluted with Et_2O (6 mL). Then, the reaction was quenched with a 0.1 M aqueous NaOH solution. The mixture was dried over anhydrous K_2CO_3 and the precipitate was filtered through with a short pad of Celite 545. The filtrate was evaporated under reduced pressure to give a residue, which was purified by column chromatography (Et_2O/hexane=1:1) to give **23** (0.020 g, 44%) as a colorless oil and **22** (0.017 g, 38%); ^{1}H NMR (500 MHz) δ 4.90 (1H, br s), 4.86, 4.75 (each 1H, each s), 4.71, 4.57 (each 1H, each d, $J=7$ Hz), 4.62, 4.54 (each 1H, each d, $J=6.4$ Hz), 4.23 (1H, t, $J=6.7$ Hz), 3.34, 3.33 (each 3H, each s), 3.29 (1H, dd, $J=3.7$, 11.9 Hz), 3.17–3.29 (1H, m), 3.02–3.11 (1H, m), 2.68, 1.98 (each 1H, each d, $J=15.3$ Hz), 2.73 (1H, dd, $J=7.3$, 14 Hz), 2.30 (1H, dd, $J=5.1$, 8.9 Hz), 2.03–2.08 (1H, m), 1.76–1.86 (2H, m), 1.65–1.75 (2H, m), 1.38–1.60 (4H, m), 1.41 (9H, s), 1.11 (1H, dt, $J=5.3$, 13.2 Hz), 0.87 (3H, d, $J=6.4$ Hz); ^{13}C NMR (125 MHz) δ 156.3, 106.5, 95.8, 95.5, 77.7, 77.5, 57.2, 55.8, 55.6, 50.6, 41.4, 40.5, 38.9, 38.1, 36.9, 35.8, 32.6, 28.5, 26.8, 22.2; IR (neat) 3365, 1715, 1518, 1455 cm^{-1}; EI MS *m/z* 453 (M^+); high-resolution mass *m/z* calcd for $C_{25}H_{43}NO_6$ (M^+) 453.3096. Found: 453.3090.

4.4. Conversion of olefin (23) to benzoyl esters (24a,b) (Table 2, entry 2)

To a solution of **23** (0.0112 g, 0.25 mmol) in THF (5 mL) was added at rt BH_3·THF (0.75 mL, 0.75 mmol). After stirring for 1 h, the reaction was quenched with water. Then, 3 M NaOH (1.5 mL) and 30% H_2O_2 (1.5 mL) were added and the whole mixture was further stirred for 0.5 h. The mixture was extracted with Et_2O. The organic extracts were washed with brine, then dried (K_2CO_3) and evaporated in vacuo to give a crude alcohol (0.128 g). Without purification, the alcohol was treated with Et_3N (105 μL, 0.75 mmol), DMAP (0.0034 g, 0.028 mmol) and benzoyl chloride (75 μL, 0.65 mmol) in $CHCl_3$ (3 mL) for 2 h. After addition of water, the mixture was extracted with $CHCl_3$. The organic extracts were washed with 1 M HCl, saturated $NaHCO_3$ and brine, then dried and evaporated in vacuo to give a residue, which was purified by TLC (AcOEt/hexane=1:2) to afford **24a** (0.0202 g, 14.0%) and **24b** (0.0794 g, 55.2%) as colorless oils.

4.4.1. (2*S,3*S**,3a*R**,4*S**,5a*S**,7*S**,9*R**,9a*S**)-2-Benzoyloxymethyl-3-*tert*-butyloxycarbonylaminoethyl-4,9-bis(methoxymethoxy)-7-methylperhydro-1*H*-cyclopenta[*c*]indene (24a).** ^{1}H NMR δ 8.04 (2H, d, $J=7.4$ Hz), 7.55 (1H, t, $J=7.4$ Hz), 7.43 (2H, t, $J=7.4$ Hz), 5.02 (1H, br s), 4.73, 4.57 (each 1H, each d, $J=6.9$ Hz), 4.69, 4.64 (each 1H, each d, $J=6.3$ Hz), 4.39 (1H, dd, $J=4.6$, 10.9 Hz), 4.23 (1H, dd, $J=6.6$, 10.9 Hz), 4.07–4.17 (1H, m), 3.39, 3.37 (each 3H, each s), 3.21 (1H, dd, $J=4.0$, 12.2 Hz), 3.15–3.45 (1H, m), 2.96–3.11 (1H, m), 2.29–2.47 (2H, m), 2.05–2.29 (3H, m), 1.72–1.93 (4H, m), 1.36–1.64 (4H, m), 1.41 (9H, s), 1.06–1.22 (1H, m), 0.89 (3H, d, $J=6.3$ Hz), 0.80–1.00 (1H, m); ^{13}C NMR δ 166.7, 155.9, 132.8, 130.6, 129.6, 128.3, 96.3, 95.2, 80.5, 78.1, 77.2, 67.6, 60.9, 55.9, 55.8, 55.4, 48.9, 45.6, 39.0, 38.0, 37.6, 36.9, 34.6, 32.8, 28.4, 26.9, 22.2; IR (neat) 3377, 1715, 1698, 1507, 1455 cm^{-1}; EI MS *m/z* 575 (M^+); high-resolution mass *m/z* calcd for $C_{32}H_{49}NO_8$ (M^+) 575.3458. Found: 575.3458.

4.4.2. (2*R,3*S**,3a*R**,4*S**,5a*S**,7*S**,9*R**,9a*S**)-2-Benzoyloxymethyl-3-*tert*-butyloxycarbonylaminoethyl-4,9-bis(methoxymethoxy)-7-methylperhydro-1*H*-cyclopenta[*c*]indene (24b).** ^{1}H NMR δ 8.02 (2H, d, $J=7.4$ Hz), 7.54 (1H, t, $J=7.4$ Hz), 7.42 (2H, t, $J=7.4$ Hz), 4.73, 4.60 (each 1H, each d, $J=6.6$ Hz), 4.60 (1H, br s), 4.64, 4.56 (each 1H, each d, $J=6.3$ Hz), 4.37 (1H, dd, $J=4$, 11.2 Hz), 4.30 (1H, dd, $J=4.3$, 11.2 Hz), 4.03–4.13 (1H, m), 3.34, 3.33 (each 3H, each s), 3.16–3.40 (2H, m), 2.98–3.15 (1H, m), 2.50–2.68 (1H, m), 2.04–2.35 (3H, m), 1.32–1.92 (9H, m), 1.40 (9H, s), 1.10–1.30 (1H, m), 0.90 (3H, d, $J=5.9$ Hz), 0.80–0.97 (1H, m); ^{13}C NMR δ 166.5, 155.9, 132.7, 130.6, 129.5, 128.3, 96.1, 96.0, 79.4, 79.0, 77.2, 65.8, 57.5, 56.0, 55.5, 55.4, 43.2, 42.0, 39.2, 38.4, 37.9, 37.0, 31.2, 30.5, 28.4, 27.8, 27.2, 18.4; IR (neat) 3378, 1714, 1698, 1517, 1454 cm^{-1}; EI MS *m/z* 575 (M^+); high-resolution mass *m/z* calcd for $C_{32}H_{49}NO_8$ (M^+) 575.3458. Found: 575.3453.

4.4.3. (2*S,3*S**,3a*R**,4*S**,5a*S**,7*S**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-2-hydroxymethyl-4,9-bis(methoxymethoxy)-7-methylperhydro-1*H*-cyclopenta[*c*]indene (25a).** A mixture of **24a** (0.081 g, 0.14 mmol) and 1 M NaOH (1 mL) in THF (1 mL)-MeOH (1 mL) was stirred at rt for 4 h. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried (K_2CO_3) and evaporated in vacuo to give an oily residue, which was purified by TLC (AcOEt/hexane=2:1) to furnish **25a** (0.060 g, 91%) as a colorless oil; ^{1}H NMR δ 5.00 (1H, br s), 4.72, 4.56 (each 1H, each d, $J=6.9$ Hz), 4.69, 4.64 (each 1H, each d, $J=6.3$ Hz), 4.10–4.18 (1H, m), 3.72 (1H, dd, $J=3.0$, 10.9 Hz), 3.59 (1H, dd, $J=5.0$, 10.9 Hz), 3.39, 3.38 (each 3H, each s), 3.29 (1H, dd, $J=3.6$, 11.9 Hz), 3.20–3.41 (1H, m), 3.03 (1H, dt, $J=6.6$, 13.5 Hz), 3.36 (1H, dd, $J=7.6$, 9.2 Hz), 2.01–2.39 (3H, m), 1.45–1.90 (10H, m), 1.44 (9H, s), 1.14 (1H, dt, $J=4.6$, 13.2 Hz), 0.89 (3H, d, $J=6.3$ Hz), 0.80–1.00 (1H, m); ^{13}C NMR δ 156.3, 96.2, 95.3, 80.2, 77.9, 65.3, 60.7, 55.8, 55.7, 55.1, 52.3, 45.3, 39.4, 38.8, 36.7, 36.2, 34.9, 32.7, 28.5, 26.8, 22.3; IR (neat) 3365, 1717, 1686, 1507, 1456 cm^{-1}; EI MS *m/z* 471 (M^+); high-resolution mass *m/z* calcd for $C_{25}H_{45}NO_7$ (M^+) 471.3196. Found: 471.3185.

4.4.4. (2*R,3*S**,3a*R**,4*S**,5a*S**,7*S**,9*R**,9a*S**)-3-*tert*-Butyloxycarbonylaminoethyl-2-hydroxymethyl-4,9-bis-(methoxymethoxy)-7-methylperhydro-1*H*-cyclopenta-[*c*]indene (25b).** A mixture of **24b** (0.207 g, 0.36 mmol) and 1 M NaOH (2 mL) in THF (2 mL)–MeOH (2 mL) was stirred at rt for 4 h. A work-up similar to that described above gave an oily residue, which was purified by column chromatography (AcOEt/hexane=1:3 then 2:1) to furnish **25b** (0.159 g, 93.7%) as a colorless oil; ^{1}H NMR δ 4.73, 4.59 (each 1H, each d, J=6.6 Hz), 4.65, 4.56 (each 1H, each d, J=6.3 Hz), 4.12 (1H, brt, J=5.3 Hz), 3.65 (2H, d, J=3.7 Hz), 3.36, 3.35 (each 3H, each s), 3.34 (1H, dd, J=3.6, 13.2 Hz), 3.01–3.26 (2H, m), 2.02–2.40 (5H, m), 1.40–1.90 (10H, m), 1.42 (9H, s), 1.17 (1H, dt, J=5.9, 13.9 Hz), 0.89 (3H, d, J=6.3 Hz), 0.80–0.96 (1H, m); ^{13}C-NMR δ 155.9, 96.0, 95.7, 79.3, 78.9, 78.5, 64.0, 57.8, 56.1, 55.7, 55.5, 45.0, 43.7, 39.5, 38.3, 37.8, 36.9, 33.0, 30.9, 28.5, 28.1, 27.0, 22.3; IR (neat) 3369, 1700, 1525, 1456 cm^{-1}; EI MS *m*/*z* 471 (M^+); high-resolution mass *m*/*z* calcd for $C_{25}H_{45}NO_7$ (M^+) 471.3196. Found: 471.3186.

4.4.5. (2*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*R**,11a*S**)-9-*tert*-Butyloxycarbonyl-1,6-bis(methoxymethoxy)-3-methylperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (26).** To a stirred solution of **25a** (0.0706 g, 0.15 mmol) and Et_3N (68 μL, 0.49 mmol) in CH_2Cl_2 (3 mL) was added at 0 °C MsCl (30 μL, 0.39 mmol). After stirring for 0.5 h, the mixture was diluted with Et_2O (4 mL) and the precipitate was filtered through a short pad of Celite 545. The filtrate was evaporated in vacuo to furnish a mesylate (0.130 g). Without purification, the mesylate was treated with *t*-BuOK (0.150 g, 1.34 mmol) in THF (3 mL) at 0 °C. After stirring for 0.5 h, the reaction was quenched with 1 M HCl. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried (K_2CO_3) and evaporated under reduced pressure to afford a residue, which was purified by TLC (Et_2O/hexane=1:1) to produce **26** (0.0627 g, 92.3%) as a colorless oil; ^{1}H NMR δ 4.71, 4.54 (each 1H, each d, J=6.9 Hz), 4.65, 4.57 (each 1H, each d, J=6.6 Hz), 4.10–4.30 (3H, m), 3.37, 3.36 (each 3H, each s), 3.30 (1H, dd, J=4, 11.9 Hz), 2.64 (1H, brd, J=11.7 Hz), 2.40 (1H, brd, J=11.1 Hz), 2.29 (1H, dd, J=7.9, 10.2 Hz), 2.03–2.17 (1H, m), 1.40–2.02 (9H, m), 1.45 (9H, s), 1.03–1.25 (2H, m), 0.89 (3H, d, J=6.3 Hz), 0.80–1.00 (2H, m); ^{13}C NMR δ 155.1, 95.8, 95.3, 79.2, 75.7, 57.8, 56.4, 55.7, 55.6, 49.7, 47.0, 45.4, 44.1, 43.8, 38.9, 38.3, 35.4, 32.5, 31.7, 28.5, 26.5, 22.2; IR (neat) 1695, 1451 cm^{-1}; EI MS *m*/*z* 453 (M^+); high-resolution mass *m*/*z* calcd for $C_{25}H_{43}NO_6$ (M^+) 453.3090. Found: 453.3081.

4.4.6. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*R**,11a*S**)-1,6-Bis(methoxymethoxy)-3,9-dimethylperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (27).** A suspension of **26** (0.0887 g, 0.20 mmol) and $LiAlH_4$ (0.0052 g, 0.14 mmol) in THF (10 mL) was refluxed for 4 h. The reaction was quenched with a saturated aqueous Na_2SO_4 solution. The precipitate was filtered through a short pad of Celite 545 and the filtrate was evaporated in vacuo to give **27** (0.0718 g, 99.9%) as a colorless oil; ^{1}H NMR δ 4.69, 4.41 (each 1H, each d, J=7.1 Hz), 4.63, 4.56 (each 1H, each d, J=6.6 Hz), 4.31 (1H, dd, J=6.3, 7.3 Hz), 3.84 (1H, t, J=5.6 Hz), 3.60–3.73 (2H, m), 3.37, 3.35 (each 3H, each s), 3.30 (1H, dd, J=4, 11.9 Hz), 2.97 (1H, dd, J=1.7, 10.2 Hz), 2.87 (1H, brd, J=11.6 Hz), 2.30 (1H, dd, J=7.9, 10.6 Hz), 2.29 (3H, s), 1.33–2.15 (10H, m), 1.10 (1H, dt, J=5.1, 13.3 Hz), 0.88 (3H, d, J=6.3 Hz), 0.80–1.00 (2H, m); ^{13}C NMR δ 95.8, 95.2, 79.1, 75.8, 61.6, 57.7, 56.6, 56.0, 55.8, 55.5, 47.2, 46.1, 45.4, 43.0, 39.0, 38.3, 35.9, 32.5, 31.5, 26.4, 22.3; IR (neat) 3402, 3213, 1455 cm^{-1}; EI MS *m*/*z* 367 (M^+); high-resolution mass *m*/*z* calcd for $C_{21}H_{37}NO_4$ (M^+) 367.2719. Found: 367.2719.

4.4.7. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*R**,11a*S**)-1,6-Dihydroxy-3,9-dimethylperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (28).** A solution of **27** (0.0447 g, 0.12 mmol) and 6 M HCl (2 mL) in THF (4 mL) was stirred at rt for 13 h. Then, a 3 M NaOH solution (6 mL) was added and the mixture was extracted with $CHCl_3$. The organic extracts were dried (K_2CO_3) and evaporated in vacuo to give **28** (0.0339 g, 99.8%) as colorless crystals; mp 220–222 °C; ^{1}H NMR δ 4.31 (1H, t, J=6.4 Hz), 3.49–3.59 (1H, m), 3.37 (1H, dd, J=3.6, 11.9 Hz), 3.21 (2H, s), 2.93 (1H, brd, J=8.3 Hz), 2.85 (1H, brd, J=11.9 Hz), 2.26 (3H, s), 1.12–2.22 (13H, m), 0.94–1.07 (1H, m), 0.82 (3H, d, J=6.3 Hz), 0.72–0.90 (2H, m); ^{13}C NMR δ 72.5, 70.5, 61.4, 58.3, 57.8, 47.0, 45.8, 44.9, 42.4, 41.1, 34.9, 32.5, 30.6, 29.8, 29.0, 26.7, 22.1; IR (KBr) 3424, 1457 cm^{-1}; EI MS *m*/*z* 279 (M^+); high-resolution mass *m*/*z* calcd for $C_{17}H_{29}NO_2$ (M^+) 279.2198. Found: 279.2199.

4.4.8. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*R**,11a*S**)-1-Hydroxy-3,9-dimethyl-6-*tert*-buyldimethylsilyoxyperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (29).** To a solution of **28** (0.0400 g, 0.014 mmol) and 2,6-lutidine (50 μL, 0.43 mmol) in THF (3 mL) was added at −78 °C TBSOTf (40 μL, 0.17 mmol). After the mixture was stirred for 1 h, the reaction was quenched with saturated $NaHCO_3$. The mixture was extracted with $CHCl_3$. The organic extracts were dried (K_2CO_3) and evaporated in vacuo to give a residue, which was purified by TLC to afford **29** (0.0243 g, 43.1%) as a colorless oil and unchanged **28** (0.0032 g, 8.0%); ^{1}H NMR δ 4.31 (1H, t, J=6.3 Hz), 3.43 (1H, dd, J=4.0, 11.9 Hz), 3.00–3.30 (2H, m), 2.50 (3H, s), 1.42–2.38 (15H, m), 0.87 (9H, s), 0.80–1.20 (6H, m), 0.03, 0.00 (each 3H, each s); IR (neat) 3389 cm^{-1}; EI MS *m*/*z* 393 (M^+); high-resolution mass *m*/*z* calcd for $C_{23}H_{43}NO_2Si$ (M^+) 393.3060. Found: 393.3054.

4.4.9. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*R**,11a*S**)-3,9-Dimethyl-1-oxo-6-*tert*-butyldimethylsilyoxyperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (30).** To a mixture of **29** (0.0148 g, 0.038 mmol) and $NaHCO_3$ (0.0194 g, 0.23 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C the Dess–Martin periodinane (0.0327 g, 0.077 mmol). After the mixture was stirred for 0.5 h and at rt for 0.5 h, the reaction was quenched with a 10% $Na_2S_2O_3$ solution. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried (K_2CO_3) and evaporated in vacuo to give a residue, which was purified by TLC ($CHCl_3$/MeOH=5:1) to give **30** (0.0118 g, 80.1%) as a colorless oil; ^{1}H NMR δ 4.16–4.21 (1H, m), 3.03–3.09 (2H, m), 2.93 (1H, dd, J=7.3, 9.9 Hz), 2.32 (3H, s), 1.51–2.58 (14H, m), 1.24–1.38 (2H, m), 0.97 (3H, d, J=6.3 Hz, Me), 0.87 (9H, s), 0.01, 0.00 (each 3H, each s); IR (neat) 1687 cm^{-1}; EI MS *m*/*z* 391 (M^+); high-resolution mass *m*/*z* calcd for $C_{23}H_{41}NO_2Si$ (M^+) 391.2903. Found: 391.2898.

4.4.10. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*R**,11a*S**)-3,9-Dimethyl-1-oxo-6-*tert*-butyldimethylsilyoxyperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (31).** To a stirred solution of diisopropylamine (15 μL, 0.11 mmol) in THF (0.3 mL) at −78 °C was added *n*-BuLi (45 μL, 0.07 mmol) and the mixture was stirred for 10 min. Then, a solution of **30** (0.0049 g, 0.013 mmol) in THF (0.2 mL) was added. After stirring for another 10 min, a solution of *N*-*tert*-butylbenzenesulfinimidoyl chloride (0.0169 g, 0.079 mmol) in THF (0.2 mL) was added. Then, the mixture was warmed up to 0 °C for 1 h and stirring was continued at the same temperature for 1 h. The reaction was quenched with water. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried (K_2CO_3) and evaporated in vacuo to give a residue, which was purified by TLC ($CHCl_3$/MeOH=5:1) to give **31** (0.0029 g, 59%) as an amorphous solid; ^{1}H NMR δ 5.82 (1H, s), 4.03–4.10 (1H, m), 2.75–2.83 (2H, m), 2.40–2.65 (4H, m), 2.22 (3H, s), 1.95–2.38 (5H, m), 1.90 (3H, s), 1.80–1.90 (1H, m), 1.48–1.68 (4H, m), 0.86 (9H, s), 0.02, 0.01 (each 3H, s); ^{13}C NMR δ 203.3, 158.6, 125.6, 72.3, 60.6, 59.0, 56.2, 55.1, 46.4, 42.4, 40.6, 40.1, 37.5, 37.0, 30.5, 26.3, 25.5, 24.5, 18.0, −4.6; MS *m*/*z* 389 (M^+); high-resolution mass *m*/*z* calcd for $C_{23}H_{39}NO_2Si$ (M^+) 389.2750, found: 389.2761.

4.4.11. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,11a*S**)-9-*tert*-Butyloxycarbonyl-1,2,3,4,4a,5,6,6a,6b,7,8,9-dodecahydro-1,6-bis(methoxymethoxy)-3-methylbenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (32).** A mixture of **25b** (0.100 g, 0.21 mmol) and Dess–Martin periodinane (0.180 g, 0.42 mmol) in CH_2Cl_2 (6 mL) was stirred at rt for 2 h. The reaction was quenched with a 10% $Na_2S_2O_3$ solution. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried and evaporated in vacuo to give a residue, which was purified by column chromatography (AcOEt/hexane=1:1) to give **32** (0.079 g, 82%) as colorless crystals; mp 91–92 °C; ^{1}H NMR δ 6.69, 6.57 (together 1H, each s), 4.54–4.73 (4H, m), 4.35–4.42 (1H, dt, *J*=2.3, 8.1 Hz), 3.92–4.11 (1H, m), 3.36 (6H, s), 3.29 (1H, dd, *J*=4, 11.5 Hz), 2.97–3.10 (1H. m), 2.74 (1H, br s), 2.55–2.61 (1H, m), 1.97–2.30 (5H, m), 1.48 (9H, s), 1.40–1.82 (3H, m), 1.07–1.31 (2H, m), 0.90 (3H, d, *J*=6.3 Hz), 0.78–0.95 (2H, m); ^{13}C NMR δ 152.4, 125.0, 124.2, 118.0, 117.6, 95.7, 95.5, 80.2, 57.1, 55.4, 43.2, 41.0, 38.2, 38.1, 36.5, 32.4, 33.2, 28.6, 28.4, 26.5, 22.2; IR (KBr) 1703, 1684, 1450 cm^{-1}; EI MS *m*/*z* 451 (M^+); high-resolution mass *m*/*z* calcd for $C_{25}H_{41}O_6N$ (M^+) 451.2931. Found: 451.2934.

4.4.12. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*S**,11a*S**)-9-*tert*-Butyloxycarbonyl-1,6-bis(methoxymethoxy)-3-methylperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (33).** To a stirred solution of **25b** (0.0454 g, 0.074 mmol) and Et_3N (36 μL, 0.26 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C MsCl (14 μL, 0.18 mmol). After stirring for 30 min, the mixture was diluted with Et_2O (2 mL) and the precipitate was filtered through a short pad of Celite 545. The filtrate was evaporated in vacuo to furnish a mesylate (0.073 g). Without purification, the mesylate was treated with *t*-BuOK (0.075 g, 0.67 mmol) in THF (2 mL) at 0 °C. After stirring for 0.5 h, the reaction was quenched with 1 M HCl. The mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried (K_2CO_3) and evaporated under reduced pressure to afford a residue, which was purified by TLC (Et_2O/hexane=1:1) to produced **33** (0.0407 g, 92.4%) as a colorless oil; ^{1}H NMR δ 4.76, 4.56 (each 1H, each d, *J*=6.9 Hz), 4.65, 4.57 (each 1H, each d, *J*=6.6 Hz), 4.11 (1H, dt, *J*=2.8, 4.5 Hz), 3.76–3.97 (2H, m), 3.36, 3.35 (each 3H, each s), 3.29 (1H, dd, *J*=3.5, 12 Hz), 3.06 (1H, dd, *J*=13.5, 13.4 Hz), 2.69 (1H, brt, *J*=12 Hz), 1.97–2.18 (3H, m), 1.74–1.93 (3H, m), 1.10–1.70 (8H, m), 1.45 (9H, s), 0.89 (3H, d, *J*=6.3 Hz), 0.80–0.96 (1H, m); ^{13}C NMR δ 155.6, 95.8, 95.4, 78.8, 78.5, 78.4, 58.6, 56.3, 55.8, 55.4, 43.1, 38.9, 38.2, 37.3, 36.9, 33.3, 29.2, 28.5, 27.2, 27.8, 22.3; IR (neat) 1693, 1425 cm^{-1}; EI MS *m*/*z* 453 (M^+); high-resolution mass *m*/*z* calcd for $C_{25}H_{43}NO_6$ (M^+) 453.3090. Found: 453.3081.

4.5. Reduction of 32 to 33

(a) With PtO_2. A suspension of **32** (0.0135 g, 0.03 mmol) and PtO_2 (0.0013 g) in MeOH (1 mL) under an H_2 atmosphere was stirred at rt for 29 h. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to give oily **33** (0.0135 g, 99.6%), of which the ^{1}H NMR spectrum was identical with that of **33** obtained directly from **25b**.

(b) With 10% Pd/C. A suspension of **32** (0.0136 g, 0.03 mmol) and 10% Pd/C (0.0014 g) in MeOH (1 mL) under an H_2 atmosphere was stirred at rt for 9 h. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to give oily **33** (0.0124 g, 91.2%), of which the ^{1}H NMR spectrum was identical with that of **33** obtained directly from **25b**.

4.5.1. (1*R,3*S**,4a*S**,6*S**,6a*R**,6b*S**,10a*S**,11a*S**)-1,6-Bis(methoxymethoxy)-3,9-dimethylperhydrobenzo[3*a*,4]pentaleno[2,1-*c*]pyridine (35).** A suspension of **33** (0.0135 g, 0.03 mmol) and $LiAlH_4$ (0.006 g, 0.16 mmol) in THF (2 mL) was refluxed for 2 h. The reaction was quenched with a saturated aqueous Na_2SO_4 solution. The precipitate was filtered through a short pad of Celite 545 and the filtrate was evaporated in vacuo to give **35** (0.010 g, 91%) as a colorless oil; ^{1}H NMR δ 4.76, 4.55 (each 1H, each d, *J*=6.9 Hz), 4.63, 4.56 (each 1H, each d, *J*=6.6 Hz), 4.07–4.11 (1H, m), 3.35, 3.33 (each 3H, each s), 3.29 (1H, dd, *J*=3.6, 11.9 Hz), 2.60–3.27 (1H, m), 2.18 (3H, s), 1.11–2.19 (16H, m), 0.87 (3H, d, *J*=6.3 Hz), 0.77–0.93 (1H, m); ^{13}C NMR δ 95.9, 95.2, 77.9, 56.6, 56.1, 55.9, 55.6, 53.9, 45.8, 43.7, 38.5, 37.9, 37.4, 35.1, 32.8, 31.1, 30.1, 29.7, 27.0, 25.5, 22.3; EI MS *m*/*z* 367 (M^+); high-resolution mass *m*/*z* calcd for $C_{21}H_{37}NO_4$ (M^+) 367.2719. Found: 367.2733.

4.6. Reduction of 32 to 35 via enamine (34)

A suspension of **32** (0.0090 g, 0.02 mmol) and $LiAlH_4$ (0.0040 g, 0.11 mmol) in THF (1 mL) was refluxed for 5 h. The reaction was quenched with a saturated aqueous Na_2SO_4 solution. The precipitate was filtered through a short pad of Celite 545 and the filtrate was evaporated in vacuo to give **34** (0.0069 g) as an oil; ^{1}H NMR δ 5.59 (1H, br s), 4.67, 4.51 (each 1H, each d, *J*=6.9 Hz), 4.60, 4.57 (each 1H, each d, *J*=6.6 Hz), 4.31–4.39 (1H, m), 3.65–3.70 (1H, m), 3.34, 3.33 (each 3H, each s), 3.25 (1H, dd, *J*=4.0, 11.9 Hz), 2.46–2.95 (4H, m), 2.48 (3H, s), 1.04–2.30 (10H,

m), 0.87 (3H, d, $J=6.3$ Hz), 0.84–0.88 (1H, m). A suspension of the enamine (**34**) and 10% Pd/C (0.0010 g) in MeOH (1 mL) under an H_2 atmosphere was stirred for 3 h. After the catalyst was removed by filtration, the filtrate was evaporated under reduced pressure to give oily **35** (0.0068 g, 93%), of which the ^{1}H NMR spectrum was identical with that of **35** obtained directly from **33**.

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Octaalkylphthalocyaninato ruthenium(II) complexes with mixed axial ligands and supramolecular porphyrin:phthalocyanine structures derived from them

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Abstract—Complementary syntheses of 1,4,8,11,15,18,22,25-octakis(alkyl) substituted ruthenium phthalocyanines, in which either one or two axial ligands can be added, are described. Their utility in the preparation of further (pyridyl) ligated derivatives has been shown to be straightforward. The chemistry is sufficiently robust and efficient to permit elaborate, supramolecular complexes to be prepared, as demonstrated by the synthesis of porphyrin–phthalocyanine multichromophore arrays.

1. Introduction

Phthalocyanines (Pcs) are a widely studied class of organic chromophores.[1] They have proved useful for a variety of applications ranging from molecular electronics to medicine.[2] Their utility derives, in part, from the ease with which their properties (solubility, electronic absorption, fluorescence, self-assembly etc.) can be modified through synthetic manipulation. Syntheses of new Pcs typically concentrate on a combination of modifications of the benzenoid substituents and variation of the central metal ion (Fig. 1). With regard to metal ion insertion, attention has focused most extensively on metal(II) derivatives and metal(III) derivatives, the latter providing a further site for incorporation of a substituent as an axial ligand.[2]

Among M(II) metallated phthalocyanines, ruthenium(II) phthalocyanines have received relatively limited study but are of interest for a number of reasons. Non-ligated derivatives are hard to access[3–5] and most attention has focused on the merits of either single or double axial ligation. The latter provides a ligand both above and below the ring and the more common examples are those where the two ligands are the same. Examples have been exploited,

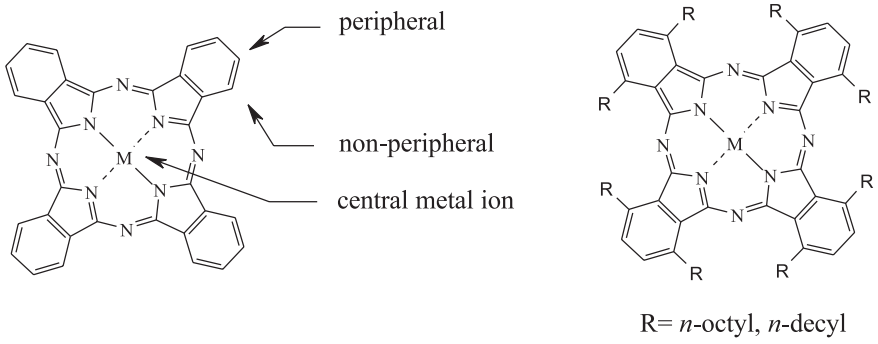

Figure 1. The left hand side structure shows the general phthalocyanine structure and derivatisation available through metal ion insertion and substitution, the latter at so-called 'peripheral' and 'non-peripheral' (1,4,8,11,1,5,18,22,25) sites on the benzenoid rings. The right hand side structure shows the 1,4,8,11,15,18,22,25-octakis(alkyl)phthalocyanines that are the subject of the present paper.

Keywords: Ruthenium; Phthalocyanine; Porphyrin; Supramolecular arrays.
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particularly by Hanack and co-workers,[3,4] in developing polymeric structures using bidentate ligands such as unsubstituted and substituted *p*-diisocyanobenzenes to form so-called 'shish-kebab' polymers. Less complex structures have received attention in the light of their potential application as the photosensitising molecular element of photovoltaic cells based on nanocrystalline TiO_2.[6,7] Derivatives bearing two different ligands can be more difficult to access[7,8] but sometimes have been favoured as precursors to those having two identical ligands.[8]

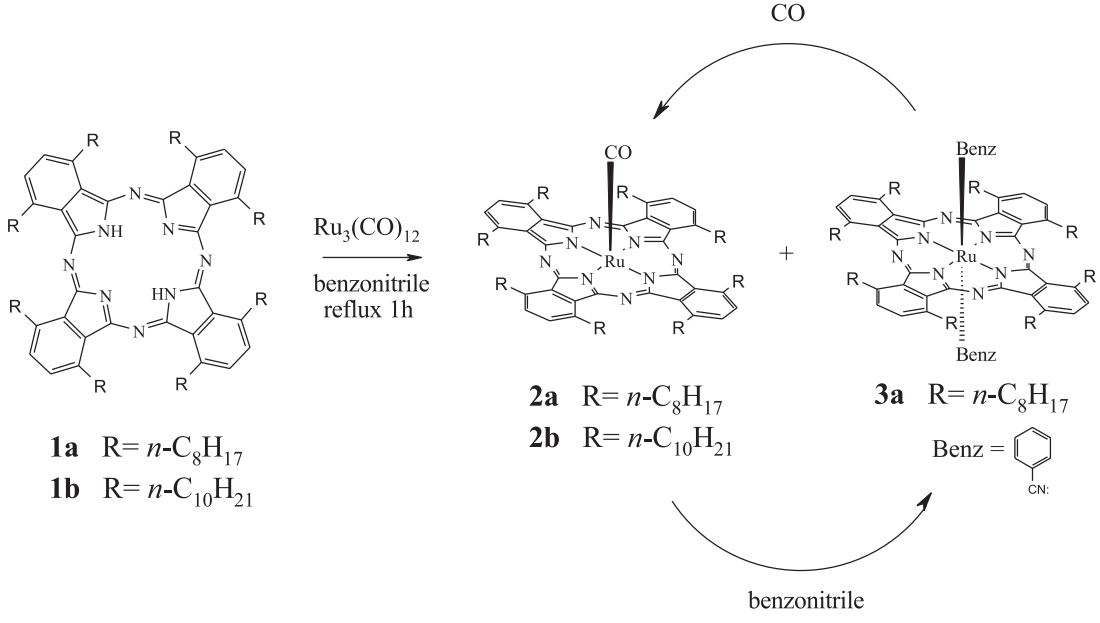
We have for some time been interested in the synthesis and properties of Pcs bearing eight alkyl substituents at the non-peripheral (1,4,8,11,15,18,22,25) positions (Fig. 1).[9] Derivatives of this general structure are particularly interesting because they show good solubility in organic solvents and their tendency to aggregate in solution is much less than that of their peripherally substituted counterparts. Furthermore, introduction of substituents onto these positions leads to interesting red-shifted absorption spectra.[10,11] These properties are advantageous for device and other applications. In the present work we have focused our attention on the incorporation of ruthenium as the metal centre into the cavity of non-peripheral octaalkyl substituted phthalocyanines and in particular on developing an efficient, direct synthesis for these compounds. In doing so, we have identified convenient methods for preparing doubly ligated derivatives bearing either two identical or non-identical ligands. These findings have been exploited to synthesise novel mixed porphyrin–phthalocyanine arrays.[12]

2. Discussion

In general, metallated phthalocyanines are prepared by two methods: (i) cyclotetramerisation of a phthalic acid derivative (such as a phthalonitrile or diiminoisoindolene) in the presence of a metal salt, (ii) insertion of the desired metal ion into the preformed phthalocyanine ring either as its metal-free or dilithiated derivative. The more commonly used method for the preparation of ruthenium phthalocyanine derivatives has tended to be the former.

Despite this, we have focused our efforts on the second protocol, selecting metal-free octaalkyl Pcs (**1**) as starting materials.[13] Two ruthenium reagents frequently used for the synthesis of ruthenium phthalocyanines are $RuCl_3$ and $Ru_3(CO)_{12}$. We have investigated both but have favoured the latter. In initial experiments, **1a** was treated with $Ru_3(CO)_{12}$ in refluxing benzonitrile and we were pleased to observe efficient and rapid metallation of the Pc. Work-up and characterisation of the isolated product, however, indicated it to comprise a mixture of two ruthenium Pcs. These were identified by ^{1}H NMR spectroscopy as **2a** and **3a** and we believe the formation of such a mixture is unprecedented. This somewhat serendipitous observation inspired a careful examination of the experimental conditions in order to devise exclusive syntheses of the two derivatives (which we anticipated to have complementary coordination properties). Synthesis of either material can, in fact, be easily achieved, Scheme 1. Careful control of the reaction time permits the initially formed **2a** to be isolated in yields $>90\%$. A similar result was obtained for the conversion of **1b** into **2b**. It was also found that treatment of a reaction mixture containing both **2a** and **3a** with CO leads exclusively to the former. On the other hand, prolonged heating of the reaction of **1a** with $Ru_3(CO)_{12}$ in benzonitrile under a stream of nitrogen leads smoothly to **3a** in 71% yield. All compounds were purified by flash chromatography and isolated by reprecipitation.

The mono carbonyl and dibenzonitrile ligated compounds are readily distinguishable by ^{1}H NMR spectroscopy. The two sides of the phthalocyanine ring of compounds **2a** and **2b** are different by virtue of the single ligand and thus



Scheme 1. The direct, complementary syntheses of two non-peripherally substituted ruthenium phthalocyanines.

methylene protons within the side chains are diastereotopic. The non-equivalence that follows from this is manifested most clearly by the signals for the benzylic protons which partially overlap. Signals appear at ca. 4.9 ppm as a multiplet. On the other hand, **3a** is a symmetrical compound and the benzylic protons appear as a triplet. Moreover, a set of three signals due to the aromatic protons of the benzonitrile ligands is also apparent. These are shielded by the phthalocyanine ring and are found at 5.9, 5.6 and 4.45 ppm.

Differences in the lability of the ligands during FAB mass spectrometry measurements is evident from the fact that **2a** yielded a molecular ion peak, whereas **3a** did not. The latter showed a peak corresponding to unligated ruthenium phthalocyanine indicating that the benzonitrile ligands were lost under the conditions of the measurement. Both compounds exhibit a blue shift of the intense visible region absorption, the Q-band, relative to their metal-free precursors (from 730 to ca. 660–670 nm). Metallation of phthalocyanines often results in a blue shift but seldom of this magnitude.

3. Complexation chemistry

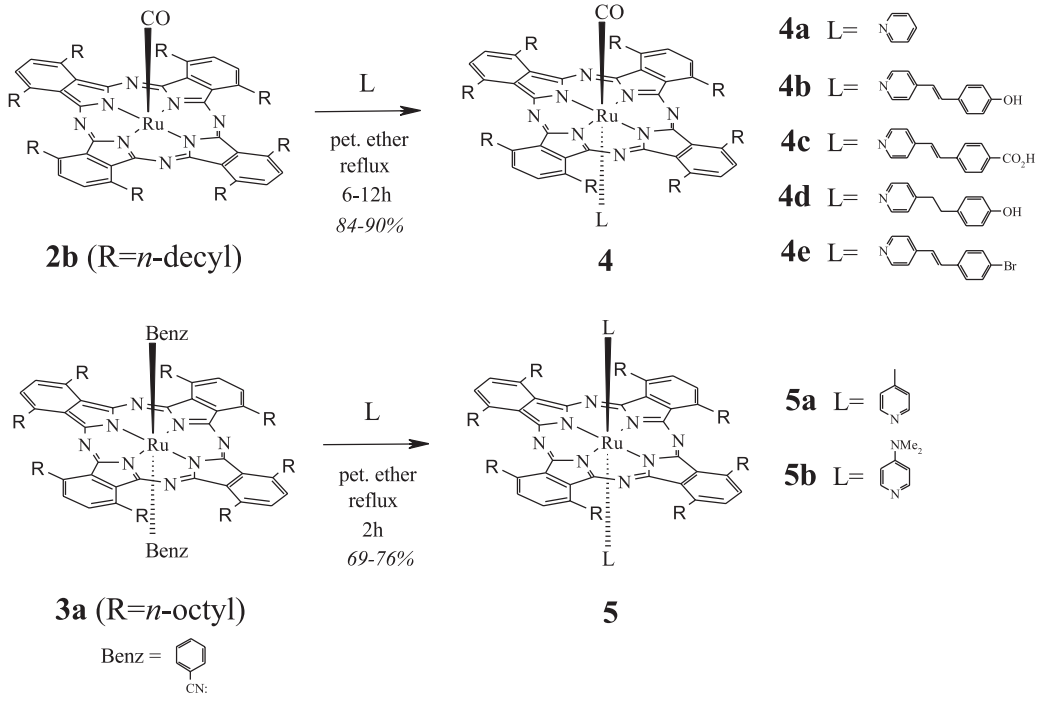
Various pyridine ligands were employed in the investigation of the coordination chemistry of the new ruthenium Pcs. Treatment of **2b** with a pyridine derivative (1 equiv) in petroleum ether at reflux (40–60 °C) for 45 min resulted in smooth formation of the complexes **4a**–**e** which were purified by reprecipitation (Scheme 2). It is worth noting that the complexes are stable to prolonged treatment with excess ligand under the same conditions. This further exemplifies the strength of the metal–carbonyl bond. Following complexation, the molecule remains unsymmetrical with the binding of two different ligands. Besides the presence of the peaks attributable to the added ligand, the ^{1}H NMR spectroscopic signals from the diastereotopic benzylic protons show distinctive chemical shift differences. As observed earlier, the ligand protons closest to the phthalocyanine ring undergo an upfield shift. The ^{13}C NMR spectroscopic signals were fully consistent with the structures. We obtained the (small) molecular ion peaks in the FAB MS for only **4b**,**c** and **e**; the other compounds failed to show molecular ion peaks but rather showed those from fragmentation corresponding to **2b** and the unligated ruthenium phthalocyanine.

Compound **3a** has two labile ligands and, unsurprisingly, reacts readily with 2 equiv of (pyridine) ligand to give complexes **5a**–**b**. It is interesting to note that the ‘intermediate’ bearing one benzonitrile ligand and one pyridine ligand on the metal was never detected and reaction of **3a** with 1 equiv of ligand led to a 1:1 mixture of **3a** and **5** (Scheme 2).

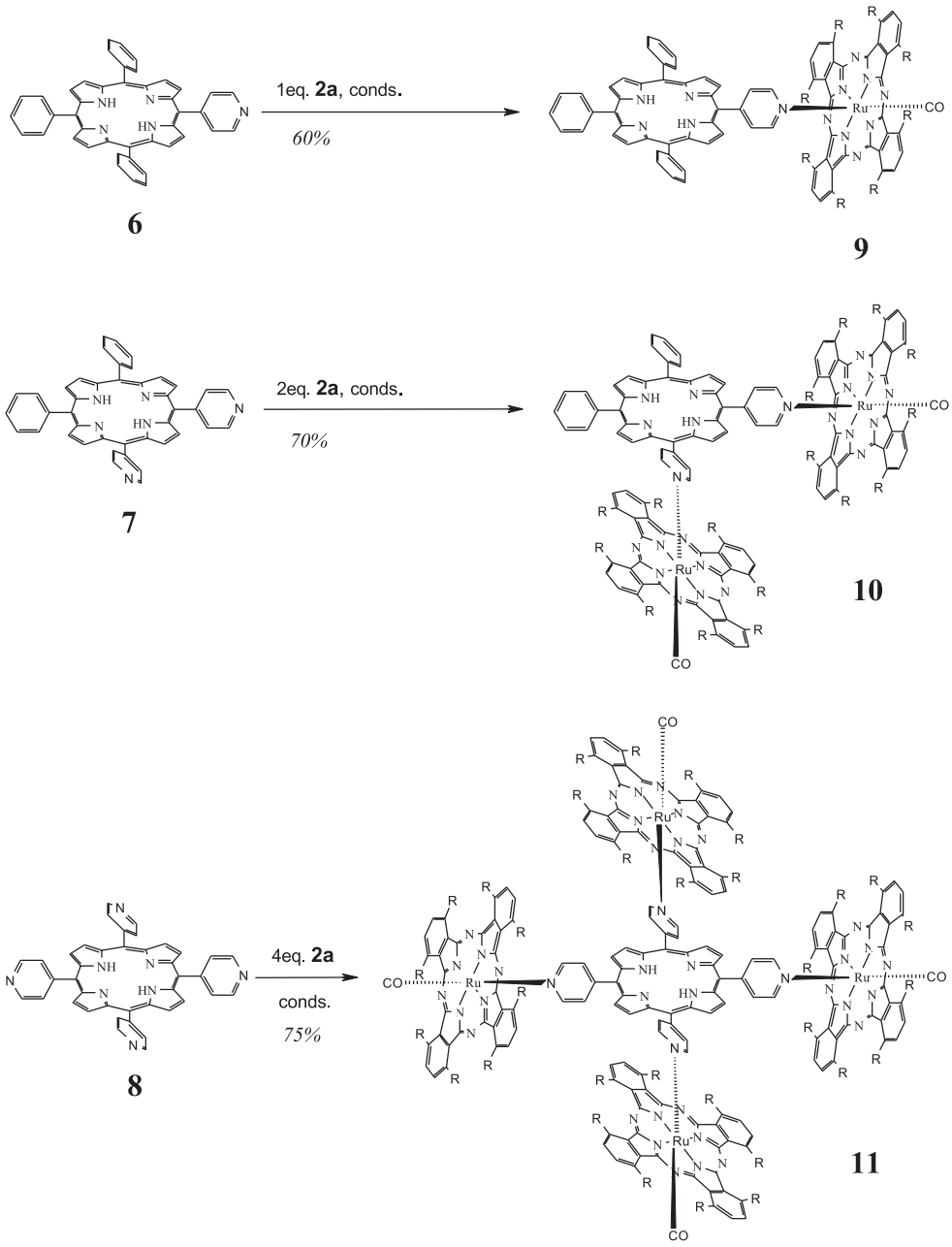
Compounds **5a** and **5b** are symmetrical molecules and as such the benzylic protons appear as a triplet in the ^{1}H NMR spectra. The signals attributable to the ligands are well-defined and shifted upfield. The effect of the phthalocyanine ring current extends as far as the methyl substituent on the pyridine ligand in **5a** which is shifted to 0.38 ppm. The UV–vis spectra show absorption maxima at 645 and 643 nm for **5a** and **5b** respectively, the most blue shifted examples in the series.

4. Multichromophore arrays

The level of synthetic control possible in these ruthenium Pcs permits their exploitation as useful building-blocks for



Scheme 2. Formation of complexes **4a**–**e** from **2b** and **5a**–**b** from **3a**.

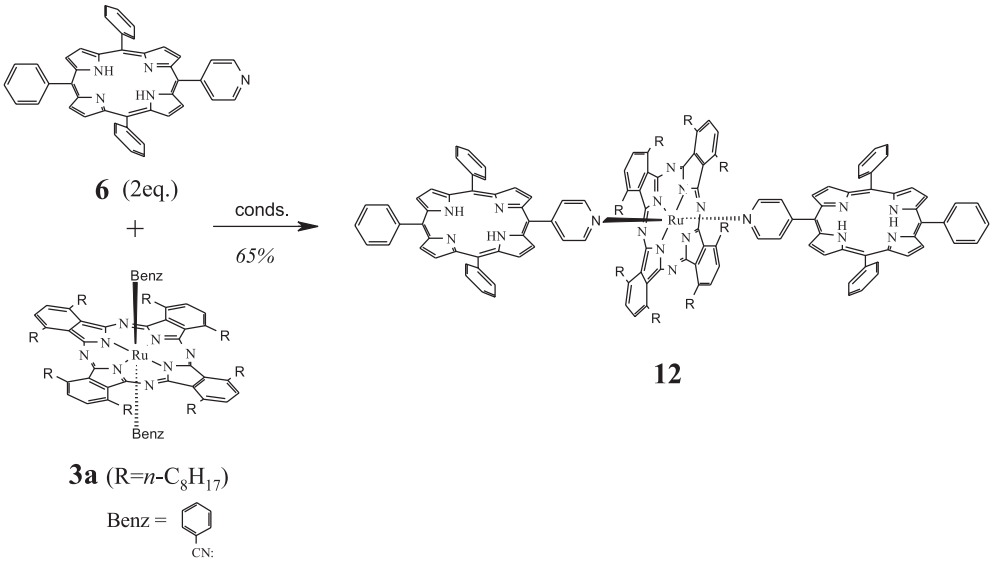


Scheme 3. Synthesis of multichromophore arrays **9**, **10** and **11** by reaction of **2a** (R = *n*-C_8H_{17}) with **6**, **7**, and **8** respectively. Conditions: pet. ether/CH_2Cl_2, reflux 24 h.

more adventurous supramolecular targets. Multichromophore supramolecular arrays[14] are particularly interesting from both a synthetic point of view and, in terms of potential applications, in optical devices and light harvesters etc. The complementary coordination chemistry of **2a** and **2b** has therefore been employed, in conjunction with porphyrins bearing one, two or three pyridine substituents at the meso sites, to access 'first generation' porphyrin–phthalocyanine (Pn/Pc) arrays.

The porphyrin starting materials were prepared by a simple mixed condensation reaction[15] between pyrrole, benzaldehyde and pyridine-4-carbaldehyde, followed by chromatographic separation of the products. Synthesis of the simplest 1:1 Pn/Pc **9** system was achieved by the smooth reaction of **2a** with monopyridylporphyrin **6** in an analogous fashion to the synthesis of the simple pyridyl ruthenium Pcs of type **4**. Similarly, reaction with di- and tetrapyridylporphyrins yielded the more complex arrays **10** and **11** (Scheme 3). The complementary 2:1 Pn/Pc complex **12** was prepared using **3a** in conjunction with monopyridylporphyrin (Scheme 4). Formation of the arrays was monitored by tlc and confirmation of products by ^{1}H NMR spectroscopy.

Indeed, characterisation of the Pn/Pc arrays centred primarily on ^{1}H NMR spectroscopy. Each compound showed features already identified earlier for the simpler pyridine ligated compounds. The significant upfield shifts for protons which become located in the powerful shielding



Scheme 4. Complementary synthesis of the 1:2 array **12** from **3a**. Conditions: pet. ether/CH_2Cl_2, reflux 6 h.

region above/below the RuPc moiety proved a particularly important aid for confirming structures. For example, the characteristic singlet from the β-pyrrolic protons on the central porphyrin of **11** is shifted more than 3 ppm to $\delta =$ 5.9 ppm on formation of the complex. These signals, combined with the characteristic pyridyl proton signals (shifted to ca. 4.6 and 2.6 ppm), confirm the formation of the arrays unambiguously. FAB mass spectrometry delivered results that corresponded with trends observed for the simpler ligated complexes of the ruthenium phthalocyanines. Indeed, a molecular ion was observed only in the case of **6a**. In other cases spectra showed signals for the fragmented molecules. Satisfactory ^{13}C NMR spectra were likewise difficult to obtain due to their expected complexity and the weakness of the signals due to quarternery carbons (not resolved even after >4000 scans). In the case of **12**, some decomposition of the material was also evident after long acquisitions.

The absorption spectra of the arrays are essentially composites of the starting materials (or more accurately composites of the porphyrin starting material and the corresponding simple $RuPc(L)_x$ complex). Thus there are intense absorptions attributable to the Q-band of the phthalocyanine moiety in the 660–670 nm region and to the Soret band of the porphyrin chromophore in the 419–423 nm region. These indicate that there is little ground state electronic interaction between the (perpendicular) π-systems.

5. Conclusions

The attempted synthesis of ruthenium metallated derivatives of 1,4,8,11,15,18,22,25-octakis(alkyl)phthalocyanines using $Ru_3(CO)_{12}$ in benzonitrile afforded ruthenium phthalocyanines either mono-ligated with CO or di-ligated with benzonitrile. Conditions have been established to prepare both selectively. Their utility in the preparation of further (pyridyl) ligated derivatives has been shown to be straightforward. The chemistry is sufficiently robust and efficient to permit elaborate, supramolecular complexes to be prepared, as demonstrated by the synthesis of porphyrin–phthalocyanine multichromophore arrays. These heterochromophore structures thus complement those reported, for example, by Sanders et al.[14a] which contain solely porphyrin moieties, the present work providing derivatives with complementary red and violet absorbing chromophoric units.

6. Experimental

6.1. General

^1H NMR spectra were recorded at 270 MHz on a Jeol EX270 FT, at 300 MHz on a Varian 300 and at 400 MHz on a Varian unity plus spectrometer. Signals are quoted in ppm as δ downfield from tetramethylsilane (δ 0.00) as internal standard. ^{13}C NMR spectra were recorded at 67.9, 75.4 or 100 MHz on the same spectrometers, respectively. IR spectra were recorded on a Perkin–Elmer 1720X FT-IR spectrophotometer as neat liquid films or nujol mulls for solid materials. UV–visible spectra were recorded on a Hitachi U-3000-X spectrometer.

Elemental analyses were performed by Mr A. W. R. Saunders at the University of East Anglia and are quoted to the nearest 0.01%. Mass spectra were obtained via the EPSRC National Mass Spectroscopy Service Centre at the University of Wales at Swansea. Melting points are uncorrected and recorded using a Kofler hot-stage melting point apparatus with a digiton model 2751-K display.

Reaction solvents were dried and distilled prior to use following standard procedures. Other solvents were SLR-grade and used without drying, unless stated otherwise.

Compounds **1a** and **1b**[13] and the pyridyl porphyrin derivatives **6**, **7**, and **8**[15] were prepared according to published literature procedures.

6.1.1. Mono-carbonyl ligated complexes 2. *Compound* **2a**. To a flame dried flask under a nitrogen atmosphere was added **1a** (0.49 g, 0.35 mmol) and triruthenium dodecacarbonyl (0.45 g, 0.70 mmol). Benzonitrile (20 mL, 195.88 mmol) was added and the reaction mixture was heated at reflux for 100 min. The cooled reaction mixture was poured onto cold methanol (400 mL) causing the formation of some crystals. After cooling at 5 °C for a further 12 h the excess solvent was decanted. The crude product was purified by a flash column chromatography (eluting with methanol to remove benzonitrile and then with petroleum ether (40–60 °C)). Reprecipitation (petroleum ether–methanol) gave the title compound as a dark blue, amorphous solid (0.54 g, 96%). IR (neat)/cm^{-1} 1966 (carbonyl). δ_H (300 MHz, C_6D_6) 7.89 (s, 8H), 4.93–4.79 (m, 16H), 2.38–2.52 (m, 16H), 1.79–1.90 (m, 16H), 1.45–1.21 (m, 64H), 0.82 (t, 24H, $J=6.9$ Hz). δ_C (67.94 MHz, C_6D_6) 183.1, 145.75, 138.36, 137.34, 130.38, 33.24, 32.36, 31.55, 30.51, 29.88, 29.84, 23.04, 14.30. UV–vis (petroleum ether) $\lambda_{max/nm}$ (log ε) 669 (4.62); FAB MS 1539 (M^+).

Compound **2b**. This was prepared as above from **1b** to give the product as a dark blue, amorphous solid (0.50 g, 81%). IR (neat)/cm^{-1} 1966 (carbonyl). δ_H (270 MHz, C_6D_6) 7.90 (s, 8H), 4.78–5.02 (m, 16H), 2.39–2.52 (m, 16H), 1.79–1.90 (m, 16H), 1.1–1.5 (m, 88H), 0.86 (t, 24H, $J=6.6$ Hz). δ_C (67.94 MHz, C_6D_6) 182.9, 145.58, 138.40, 137.84, 130.29, 33.24, 32.38, 31.61, 30.69, 30.31, 30.24, 29.99, 29.86, 23.16, 14.43. UV–vis (THF) $\lambda_{max/nm}$ 676.

6.1.2. Bis-benzonitrile ligated complex 3a. To a flame dried flask under a nitrogen atmosphere was added **1a** (0.49 g, 0.35 mmol) and triruthenium dodecacarbonyl (0.45 g, 0.70 mmol). Benzonitrile (20 mL, 195.88 mmol) was added and the reaction mixture was heated at rapid reflux for 21 h. The cooled reaction mixture was poured onto cold methanol (500 mL) and left at 5 °C for a further 65 h. The excess solvent was decanted and the crude product was purified by a flash column chromatography (eluting with methanol to remove benzonitrile and then with petroleum ether (40–60 °C)). Reprecipitation (petroleum ether–ethanol) gave the title compound as a dark blue, amorphous solid (0.40 g, 71%). δ_H (300 MHz, C_6D_6) 7.82 (s, 8H), 5.91 (2H, t, $J=7.4$ Hz), 5.61 (4H, m), 4.96 (16H, t, $J=7.0$ Hz), 4.45 (4H, d, $J=7.4$ Hz), 2.44–2.51 (m, 16H), 1.79–1.85 (m, 16H), 1.44–1.18 (m, 64H), 0.90 (t, 24H, $J=6.9$ Hz). UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 658 (4.34).

6.1.3. Mono-pyridyl/mono-carbonyl ligated complexes 4. *General procedure*. Compound **2b** (0.10 g, 0.06 mmol) and ligand (1 equiv, 0.06 mmol) were dissolved in petroleum ether and the resulting mixture was heated at reflux for 6–12 h. The reaction mixture was allowed to cool and the solvent was removed in vacuo. The product was purified by column chromatography over silica using petroleum ether (40–60 °C) first as eluent to remove some impurities. The eluent was changed to petroleum ether (40–60 °C)–CH_2Cl_2 (10:1) to yield a dark blue solid which was reprecipitated several times from petroleum ether:methanol (10:1) affording the pure complex **4** as a dark blue, amorphous solid.

Compound **4a**. 94 mg, 90%. Found: C, 76.68; H, 10.01; N, 6.6%. $C_{118}H_{181}N_9ORu$ requires: C, 76.91; H, 9.89; N, 6.84%. δ_H (400 MHz, C_6D_6) 7.88 (s, 8H), 4.93 (m, 8H), 4.83 (m, 9H), 4.10–4.14 (m, 2H), 2.40–2.45 (m, 16H), 2.20–2.21 (m, 2H), 1.81–1.86 (m, 16H), 1.46–1.15 (m, 96H), 0.88 (t, 24H, $J=6.4$ Hz). δ_C (100 MHz, C_6D_6) 145.46, 143.95, 138.3, 137.73, 130.19, 122.34, 33.13, 32.29, 31.49, 30.57, 30.19, 30.12, 29.85, 29.76, 23.07, 14.34. UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 671 (5.04). FAB MS 1764 (M^+-L).

Compound **4b**. 98 mg, 89%. IR (neat)/cm^{-1} 1980. δ_H (300 MHz, C_6D_6) 7.88 (s, 8H), 6.56 (d, 2H, $J=7.0$ Hz), 6.16 (d, 2H, $J=7.0$ Hz), 5.54 (d, 1H, $J=16.8$ Hz), 5.02–4.79 (m, 17H), 4.14 (d, 2H, $J=6.2$ Hz), 2.41–2.47 (m, 16H), 2.08 (d, 2H, $J=6.2$ Hz), 1.80–1.90 (m, 16H), 1.36–1.10 (m, 96H), 0.86 (t, 24H, $J=6.4$ Hz). δ_C (67.94 MHz, C_6D_6) 181.11, 145.47, 143.89, 138.29, 137.82, 130.16, 129.21, 128.85, 128.01, 122.04, 120.45, 119.35, 115.75, 33.23, 32.36, 31.61, 30.65, 30.26, 30.20, 29.82, 23.10, 14.35. UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 667 (4.79). FAB MS 1960 (M^+), 1763 (M^+-L).

Compound **4c**. 101 mg, 90%. IR (neat)/cm^{-1} 1984, 1743, 1603. δ_H (270 MHz, C_6D_6) 7.87 (s, 8H), 7.66 (d, 2H, $J=8.6$ Hz), 6.44 (d, 2H, $J=8.6$ Hz), 5.78 (s, 1H), 5.30 (d, 1H, $J=16.1$ Hz), 5.06–4.86 (m, 9H), 4.85–4.75 (m, 8H), 4.03 (d, 2H, $J=6.9$ Hz), 2.38–2.45 (m, 16H), 2.07 (d, 2H, $J=6.9$ Hz), 1.78–1.90 (m, 16H), 1.48–1.10 (m, 96H), 0.84 (t, 24H, $J=6.2$ Hz). δ_C (67.94 MHz, C_6D_6) 181.31, 164.29, 144.48, 144.19, 142.77, 140.12, 138.28, 137.75, 132.63, 130.48, 130.22, 129.20, 126.58, 125.88, 119.75, 33.15, 32.27, 31.54, 30.57, 30.19, 30.12, 29.88, 29.74, 23.04, 14.30. UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 671 (4.22). FAB MS 1987 (M^+), 1763 (M^+-L).

Compound **4d**. 97 mg, 89%. Found: C, 77.12; H, 10.04; N, 6.08%. $C_{126}H_{189}N_9RuO_2$ requires: C, 77.09; H, 9.70; N, 6.42%. IR (neat)/cm^{-1} 3429, 1980. δ_H (300 MHz, C_6D_6) 7.86 (s, 8H), 6.06 (d, 2H, $J=7.8$ Hz), 5.87 (d, 2H, $J=7.8$ Hz), 5.01–4.89 (m, 8H), 4.88–4.74 (m, 8H), 3.94 (d, 2H, $J=5.7$ Hz), 2.43 (q, 16H, $J=7.2$ Hz), 2.0 (d, 2H, $J=5.7$ Hz), 1.90–1.78 (m., 16H), 1.47–1.03 (m, 100H), 0.88 (t, 24H, $J=6.3$ Hz). δ_C (67.94 MHz, C_6D_6) 181.07, 154.62, 150.36, 145.46, 143.57, 138.30, 137.8, 131.21, 130.16, 128.67, 122.74, 115.00, 35.90, 33.80, 33.15, 32.31, 31.52, 30.60, 30.22, 30.15, 29.88, 29.78, 23.07, 14.33. UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 667 (4.35).

Compound **4e**. 96 mg, 84%. IR (neat)/cm^{-1} 1981, 1608. δ_H (300 MHz, C_6D_6) 7.89 (s, 8H), 6.93 (d, 2H, $J=8.2$ Hz), 6.29 (d, 2H, $J=8.2$ Hz), 5.35 (d, 1H, $J=16.2$ Hz), 5.01–4.78 (m, 17H), 4.11 (d, 2H, $J=6.9$ Hz), 2.45 (q, 16H, $J=7.2$ Hz), 2.13 (d, 2H, $J=6.9$ Hz), 1.92–1.78 (m., 16H), 1.43–1.20 (m, 96H), 0.86 (t, 24H, $J=6.3$ Hz). δ_C (67.94 MHz, C_6D_6) 181.17, 145.48, 144.19, 143.22, 138.30, 137.76, 134.13, 132.85, 131.95, 130.19, 123.78, 123.10, 119.57, 33.14, 32.29, 31.52, 30.57, 30.17, 30.122, 29.87, 29.75, 23.04, 14.31. UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 671 (4.18). FAB MS 2022 (M^+), 1763 (M^+-L).

6.1.4. Bis-pyridyl ligated complexes 5. *General procedure*. Compound **3a** (200 mg, 0.12 mmol) was refluxed in petroleum ether (40–60 °C, 40 mL) in the presence of excess pyridyl ligand (1.2 equiv, 0.15 mmol) for 2 h. The mixture was washed with aq HCl (20%), brine, dried

($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by chromatography over silica (eluent: petroleum ether 40–60 °C/CH_2Cl_2 3:1) to yield the pure product.

Compound **5a**. Dark blue amorphous solid (150 mg, 76%). Found: C, 76.12; H, 9.38; N, 7.90%. $C_{108}H_{158}N_{10}Ru$ requires: C, 76.41; H, 9.38; N, 8.25%. δ_H (400 MHz, C_6D_6) 7.76 (s, 8H), 4.88 (t, 16H, $J=6.8$ Hz), 3.92 (d, 4H, $J=5.6$ Hz), 2.56 (d, 4H, $J=5.6$ Hz), 2.41–2.48 (m, 16H), 1.79–1.87 (m, 16H), 1.38–1.46 (m, 16H), 1.20–1.30 (m, 48H), 0.85 (t, 24H, $J=6.4$ Hz), 0.39 (s, 6H). δ_C (100 MHz, C_6D_6) 149.12, 144.98, 143.96, 138.9, 137.46, 129.26, 123.19, 33.07, 32.36, 31.65, 30.6, 30.18, 29.84, 23.04, 14.33. UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 645 (4.53).

Compound **5b**. Dark blue microcrystalline solid (155 mg, 69%). Mp 133 °C. Found: C, 75.25; H, 9.52; N, 9.38%. $C_{108}H_{164}N_{12}Ru$ requires: C, 74.86; H, 9.55; N, 9.71%. δ_H (270 MHz, C_6D_6) 7.76 (s, 8H), 4.91 (t, 16H, $J=6.9$ Hz), 3.35 (d, 4H, $J=7.3$ Hz), 2.52 (d, 4H, $J=7.3$ Hz), 2.41–2.50 (m, 16H), 1.81–1.86 (m, 16H), 1.38–1.47 (m, 16H), 1.10–1.35 (m, 48H), 0.86 (t, 24H, $J=6.4$ Hz), 0.38 (s, 12H). δ_C (75.4 MHz, C_6D_6) 150.05, 148.28, 145.07, 139.18, 137.19, 128.82, 105.27, 37.02, 33.07, 32.41, 31.65, 30.64, 29.89, 29.87, 23.05, 14.37. UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 643 (4.7).

6.1.5. Synthesis of Pc–porphyrin arrays 9, 10, and 11. *General procedure*. Compound **2a** (0.037 g, 0.024 mmol, 1 equiv), pyridylporphyrin **6**, **7** or **8** (1, 2 or 4 equiv) were dissolved in dichloromethane (5 mL) and petroleum ether (5 mL). The reaction mixture was heated at reflux for 24 h and then allowed to cool. The solvent was removed in vacuo and the residue was purified by passing through a plug of silica gel (gradient elution with methanol to dichloromethane) followed by reprecipitation from petroleum ether:methanol (9:1) to give the products as dark blue/green amorphous solids.

Array **9**. (31 mg, 60%). IR (neat)/cm^{-1} 3932, 1980. δ_H (270 MHz, C_6D_6) 8.70–8.64 (q, 4H, $J=4.9$ Hz), 8.20 (d, 2H, $J=4.9$ Hz), 7.88 (s, 8H.), 7.82–7.36 (m, 15H), 6.83 (d, 2H, $J=4.9$ Hz), 5.39 (d, 2H, $J=6.9$ Hz), 4.98–4.87 (m, 16H), 2.82 (d, 2H, $J=6.6$ Hz), 2.46–2.38 (m, 16H), 1.85–1.80 (m, 16H), 1.44–0.66 (m, 64H), 0.87 (t, 24H, $J=6.6$ Hz), −2.95 (s, 2H). δ_C (67.94 MHz, C_6D_6) 201.82, 150.42, 145.76, 142.78, 142.29, 138.48, 137.91, 134.67, 134.60, 130.34, 128.89, 128.67, 126.86, 126.79, 121.59, 120.71, 113.45, 32.26, 32.25, 32.07, 31.59, 30.81, 29.80, 22.71, 14.37. UV–vis (DCM) $\lambda_{max/nm}$ 671, 604, 551, 516, 419. *m/z* (FAB) 2155 (M^+).

Array **10**. (62 mg, 70%). IR (neat)/cm^{-1} 3924, 1981. δ_H (270 MHz, C_6D_6) 8.46 (2H, s), 8.02 (2H, d, $J=5.0$ Hz), 7.94 (16H, s), 7.63 (4H, d, $J=8.0$ Hz), 7.34 (2H, t, $J=7.8$ Hz), 7.24 (4H, t, $J=7.8$ Hz), 6.66 (2H, d, $J=5.0$ Hz), 6.29 (2H, s), 5.26 (4H, d, $J=6.4$ Hz), 5.05–5.11 (16H, m), 4.82–4.86 (16H, m), 2.76 (4H, d, $J=6.4$ Hz), 2.41–2.51 (32H, m), 1.78–1.85 (32H, m), 1.45–0.85 (128H, m), 0.65 (48H, t, $J=6.9$ Hz), −1.40 (2H, br s): UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 671 (5.07), 606 (4.46), 542 (3.90), 517 (4.01), 421 (5.11).

Array **11**. From **2a** (19 mg), (61 mg, 75%). IR (neat)/cm^{-1} 3929, 1984. δ_H (300 MHz, C_6D_6) 7.88 (s, 32H), 5.92 (s, 8H, pyrrole), 5.08–5.03 (m, 32H), 4.87 (d, 8H, $J=6.2$ Hz), 4.69–4.65 (m, 32H), 2.59 (d, 8H, $J=6.2$ Hz), 2.47–2.40 (m, 64H), 1.87–1.82 (m, 64H), 1.54–0.30 (m, 256H), 0.67 (t, 96H, $J=7.2$ Hz), −2.98 (s, 2H). UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ 670, 606, 516, 423.

6.1.6. Synthesis of Pc–porphyrin array 12. Compound **3a** (0.019 g, 0.011 mmol), monopyridyltriphenylporphyrin **6** (0.015 g, 0.024 mmol) were dissolved in dichloromethane (7 mL) and petroleum ether (7 mL). The reaction mixture was heated at reflux for 6 h and then allowed to cool. The solution was filtered and the solvent was removed in vacuo. The residue was purified by reprecipitation from petroleum ether:methanol to give **12** (0.02 g, 65%) as a dark green/blue amorphous solid. δ_H (300 MHz, C_6D_6) 8.74 (4H, d, $J=4.0$ Hz), 8.70 (4H, d, $J=4.0$ Hz), 8.27 (4H, d, $J=4.0$ Hz), 7.95–7.87 (12H, m), 7.82 (8H, s), 7.47–7.32 (18H, m), 7.06 (4H, d, $J=4.0$ Hz), 5.51 (4H, d, $J=5.2$ Hz), 5.04 (16H, t, $J=6.8$ Hz), 3.46 (4H, d, $J=5.2$ Hz), 2.52–2.60 (16H, m), 1.88–1.96 (16H, m), 1.50–0.84 (64H, m), 0.56 (24H, t, $J=7.0$ Hz), −2.85 (4H, br s): UV–vis (CH_2Cl_2) $\lambda_{max/nm}$ (log ε) 662 (4.25), 646 (4.26), 591 (4.12), 554 (4.01), 515 (4.15), 419 (5.35).

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New insight into the oxidative chemistry of noradrenaline: competitive *o*-quinone cyclisation and chain fission routes leading to an unusual 4-[bis-(1*H*-5,6-dihydroxyindol-2-yl)methyl]-1,2-dihydroxybenzene derivative

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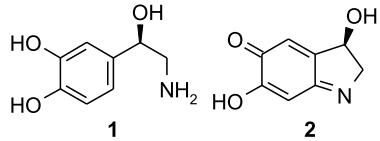
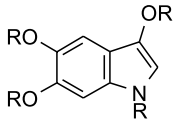
Abstract—Oxidation of 5×10^{-3} M noradrenaline in aqueous phosphate buffer, pH 7.4, with $K_3Fe(CN)_6$, $NaIO_4$ or Fe^{2+}/EDTA/H_2O_2 followed by extraction with ethyl acetate and acetylation with Ac_2O/Pyr led to a main reaction product which was isolated and identified as 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene, an unprecedented [bis-(indol-2-yl)methyl]-benzene derivative unsubstituted on the 3-position of the indole rings. This product was also obtained in 40% yield by reaction of 5,6-dihydroxyindole with 3,4-dihydroxybenzaldehyde. Other components of the oxidation mixture were 1-acetyl-3,5,6-triacetoxyindole, derived from noradrenolutin, and 5,6-diacetoxyindole, originating from cyclisation/dehydration of the *o*-quinone of noradrenaline, along with some 3,4-diacetoxybenzaldehyde. Inspection of the aqueous phase revealed the presence of 3,4-dihydroxymandelic acid and 3,4-dihydroxybenzaldehyde, derived from oxidative breakdown of the 2-amino-1-hydroxyethyl chain via a *p*-quinomethane intermediate. These results disclose new aspects of the oxidative chemistry of noradrenaline beyond the aminochrome stage and provide a route to novel [bis-(indol-2-yl)methyl]-benzene derivatives of potential pharmacological interest.

1. Introduction

The elucidation of the oxidative pathways of catecholamines involving the spontaneous cyclisation and/or tautomerism of their *o*-quinones has traditionally been an important goal in organic chemistry.[1–6] The biological significance of these reactions is that they appear to be the mechanism of formation of a series of reactive indolic species and/or quinomethane (quinone methide) intermediates involved in the synthesis of neuromelanin and related pigments,[7–9] in neuronal degeneration,[10–13] in the sclerotisation of insect cuticle,[14] and in the autoactivation of tyrosinase.[15] Catecholamine oxidation represents also a convenient entry to 5,6-dihydroxyindoles and related systems of biological and pharmacological relevance.[16,17]

Whereas several insights have been gained into the oxidative pathways of dopamine and adrenaline,[1–6,18,19] knowledge of the oxidative chemistry of noradrenaline (norepinephrine, **1**) has remained surprisingly scanty. This neurotransmitter is produced mainly in the *locus coeruleus*, one of the putative candidates for the brain's 'pleasure' centre implicated in physical and mental arousal and elevated mood.





3a R = H
3b R = CH_3CO

Oxidation of **1** leads to the formation of the unstable *o*-quinone. This undergoes cyclisation and oxidation to give noradrenochrome (**2**) via an indoline intermediate

Keywords: Noradrenaline; Noradrenolutin; Oxidation; Quinomethane; [Bis-(indol-2-yl)methyl]-benzene.
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commonly referred to as leuconoradrenochrome.[20,21] The subsequent steps of the pathway are believed to involve isomerisation of **2** to a fluorescent indoxyl derivative, known as noradrenolutin (**3a**).[22] Whereas the analogous oxidation product of adrenaline, adrenolutin (3,5,6-trihydroxy-1-methylindole), was isolated and characterised as early as 1949,[23] compound **3a** has never been obtained by direct oxidation of **1**, and has become available only by a synthetic approach.[24] Apart from **2**, no other product of noradrenaline oxidation has so far been identified.

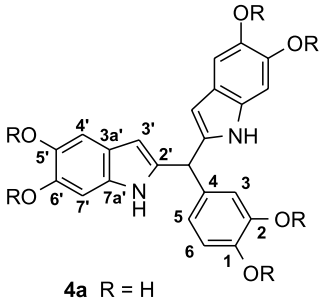
In an attempt to fill this gap, we have re-examined the oxidation of **1**, and have succeeded in isolating a major product whose spectral features are different from those of the known oxidation products of catecholamines. We report herein the isolation and structural characterisation of this new product and the elucidation of new aspects of the oxidative chemistry of **1**.

2. Results and discussion

In preliminary experiments, the oxidation of **1** (5×10^{-3} M) was investigated using a range of oxidising systems, including potassium ferricyanide, sodium periodate and the Fe^{2+}/EDTA/H_2O_2 system (Fenton reagent) in 0.1 M phosphate buffer, pH 7.4. In all cases, the reaction mixture became red in colour and then turned to purplish and dark brown. Ethyl acetate extraction, followed by acetylation with Ac_2O/Pyr to prevent oxidation of the phenolic components, afforded four main products (HPLC). When little sodium dithionite was added prior to extraction, to halt the reaction and prevent degradation of oxidisable species, a modest increase in the yield of extractable material was observed without, however, appreciable changes in product distribution. Accordingly, this precaution was included in all work-up procedures for preparative purposes.

The most abundant of the four products, which was relatively more retained on reverse phase, displayed in the ESI(+)-MS spectrum a pseudomolecular ion peak at *m/z* 671 ($[M+H]^+$), with peaks at 693 ($[M+Na]^+$) and 709 ($[M+K]^+$). The ^{1}H NMR spectrum displayed a broad singlet (2H) at δ 10.20 for N–H protons, three apparent singlets at δ 6.86, 7.14 and 7.28 (2H each), the signals (1H each) for an ABX spin system at δ 7.17 (d, $J=8.0$ Hz), 7.21 (d, $J=2.0$ Hz) and 7.31 (dd, $J=8.0$, 2.0 Hz), and a singlet (1H) at δ 5.91. The signals for six acetyl groups completed the ^{1}H NMR spectrum. The ^{1}H,^{1}H COSY spectrum revealed correlations between the signal at δ 10.20 and those at δ 6.86 and 7.14, ascribable to the H-3 and H-7 protons of a 5,6-diacetoxyindole system, respectively.[25]

The ^{13}C NMR spectrum showed the presence of fourteen signals in the sp^2 region between δ 144.0 and 105.9 and one signal at δ 40.7 correlating with the proton resonance at δ 5.91. This latter displayed multibond proton–carbon connectivities with several sp^2 carbons, including indolic ones, suggesting a methine group linking two indole rings and a disubstituted phenyl moiety. Overall, these data were consistent with the structure of the unusual 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene (**4b**). A complete assignment of the proton and carbon resonances, as deduced from ^{1}H,^{13}C HMQC and ^{1}H,^{13}C HMBC experiments, is reported in Table 1.



Consistent with the proposed formulation, a ROESY experiment revealed contacts of the methine singlet at δ 5.91 with the protons of the catechol moiety at δ 7.21 and

Table 1. NMR spectroscopic data of compound **4b** ($(CD_3)_2CO$)

	δ ^{13}C	δ ^{1}H (mult, *J* Hz)	^{1}H,^{1}H COSY	^{1}H,^{13}C HMBC
C–H	40.7	5.91 (bs)	6.86, 10.20	118.8, 120.3, 123.5, 124.1, 126.3, 127.1
C-1	142.0	—	—	—
C-2	144.0	—	—	—
C-3	124.1	7.21 (d, 2.0)	7.31	40.7, 142.0
C-4	127.1	—	—	—
C-5	123.5	7.31 (dd, 8.0, 2.0)	7.17, 7.21	40.7, 124.1, 142.0
C-6	124.1	7.17 (d, 8.0)	7.31	127.1, 144.0
C-2′	120.3	—	—	—
C-3′	126.3	6.86 (bs)	5.91, 7.14, 10.20	118.8, 127.1, 134.1
C-3a′	118.8	—	—	—
C-4′	105.9	7.28 (s)	7.14	126.3, 136.3, 138.6
C-5′	136.3	—	—	—
C-6′	138.6	—	—	—
C-7′	112.9	7.14 (s)	6.86, 7.28, 10.20	118.8, 134.1, 136.3, 138.6
C-7a′	134.1	—	—	—
N–*H*		10.20 (s)	5.91, 6.86, 7.14	—
COO*C*H_3	21.3	2.20 (s)	—	169.5
COO*C*H_3	21.3	2.24 (s)	—	169.8
*C*OOCH$_3$	169.5	—	—	—
*C*OOCH$_3$	169.8	—	—	—

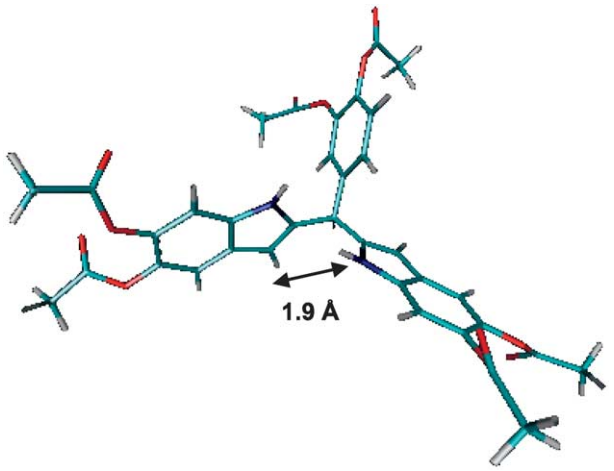
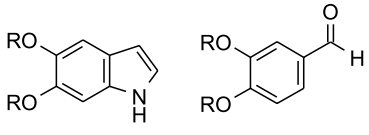


Figure 1. Energy minimised (MM+) structure of compound **4b**. Highlighted is the distance between the H-3 and the NH proton of two different indole units.

7.31 and between the N–H proton of one indole unit with the H-3 proton of the other indole unit. In accord with this conclusion, brief inspection of the geometry optimised structure of **4b** (MM+) indicated a low energy conformation in which the planes of the indole units form a dihedral angle of about 89° and the distance between the NH of one indole unit and the H-3 proton of the other one was 1.9 Å, that is, low enough to account for a well detectable contact (Fig. 1). In addition, a distinct cross peak in the ROESY spectrum between the signals at δ 6.86 and 7.28, the latter due to the indolic H-4 proton, provided further support to the 2-substitution of the indole rings, consistent with previous reports.[26,27] The alternative substitution through the 3-position, that is, with the $\delta=6.86$ H being H-2 rather than H-3, is untenable on the basis of the observed through-space contacts and the chemical shift values reported in the literature for the H-2 protons of 5,6-dihydroxyindoles, which never fall at $\delta<7.0$.[27–29]

Scrutiny of the parent structure **4a** shows that it conceivably arises by coupling of two 5,6-dihydroxyindole (**5a**) units through the 2-position with one molecule of 3,4-dihydroxybenzaldehyde (**6a**). This mechanism was supported by the identification of 5,6-diacetoxyindole (**5b**) and 3,4-diacetoxybenzaldehyde (**6b**) among the four main products obtained by oxidation of **1**, and was definitively secured by reaction of **5a** with **6a** in 0.1 M phosphate buffer at pH 7.4 under a vigorous stream of argon. After extraction and acetylation it was possible to isolate by PLC fractionation a product identical in all respects with **4b** (40% yield).



5a R = H
5b R = CH_3CO
6a R = H
6b R = CH_3CO

In separate experiments, attempts were made to detect the [bis-(indol-2-yl)methyl]-benzene derivative **4a** in the oxidation mixture from **1** by direct HPLC analysis. To this aim, compound **4b** was deacetylated with 1 M NaOH under carefully controlled conditions ensuring rigorous exclusion of oxygen. As obtained, the compound was rapidly converted into a species exhibiting a reddish purple chromophore ($\lambda_{max}=476$, 553 nm) denoting an oxidation product. This, however, proved to be too unstable to be isolated and characterised by spectroscopic techniques, despite several attempts.

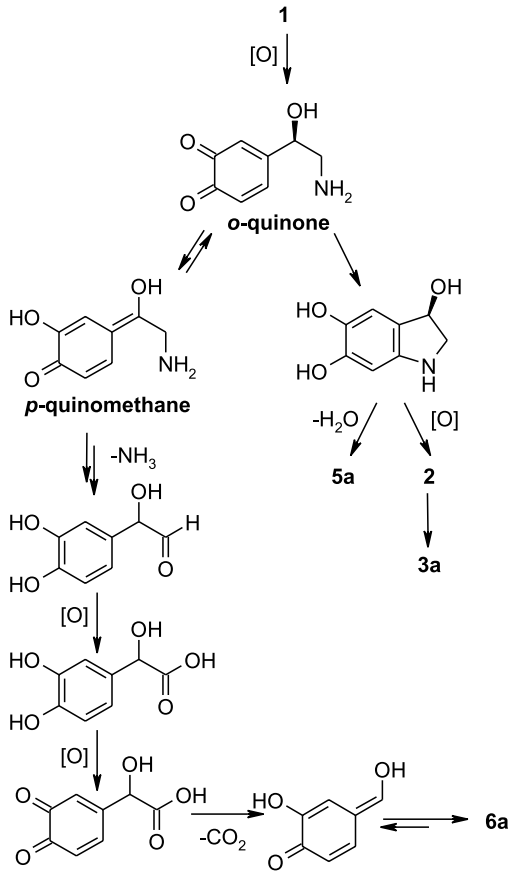
The fourth product isolated from the oxidation mixture of **1** was formulated as 1-acetyl-3,5,6-triacetoxyindole (**3b**). It exhibited a pseudomolecular ion peak ($[M+H]^+$) in the ESI(+)-MS spectrum at *m/z* 334, with ($[M+Na]^+$) and ($[M+K]^+$) peaks at *m/z* 356 and 372. The ^1H NMR spectrum showed three singlets (1H each) in the aromatic region, two of which shifted downfield at δ 7.87 and 8.28, and signals for four acetyl groups. The ^{13}C NMR spectrum consistently showed eight signals in the range between δ 141.0 and 111.4, besides the signals for four acetyl groups.

The overall yields of the isolated products **3b–6b** were less than 10% of the starting material. The remainder of the oxidation mixture was accounted for by significant amounts of insoluble dark polymeric materials together with a series of products all in very small amounts, which could not be isolated for spectroscopic characterisation. The poor mass balance was apparently due to the relative instability of the products which do not tend to accumulate in the reaction mixture but, as generated, are rapidly degraded to polymeric materials.

The formation of structure **4a** by oxidation of **1** was remarkable, since it incorporated the 5,6-dihydroxyindole system which is at a lower oxidation state compared to **2**. As mentioned earlier, the possibility that its incorporation into the structure of **4a** could be due to the reduction of **2** following treatment with dithionite[30] was ruled out by a careful analysis of the ethyl acetate extractable fraction obtained omitting treatment with dithionite. Under these conditions, acetylation of the extract gave a more complex mixture in which **4b** was clearly present, along with some **5b**, indicating the presence of **5a** in the crude mixture. On this basis, it is argued that **5a** is formed by dehydration of leuconoradrenochrome, a process that would favourably compete with the usual oxidative route to **2**. To the best of our knowledge, this is the first study demonstrating the direct formation of **5a** by oxidation of **1** under physiologically relevant conditions without a reductive step.[30]

The mechanism of formation of **6a** is likewise worthy of note, as it reflects the oxidative breakdown of the side chain of **1**. This would likely proceed through the intermediacy of 3,4-dihydroxymandelic acid, which had previously been proposed as the direct precursor of **6a** under oxidative conditions.[31,32] Consistent with this prediction, analysis of the oxidation mixture of **1** showed the presence of detectable amounts of 3,4-dihydroxymandelic acid. Moreover, when reacted under the above conditions, the acid was converted to **6a**.

On this basis, a possible mechanistic scheme for the oxidation of **1** is outlined in Scheme 1. Formation of 3,4-dihydroxymandelic acid from **1** would involve oxidation of the catecholamine to the *o*-quinone followed by rapid



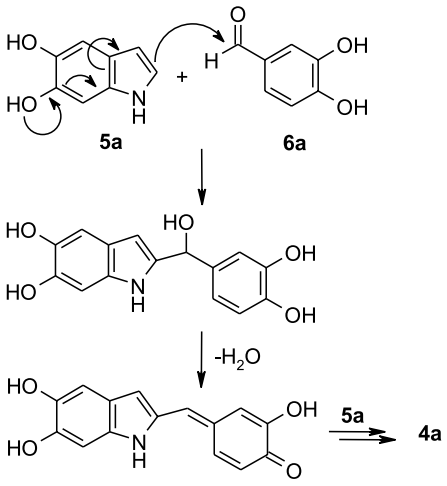
Scheme 1. Proposed mechanism of formation of compounds **3a**, **5a** and **6a** by oxidation of **1**.

tautomerism leading to a *p*-quinomethane intermediate and then to 3,4-dihydroxymandelic aldehyde, which would then be readily oxidised to the carboxylic acid. Quinomethane formation from catecholamine quinones is usually much slower than cyclisation and only occurs when the latter process is unfavourable.[33] This is consistent with the notion that *o*-quinone of **1** undergoes cyclisation at a relatively slower rate[34] and is therefore susceptible to tautomerism, a process favoured by the hydroxyl group enhancing the acidity of the β-proton.

As shown in Scheme 1, cyclisation and tautomerism of the *o*-quinone of **1** represent two competing routes leading to **5a** and **6a**, respectively. These latter, as confirmed by the synthetic experiment described before, would then concur to the formation of **4a** through coupling processes reminiscent of the reaction of indoles with the Ehrlich reagent (Scheme 2).[35]

The unusual regiochemical course of the coupling reaction would be dictated by frontier orbital interactions, as argued by the high HOMO coefficient on the C-2 position of **5a**,[36] due to the electron-releasing effect of the hydroxyl group on the 6-position of the indole ring.

In conclusion, the identification of a novel [bis-(indol-2-yl)methyl]-benzene derivative provides the first detailed insight into the oxidative pathway of **1** beyond the aminochrome stage and fills a gap in the chemistry of



Scheme 2. Proposed mechanism of formation of compound **4a**.

catecholamines. Other highlights of this study include the hitherto unrecognised conversion of **1** quinone to 3,4-dihydroxymandelic acid under non-enzymatic conditions; the isolation of **3a** as the acetylated derivative by direct oxidation of **1**; and the identification of **5a** among the products spontaneously formed by oxidation of **1** without reductive treatment of the mixture.

The chemistry described in this paper may also hint at practical routes to novel [bis-(indol-2-yl)methyl]-benzene compounds. [Bis-(indolyl)methyl]-benzene derivatives are the focus of increasing interest because of their biological activities, as exemplified by their antibacterial, anticarcinogenic, antiinflammatory and toxic properties.[37–39] Generally, these compounds are prepared by protic or Lewis acid catalysed condensations of indoles with aldehydes.[40–42] In all cases, however, [bis-(indol-3-yl)methyl]-benzene derivatives are obtained, unless the 3-position is substituted, for example, by an alkyl residue,[43] and no straightforward route to [bis-(indol-2-yl)methyl]-benzenes unsubstituted on the 3-position is available.

3. Experimental

3.1. General methods

ESI(+)-MS spectra were recorded with a Waters ZQ quadrupole mass spectrometer. High resolution EI-MS spectra were obtained at 70 eV and 230 °C using a Kratos MS 50 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using a Bruker WM 400 spectrometer. $^{1}H,^{1}H$ COSY, $^{1}H,^{13}C$ HMQC, $^{1}H,^{13}C$ HMBC, and ROESY experiments were run at 400 MHz using standard pulse programs from the Bruker library.

UV spectra were performed with a Beckmann DU 640 spectrophotometer. Analytical and preparative HPLC were carried out on a Gilson apparatus equipped with a UV detector set at 280 nm using a Sphereclone ODS (5 μm, 4.6×250 mm) or Econosil (10 μm, 22×250 mm) column, respectively. For analytical runs, 0.02 M acetic acid/acetonitrile 60:40 (v/v) was used as the eluant, at a flow rate of

1 mL/min. In preparative runs elution conditions were 0.02 M acetic acid/acetonitrile 50:50 (v/v), at a flow rate of 15 mL/min. TLC and PLC was carried out on silica gel plates (0.25 and 0.50 mm, respectively) from Merck. Noradrenaline hydrochloride was from Sigma and 3,4-dihydroxybenzaldehyde was from Fluka. 3,4-Dihydroxymandelic acid, hydrogen peroxide (30% solution in water), $NaIO_4$ and $K_3Fe(CN)_6$ were from Aldrich. 5,6-Dihydroxyindole was prepared as reported.[44] Molecular mechanics calculations were carried out with Hyperchem 6.01 package produced by Hypercube, Inc. (Waterloo, Ont., Canada) 2000.

3.2. Oxidation of noradrenaline (1)

A solution of **1** (60 mg, 0.29 mmol) in 0.1 M phosphate buffer, pH 7.4 (60 mL), was treated with $K_3Fe(CN)_6$ (97 mg, 0.29 mmol). After 5 min the reaction mixture was reduced with sodium dithionite (2 mg/mL), acidified to pH 5 with HCl, and extracted with ethyl acetate (2×30 mL). The organic layers were collected, dried over anhydrous sodium sulphate, evaporated under reduced pressure, and the residue was treated with acetic anhydride (0.500 mL) and pyridine (0.025 mL) overnight. The acetylated mixture was evaporated under reduced pressure and the residue was taken in ethyl acetate (5 mL) and subjected to HPLC analysis. Similar experiments were carried out by treating **1** (60 mg, 0.29 mmol) with $NaIO_4$ (63 mg, 0.29 mmol) or with $Fe(NH_4)_2(SO_4)_2\times 6H_2O$ (95 mg, 0.29 mmol), EDTA (90 mg, 0.29 mmol) and H_2O_2 (0.025 mL, 0.29 mmol). All the experiments were carried out also by omitting treatment with sodium dithionite.

3.3. Isolation of 1-acetyl-3,5,6-triacetoxyindole (3b), 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene (4b), 5,6-diacetoxyindole (5b) and 3,4-diacetoxybenzaldehyde (6b)

A solution of **1** (600 mg, 2.9 mmol) in 0.1 M phosphate buffer, pH 7.4 (600 mL), was treated with $NaIO_4$ (624 mg, 2.9 mmol). After 5 min, the reaction mixture was worked up as above. After acetylation, the mixture was subjected to preparative HPLC to give compounds **3b** (29 mg, 3% yield, $t_R=11.9$ min), **4b** (45 mg, 7% yield, $t_R=23.0$ min), **5b** (7 mg, 1% yield, $t_R=7.2$ min), and **6b** (7 mg, 1% yield, $t_R=6.8$ min). Purity of compounds **3b**–**6b** was at least 98% as determined by ^{1}H NMR.

Compound **3b**. FT-IR ($CHCl_3$) ν_{max} 1766, 1713, 1458, 1411, 1386, 1371, 1298; δ_H ($(CD_3)_2CO$), 2.30 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.67 (3H, s, CH_3), 7.39 (1H, s, H-4), 7.87 (1H, s, H-2), 8.28 (1H, s, H-7); δ_C ($(CD_3)_2CO$), 19.6 (2×CH_3), 19.8 (CH_3), 22.8 (CH_3), 111.4 (C-7), 111.7 (C-4), 115.9 (C-2), 121.6 (C-3a), 129.9 (C-7a), 133.6 (C-3), 139.4 (C-5), 141.0 (C-6), 167.6 (CH_3COO–), 168.0 (2×CH_3COO–), 168.9 (CH_3COO–); ESI(+)-MS: *m*/*z* 334 ($[M+H]^+$), 356 ($[M+Na]^+$), 372 ($[M+K]^+$); HREI-MS for $C_{16}H_{15}NO_7$: calcd 333.0848, found 333.0935.

Compound **4b**. UV λ_{max} 277, 286, 293 nm (CH_3OH); FT-IR ($CHCl_3$) ν_{max} 1766, 1602, 1505, 1469, 1371, 1329; δ_H ($(CD_3)_2CO$), see Table 1; δ_C ($(CD_3)_2CO$), see Table 1; ESI(+)-MS: *m*/*z* 671 ($[M+H]^+$), 693 ($[M+Na]^+$), 709 ($[M+K]^+$); HREI-MS for $C_{35}H_{30}N_2O_{12}$: calcd 670.1799, found 670.1823.

Compound **5b**. FT-IR ($CHCl_3$) ν_{max} 1765, 1509, 1468, 1371, 1325, 1304; δ_H (CD_3OD), 2.26 (6H, s, CH_3), 6.48 (1H, d $J=3.2$ Hz, H-3), 7.28 (1H, s, H-7), 7.36 (1H, s, H-4), 7.38 (1H, d $J=3.2$ Hz, H-2).[45]

Compound **6b**. FT-IR ($CHCl_3$) ν_{max} 1766, 1690, 1600, 1490, 1450, 1420, 1365, 1250; δ_H (CD_3OD), 2.26 (6H, s, CH_3), 7.44 (1H, d $J=8.0$ Hz, H-5), 7.77 (1H, d $J=2.0$ Hz, H-2), 7.84 (1H, dd $J=8.0$, 2.0 Hz, H-6), 9.94 (1H, s, CHO).[46]

3.4. Synthesis of 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene (4b)

Compound **5a** (100 mg, 0.67 mmol) was added to 0.1 M phosphate buffer, pH 7.4 (134 mL), previously purged with an argon stream, and treated with **6a** (464 mg, 3.4 mmol). After 24 h, the reaction mixture was acidified to pH 5 and worked up as above. After acetylation the residue was subjected to PLC (eluant chloroform/ethyl acetate 1:1 plus 1% acetic acid) to afford **4b** (90 mg, 40%, $R_f=0.37$).

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Thioamides versus amides in anion binding

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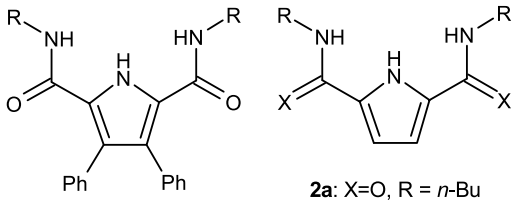
Abstract—Amide and thioamide derivatives of the 1*H*-pyrrole-2,5-dicarboxylic acid have been synthesised. Properties of these simple anion receptors and their behaviour in the presence of anions have been studied both in solution and in the solid state. The results allowed to compare anion complexation properties of thioamides versus their amide analogues.

1. Introduction

Among various areas of supramolecular chemistry, coordination of anions has been recently a subject of intensive exploration.[1] Neutral anion receptors play an important role in Nature. For this reason, artificial neutral receptors became an attractive target for studies. These studies have been focused on development of receptors having an increased selectivity and/or binding affinities, and also succeeded in practical application, namely in catalysis,[2] transport through membranes,[3] or anion detection by electrochemical,[4] colorimetric[5] and fluorometric[6] techniques. However, a growing interest in the efficiency and application of neutral receptors has one drawback—a lack of basic, fundamental papers. Without such background it is hard to generalise and consolidate information discussed by various authors. For example, the diversity of titration techniques and solvents used for studies of successive generation of ligands, makes it difficult to analyse a structural influence on anion affinity. Basic studies of simple models[7] provide reference points for more sophisticated systems. In the course of fundamental studies, our group investigated macrocyclic effects,[8] size complementarity[9] and introduced new building blocks.[10] In this paper, we compare the properties of simple amide and thioamide ligands, shown in Scheme 1.

Amide groups are extensively used in neutral anion receptors as hydrogen bond donors.[11] However, they can also act as hydrogen bond acceptors and by participation in intramolecular hydrogen bonds decrease receptor affinity toward anions. Thioamides are readily accessible from amides,[12] and are known to be weaker hydrogen-bond acceptors and stronger acids than amides.[13] For these reasons, thioamides are attractive groups for the construction of anion hosts. Thioamide groups were recently successfully introduced into macrocyclic systems by the research teams of Yamamoto[14] and Bowman-James.[15] During preparation of this manuscript, Gale et al.[16] reported synthesis and complexation properties of furane and thiophene derivatives containing thioamide groups.



1a: R = *n*-Bu
1b: R = Ph

2a: X=O, R = *n*-Bu
2b: X=O, R = Ph
2c: X=O, R = Me
3a: X=S, R = *n*-Bu
3b: X=S, R = Ph
3c: X=S, R = Me

Scheme 1.

For our studies, we decided to take into account simple compounds, a kind of scaffold for the amide and thioamide groups. The model compounds should be able to bind anions strongly enough for determination of binding constants by usual techniques, and, on the other hand, to have simple enough structures for easy data interpretation and computer modelling. Appreciating the important role of the pyrrole moiety in complexation of anions[17] and impressed by the binding constants for diaamidopyrroles **1a** and **1b** found by Gale,[18] we chose pyrrole as a scaffold. In order to minimise

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the disruptive influence of other factors on the comparison of amides versus thioamides, we used 3,4-unsubstituted pyrrole derivatives of type **2** and **3** (Scheme 1). Moreover, our model compounds resemble the known building blocks for neutral anion receptors, i.e. diamides derived from isophthalic acid and 2,6-pyridinedicarboxylic acid.[7d,f]

2. Results and discussion

2.1. Preparation of the model compounds

1*H*-Pyrrole-2,5-dicarboxylic acid **8** was synthesised via previously described procedures starting from pyrrole **4** (Scheme 2). Pyrrole **4** was reacted with phosgene trimer and, subsequently, with methanol leading to ester **5**[19] which was then formylated under Vilsmeier reaction conditions[20] yielding ester **6**. After oxidation of **6**[21] and subsequent hydrolysis of intermediate **7**, the acid **8** was obtained in good yield. This compound was then converted into the acid chloride **9**, which was immediately subjected to reaction with the corresponding amines to afford amides **2a** (72%) and **2b** (92%).

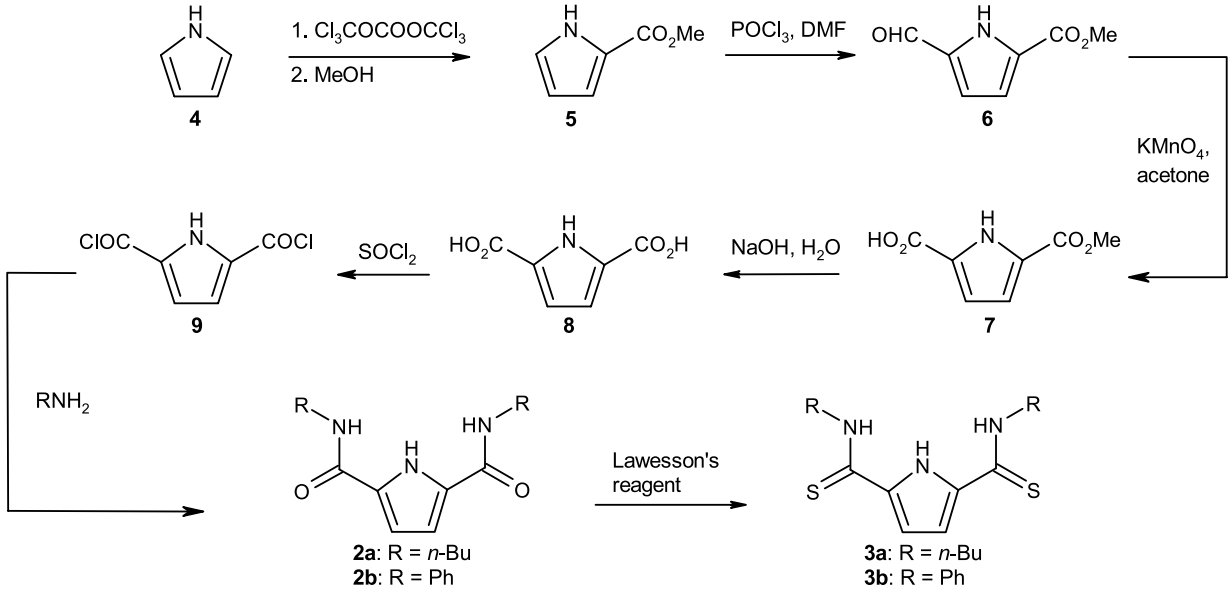
In order to prepare the thioamides, we reacted the amides with the Lawesson's reagent in boiling THF.[12] After easy workup, we got thioamides **3a** and **3b** in good yields (90 and 80%, respectively) as yellow crystals. The thioamides immediately showed their first advantage over amides, they were better soluble in organic solvents (THF, CH_3CN, CH_2Cl_2) then their amide analogues.

2.2. Anion binding by the model compounds

Having prepared our model compounds, we started to investigate their anion binding properties using the ^{1}H NMR titration technique. Upon addition of tetrabutylammonium salts into the solution of ligands type **2** in DMSO-d_6+0.5% H_2O, we observed a downfield shift of the amide protons that allowed us to determine binding constants by applying non-linear curve fitting (Table 1).

Surprisingly, the model amides **2a** and **2b** interact with anions much more weakly than Gale's derivatives of type **1**. For example, the binding constant is 560 M^{-1} for **1b** with benzoate whereas it is only 80 M^{-1} for compound **2b**. Looking for rationalisation of such results, we suspected that maybe inaccuracies in experimental technique (e.g., presence of water in DMSO or processing of the curve fitting) were responsible for such differences. To check this suspicion, we obtained ligand **1b** and carried out ^{1}H NMR titration. The measured stability constants matched the literature data.[18] The ^{1}H NMR amide proton signal of our receptors are shifted downfield relative to phenyl substituted analogues (e.g., 10.12 ppm for **2b** and 9.37 ppm for **1b**), whereas pyrrole N*H* signals are shifted upfield (12.26 ppm for **2b** and 12.67 ppm for **1b**),[18b] so the differences in the binding constants of two families of compounds cannot be interpreted in terms of receptor acidity. It is immediately apparent that phenyl substituents in the pyrrole ring are crucial for effective anion binding. However, currently we are unable to explain this phenomenon.

Despite the fact that our model compounds bind anions more weakly than receptors of type **1**, they show the same selectivity. We observed typical ligand preferences for



Scheme 2.

Table 1. Binding constants (M^{-1}) for the formation of 1:1 complexes of **2a**, **2b**, **3a** and **3b** with various anions in DMSO-d_6+0.5% H_2O at 296 K[a], determined by ^{1}H NMR titration technique

	$PhCOO^-$	$H_2PO_4^-$	Cl^-	Br^-
2a	49	150	1.7	—[b]
2b	80	203	3.8	—[b]
3a	109	139	4.6	—[b]
3b	—[b]	—[b]	11.1	—[b]

[a] Errors are estimated to be <10%. Tetrabutylammonium salts were used as anion sources.
[b] Curve fitting failed (see the text for comments).

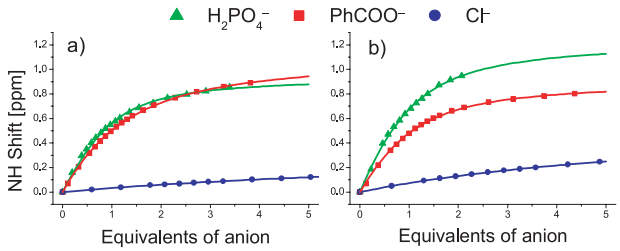


Figure 1. Curves of ^{1}H NMR titration with chloride, benzoate and dihydrogen phosphate in DMSO-d_6+0.5% H_2O: (a) compound **2a**; (b) compound **3a**.

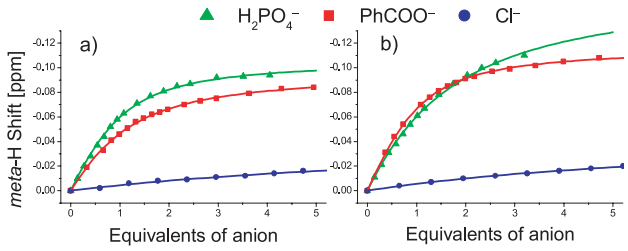


Figure 2. Phenyl meta-H chemical shift during ^{1}H NMR titration with chloride, benzoate and dihydrogen phosphate in DMSO-d_6+0.5% H_2O: (a) compound **2b**; (b) compound **3b**.

anions: dihydrogen phosphate, benzoate over chloride and bromide. Although there is a convention of presenting small association constants as '<5', we decided to report exact values calculated for the chloride anion. These results were obtained with small errors and allowed a comparison with the thioamides. Unfortunately, because of weak interactions with the bromide ion, we were unable to determine the stability constants in this case.

During the ^{1}H NMR titration of compound **3a**, we observed not only a downfield shift of thioamide protons but also severe broadening of the signal. When 2 equiv of dihydrogen phosphate were used, the signal was very wide and concealed in the baseline such that we could not assign its chemical shift. For this reason, we stopped the titration at the molar ratio of the anion to the ligand equal to 2 (Fig. 1). The broadening of the thioamide signal may be a manifestation of several phenomena, such as deprotonation by a basic anion, slow rates of complexation and decomplexation or averaging of thioamide and pyrrole N*H*'s. Unfortunately, we have no experimental data to support any of these hypotheses, however, the signal broadening is usually interpreted as an effect of deprotonation.[16]

Thioamide **3a** has a stronger affinity towards benzoate and chloride than its amide analogue **2a** (Table 1). These anions are bound more than two times stronger by **3a** than by **2a** (Table 2). On the contrary, dihydrogen phosphate seems to be stronger complexed by the amide than by the thioamide. In the case of **3a** titration with bromide, we obtained appropriate data for curve fitting, however, the calculated binding constant was about 1.

Table 2. Ratio between binding constants for thioamides and amides determined by the ^{1}H NMR titration in DMSO-d_6+0.5% H_2O

Ratio of K_a	$PhCOO^-$	$H_2PO_4^-$	Cl^-
3a/2a	2.2	0.9	2.7
3b/2b	2.0[a]	0.4[a]	2.9

[a] Ratio of K_a calculated for *meta* H in phenyl ring; see text for comments.

The above-mentioned broadening of the thioamide proton signal for **3a** was even more pronounced for thioamide **3b**. In experiments with dihydrogen phosphate and benzoate, we could only record a few initial points, insufficient for calculation of K_a. Fortunately, we observed that *meta*-protons in the phenyl ring in aromatic amides gave good response to the presence of anions (Fig. 2). The values of the *meta*-proton chemical shifts in **2b** and **3b** were used for calculations of the binding constants and allowed us to compare thioamide and amide receptors (Table 2). These results are consistent with those described previously for the butyl derivatives **2a** and **3a**.

Although we changed solvent from DMSO to acetonitrile, we still observed broadening of the thioamide proton signals in the presence of anions. We hoped that another approach—UV/Vis titration would allow us more direct comparison of binding abilities of **2b** and **3b**. The estimated binding constants in the DMSO by ^{1}H NMR titration were to small to be measured using UV/Vis technique. For this reason we used the solvent of choice for UV/Vis studies—acetonitrile, in which binding constants are much higher than in DMSO, which is a more competitive medium.

Preliminary experiments revealed interesting feature of the thioamides; in the case of amides **2a** and **2b**, addition of anions into the ligand solutions caused only decreasing of the absorbance, whereas complexation with thioamides **3a** and **3b** resulted in a bathochromic shift (Fig. 3). This observation suggests that maybe some of thioamides can be used as optical sensors for anions.

Results of our UV/Vis studies, carried out in CH_3CN, are summarised in Table 3. Amides and thioamides have approximately the same affinity for the anions. However, it has to be stressed that there was no clear isosbestic point during thioamide titration, which could indicate occurrence of higher order equilibria than 1:1 (Fig. 3e and f). Job plots could not disclose their nature, so we assumed a strong one-to-one complexation and performed curve fitting for the 1:1 model.

Values of binding constants in acetonitrile lead to the question: 'what has happened to the stronger hydrogen bond donor abilities of thioamides?'. Some insight into the problem came from the isothermal titration calorimetry (ITC). Inspection of Table 4 reveals that thioamides indeed interact more strongly with benzoate than amides (more negative ΔH°). However, the binding constants are similar owing to enthalpy/entropy compensation. The values of K_a obtained from UV/Vis and ITC are slightly different but such inconsistency between methods has been observed.[22]

2.3. Structural studies

Structure analysis can reveal important facts about supramolecular systems. For example, investigation of a receptor and its complex structure can confirm proposed binding mode, clarify observed selectivity in terms of geometric fit,

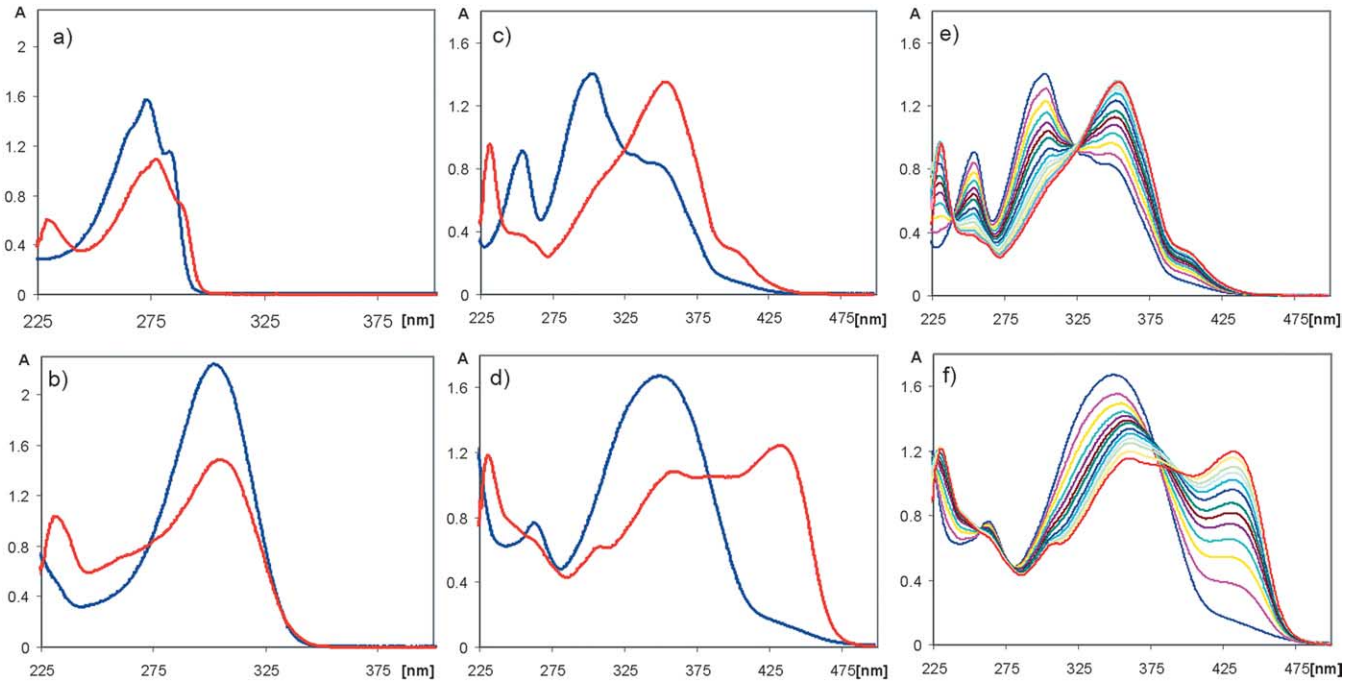


Figure 3. UV/Vis spectra of free ligand (blue) and in the presence of 5 equiv of benzoate (red) for compounds: **2a** (a), **2b** (b), **3a** (c) and **3b** (d). UV/Vis titration experiments in acetonitrile with benzoate for compounds **3a** (e) and **3b** (f).

Table 3. Binding constants (log K_a) in CH_3CN for complexes of **2a**, **2b**, **3a** and **3b** with various anions at 296 K[a], determined by UV/Vis titration technique

	$PhCOO^-$	$H_2PO_4^-$	Cl^-
2a	4.25	4.34	2.94
2b	4.40	3.90	2.77
3a	4.34	3.80	2.90
3b	4.55	3.70	—[b]

[a] Errors are estimated to be $<10\%$. Tetrabutylammonium salts were used as anion sources.
[b] Curve fitting failed.

Table 4. Thermodynamic parameters of binding of benzoate by ligands **2a**, **2b**, **3a**, **3b** in CH_3CN at 296 K, as determined by ITC

	log K_a	ΔH (kJ/mol)	$T\Delta S$ (kJ/mol)
2a	4.25	−11.43	12.66
2b	4.34	−14.71	9.90
3a	4.35	−13.67	10.98
3b	4.40	−16.40	8.54

or indicate existing intramolecular interactions that decrease ligand affinity towards guest. Hence, structure analysis is essential for contemporary studies of host–guest systems.

Amides **1a**, **1b** and their complexes were studied by X-ray diffraction method by Gale et al.[18] Structure analysis showed that free ligands exist in the *anti–anti* conformation. However, interaction with a guest results in rotation of an amide group to *syn* conformation, which allows simultaneous binding of the guest by pyrrole N*H* and amide N*H*. It was interesting to check if such behaviour is characteristic for all diamidopyrrole systems.

2.4. Structural analysis of amides

We succeeded in the preparation of diffraction-grade single crystals of amide **2a** by slow evaporation of its ethanol–acetone solution, and subjected them to X-ray analysis. Receptor molecules form an intermolecular net of hydrogen bonds and create a coordination polymer in the solid state (Fig. 4). The independent part consists of three ligand molecules (Fig. 5).

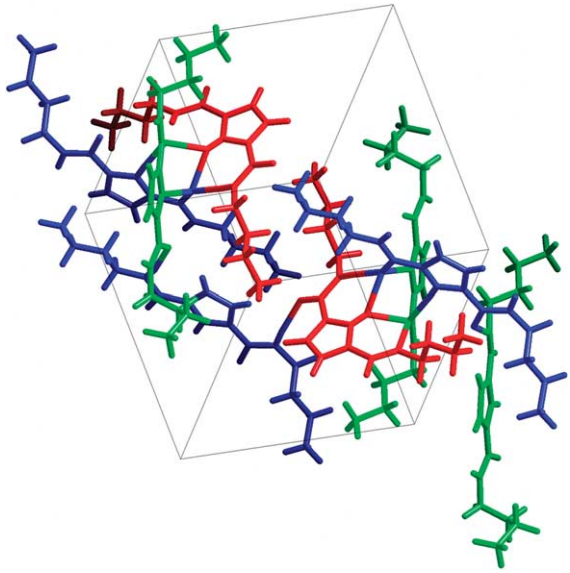


Figure 4. The X-ray crystal structure of **2a** showing the three inequivalent molecules in different colours.

There are two pyrrole moieties in the *anti–anti* conformation bound by the ligand possessing *syn–syn* conformation. This beautiful structure shows those two important

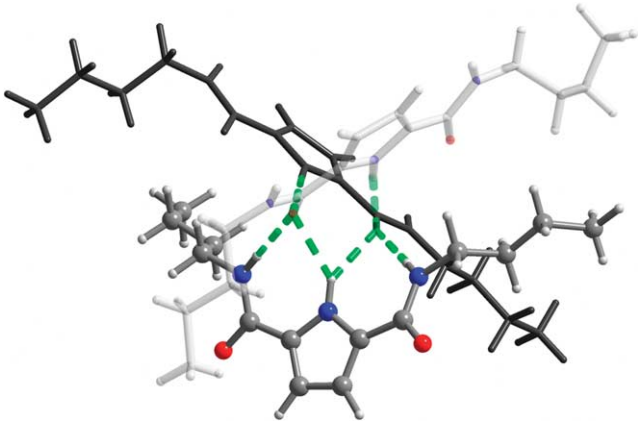


Figure 5. Crystal structure of **2a**.

aspects of diamidopyrrole receptors: they prefer *anti–anti* conformation; in the *syn–syn* conformation they can bind a guest by the convergent hydrogen bonds created by both amide and pyrrole N*H*. Amide protons participate in shorter hydrogen bonds (N–O from 2.81 to 2.87 Å) than pyrrole ones (N–O from 2.90 to 2.95 Å). It may suggest that the pyrrole hydrogen bond is weaker than that involving the amide group.

In order to investigate the conformation of **2a** in solution we carried out 2D NOESY spectra in DMSO-d_6. We found an NOE effect between amide N*H* protons and both pyrrole C*H* and N*H* protons (Fig. 6), which means that the amide groups in solution have both *anti* and *syn* relationship. During a dilution experiment we did not notice any significant changes in ^{1}H NMR spectra which discards possibility of trimer formation (similar to that in the solid phase).

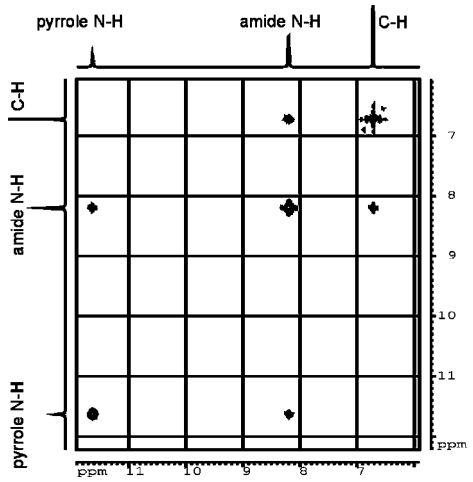


Figure 6. NOESY spectra of **2a** in DMSO-d_6 solution.

The X-ray crystal structure of amide **2b** consists of only one independent molecule in *anti–anti* conformation. In contrast to the Gale's phenylamide **1b**, compound **2b** does not form dimers but head-to-tail chains are formed (Fig. 7). The carbonyl groups of the next molecule accept hydrogen bonds from the amide group (N–O 3.07 Å) and from the aromatic ring (C–O 3.32 Å). In this structure, the pyrrole N*H* does not participate in any hydrogen bond.

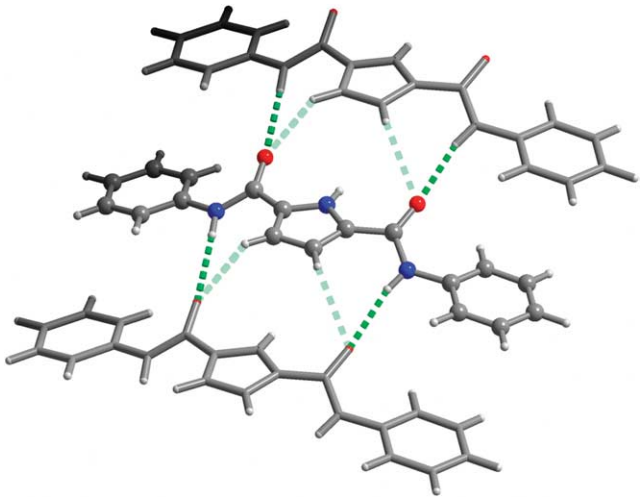


Figure 7. Crystal structure of **2b**. Symmetrically dependent molecules are presented by stick model.

2.5. Structural analysis of thioamides

Using the diffusion method ($C_2H_4Cl_2$/pentane), crystals of compound **3a** were obtained and subjected to X-ray analysis. Independent part of the structure consists of one ligand molecule with disorder in one of the butyl chains. Thioamide groups are in the *anti–anti* conformation and participate in hydrogen bonding (Fig. 8).

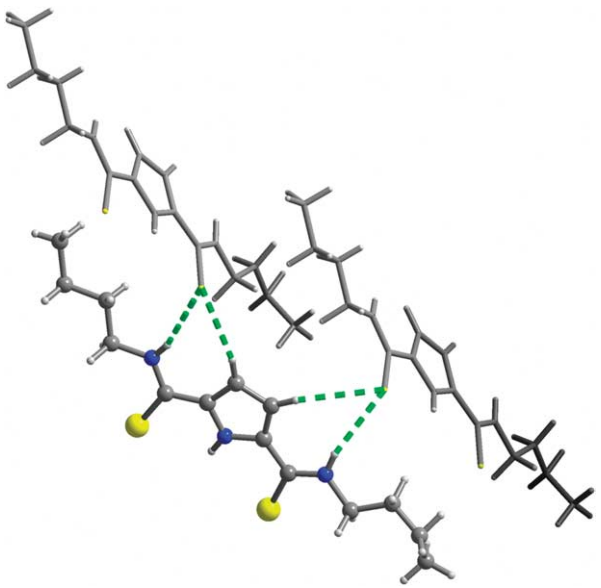


Figure 8. The X-ray crystal structure of **3a**. Part of disorder was removed for clarity.

Thioamide N*H* and pyrrole C*H* protons form hydrogen bonds with thiocarbonyl groups from neighbour molecules, in a similar way as in the case of **2b**. However, contrary to the structure of **2b**, each molecule of **3a** binds thiocarbonyl groups of two others. Inspection of hydrogen bond lengths reveals that the interactions are not equal (distances are: N–S, 3.55 Å; C–S, 3.68 Å and N–S, 3.66 Å; C–S, 3.84 Å, respectively). This structure shows that the thioamide groups act as hydrogen bond acceptors, at least in the solid state. However, comparison with average hydrogen

bond lengths and angles (with a thiocarbonyl group as acceptor)[13b] suggests that intermolecular interactions of **3a** are very weak. Crystals of **3a** have an interesting phase transition which will be discussed in the separate paper.

The 2D NOESY spectra of **3a** in DMSO-d_6 revealed close proximity between thioamide protons and pyrrole C*H* (Fig. 9) without NOE effect involving pyrrole N*H*. Therefore, ligand **3a** conformation in solution is *anti–anti* as was observed for the solid state.

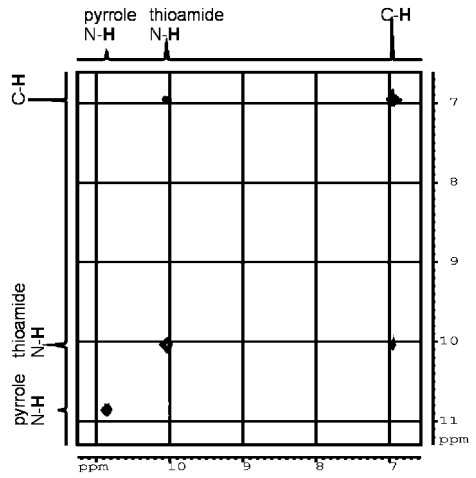


Figure 9. NOESY spectra of **3a** in DMSO-d_6 solution.

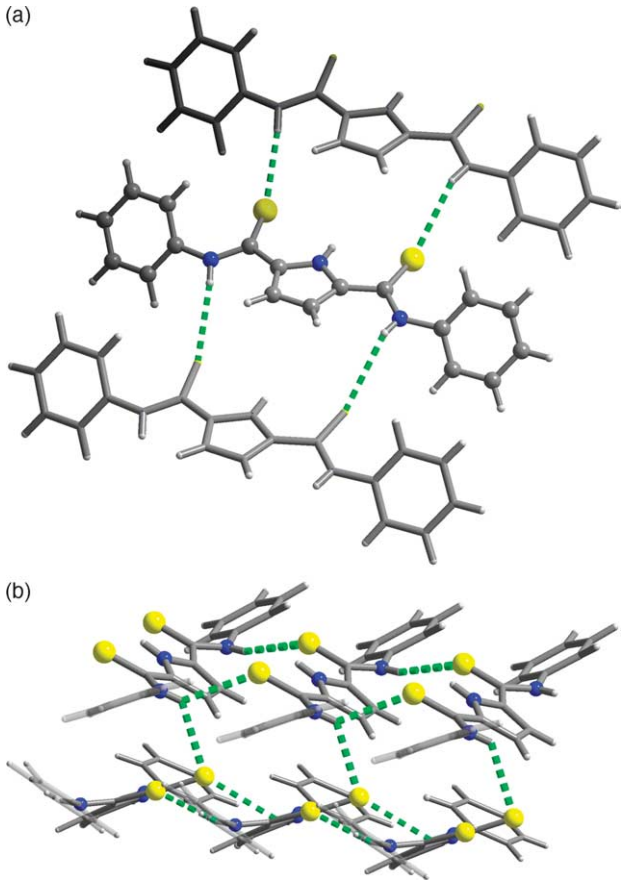


Figure 10. Crystal structure of **3b**. (a) Top view. (b) Side view.

Single crystal of compound **3b** were obtained from its solution in the mixture of acetonitrile and methanol (9:1 v/v) by slow evaporation of solvents. The X-ray crystal structure is very similar to that obtained for the amide analogue **2b** (cf. Figs. 7 and 10a). The ligand molecules have the *anti–anti* conformation and form head-to-tail chains via hydrogen bonds between thioamide groups. However, one of the thioamide groups is engaged in bifurcated hydrogen bond, which ties the chain below (Fig. 10b).

2.6. Structural analysis of anion complexes

The next diffusion experiment (**2b**, tetrabutylammonium chloride in $C_2H_4Cl_2$/pentane) led to diffraction-grade crystals of the chloride complex with **2b**. X-ray structure analysis revealed that the receptor adopts the *syn–syn* conformation and the chloride anion is bound by three hydrogen bonding interactions (Fig. 11). Each hydrogen bond has different length, the shortest being the pyrrole N*H* (N–Cl 3.07 Å) when distances of amide nitrogens to chloride are of 3.33 and 3.39 Å. Differences in amide hydrogen bond lengths may indicate that chloride anion cannot perfectly match the binding site of the receptor.

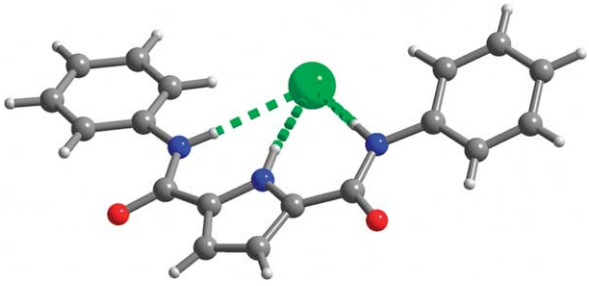


Figure 11. The crystal structure of the complex **2b**×TBACl.

Single crystals of chloride complex of thioamide **3b** were also obtained by diffusion of pentane into the solution of complex in dichloroethane. The X-ray structure analysis revealed that the ligand remained in the *anti–anti* conformation. Two chloride anions and two molecules of receptor **3b** form centrosymmetrical dimer in which anions are anchored by hydrogen bonding interactions involving amide N*H* and pyrrole C*H* (Fig. 12).

The ligand forms different contacts with chloride ions; one set consists of hydrogen bonds, which are shorter at one side

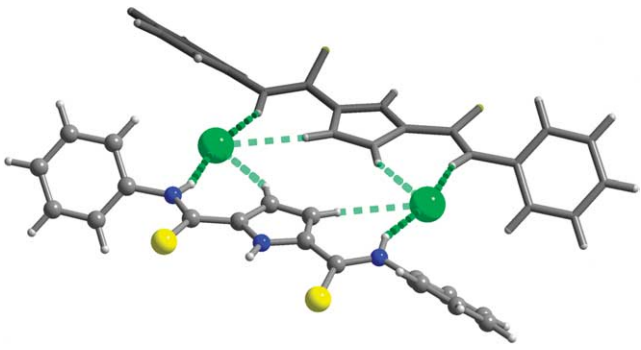


Figure 12. Crystal structure of complex **3b**×TBACl. The symmetrically dependent structure is shown in light grey.

(N–Cl 3.26 Å; C–Cl 3.55 Å, and N–Cl 3.30 Å; C–Cl 3.64 Å, respectively). In this complex, pyrrole N*H* is not engaged in any hydrogen interactions.

Similar structure was reported by Gale et al.[16] for the complex of thiophene-2,5-dicarboxylic acid diphenylamide with fluoride anion. Thiophene ligand in the *anti–anti* conformation forms a 2:2 complex with fluoride anion, which is bound by the amide N*H* and thiophene C*H*. The main difference between these two structures is that pyrrole rings of ligand **3b** and chloride anions lay in the same plane, whereas in the case of fluoride complex, the thiophene rings occupy parallel planes.

The results of the X-ray analysis of $[\mathbf{3b}\cdot\mathrm{Cl}]^-$ raised the question about the complex structure in solution. In complexes of these class of ligands, we expect the *syn–syn* conformation of the ligand, so the complex can benefit from convergent, three hydrogen bonds, impossible in the *anti–anti* conformation. We were unable to make a NOESY experiment and elucidate the complex structure in solution due to the N*H* proton signal broadening in the presence of tetrabutylammonium salts. However, during the ^{1}H NMR titration, we observed a downfield shift of the pyrrole N*H* proton signal (however, it lost intensity very fast) and curve fitting matched the 1:1 model. For these reasons, we believe, that binding mode observed in the solid state does not take place in solution, and that anions are bound by hydrogen bonds from thioamides and the pyrrole N*H* as observed for the amide analogues.

2.7. DFT energy calculations of conformers

The above-described structure $[\mathbf{3b}\cdot\mathrm{Cl}]^-$ prompted us to hypothesise that thioamides could have a greater tendency to stay in the *anti–anti* conformation than the corresponding amides. To confirm this assumption, we decided to perform an energy calculation for different conformers of 1*H*-pyrrole-2,5-dicarboxylic acid bis-methylamide **2c** and its thioamide analogue **3c**. We began by carrying out geometry optimisation using density functional method (DFT) with B3LYP functional and 6-31+G(d,p) basis set. We found three local minima (*anti–anti*, *syn–anti*, *syn–syn*) for both amide and thioamide. For each conformer, we performed single point energy calculations [B3LYP/6-311+G(3df,2pd)],[23] the results are presented in Table 5. For both amide and thioamide *anti–anti* conformer possess the lowest energy what is in agreement with our previous finding. The energy difference between *syn–syn* and *anti–anti* conformers for **2c** and **3c** are 38.8 and 41.9 kJ/mol, respectively. So, the thioamide indeed shows a larger preference for *anti–anti* conformation than the amide does (about 3 kJ/mol).

Table 5. DFT calculations of the relative energies (kJ/mol) for the conformers of amide **2c** and thioamide **3c**[a]

	Amide **2c**	Thioamide **3c**
$E_{anti-anti}$	0	0
$E_{syn-anti}$	14.0	12.3
$E_{syn-syn}$	38.8	41.9

[a] Calculations in the gas phase performed by using B3LYP method and 6-311+G(3df,2pd) basis set. Zero-point correction included.

Provided that this 3 kJ difference is compensated during complexation, we can consider what would happen if thioamides had the same energy levels of conformers as amides. It would result in decreasing ΔG of 3 kJ and hence the binding constant would be more than three times higher (Eqs. 1).

$$\Delta G_0 = -RT\ln K_0; \quad \Delta G = \Delta G_0 - 3$$

$$\ln K = -\frac{1}{RT}\Delta G; \quad \ln K = \frac{1}{RT}(\Delta G_0 - 3) \tag{1}$$

$$K = \mathrm{e}^{\frac{-\Delta G_0}{RT}}\mathrm{e}^{\frac{3}{RT}} = K_0\,\mathrm{e}^{\frac{3}{RT}} \quad K = 3.36K_0(T = 298\ \mathrm{K})$$

This is only an attempt to rationalise the quite disappointing binding properties of thioamides on the basis of the structural analysis. Therefore, we believe that thioamides would be better receptors in a preorganised system, in which conformation preferences would play a less significant role (as was shown for macrocyclic tetrathioamides[14]).

3. Conclusions

In this paper, we present results of our extensive studies on the complexation properties of the model amides and thioamides both in solution and in the solid phase. One simple transformation of an amide ligand can give a novel thioamide-based receptor. Thioamide ligands possess better physical properties (good solubility, absorbance in visible part of spectra), have a slightly modified selectivity and may have an increased affinity towards anions. However, thioamide receptors seem to require preorganisation to efficiently bind anion guests. We hope that these results encourage other researchers to make further investigations of thioamides as anions receptors.

4. Experimental

4.1. General remarks

Details concerning determination of binding constants are provided in the supplementary material. DFT calculations were done using Gaussian 03 software[24] and are briefly described in the supplementary material. The X-ray measurements were performed in the Crystallographic Unit of the Physical Chemistry Laboratory at the Chemistry Department of the Warsaw University; the crystal data are included in the supplementary material. Crystallographic data (excluding structure factors) for the structures discussed in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 256442, 256443, 256444, 256445, 256652 and 261402. 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].

If not stated otherwise, all reagents were obtained from commercial sources and used as received. The column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh), the thin-layer chromatography was carried out using Merck Kieselgel F_{254} plates.

4.1.1. 1*H*-Pyrrole-2,5-dicarboxylic acid (8). The acid **8** was prepared by hydrolysis of the 1*H*-pyrrole-2,5-dicarboxylic acid monomethyl ester **7**.[21] The ester (2.8 g) was stirred with a solution of NaOH (12 g) in water (100 ml) at 60 °C for 3 h, and the reaction mixture was acidified with concentrated HCl. The precipitated crystals were filtered off and washed with 2 M HCl to give pyrrole-2,5-dicarboxylic acid in 90%.

Colourless crystals, mp decomposition at 250 °C (lit. dc. at 250 °C);[25] ^{1}H NMR (200 MHz DMSO) $\delta=12.75$ (bs, 2H, COO*H*), 12.20 (s, 1H, N*H*-pyrrole), 6.74 (d, 2H, $J_1=$ 2.4 Hz, *H*-pyrrole).

4.1.2. 1*H*-Pyrrole-2,5-dicarboxylic acid bis-butylamide (2a). To the suspension of pyrrole-2,5-dicarboxylic acid **8** (1 g, 6.5 mmol) in dry CH_2Cl_2 (25 ml) thionyl chloride (4.7 ml, 64 mmol) was added, followed by two drops of DMF. The mixture was refluxed overnight to become a clear, yellow solution. The solvent and the excess of thionyl chloride were removed in vacuo. After dissolving the resulting acid chloride **9** in dichloromethane (15 ml) and cooling to 0 °C, a solution of butylamine (3.2 ml, 33 mmol) in 2 ml CH_2Cl_2 was added with intensive stirring. The reaction was stirred overnight, and then the solvent was removed in vacuo. The solid was washed with 2 M HCl, water and ether. The resulting crude product was recrystallised from ethyl acetate. Yield 72%.

Colourless crystals, mp 195–197 °C; ^{1}H NMR (200 MHz DMSO) $\delta=11.66$ (s, 1H, N*H*-pyrrole), 8,22 (t, 2H, $J_1=$ 5.4 Hz, CON*H*), 6.72 (d, 2H, $J_1=2.2$ Hz, *H*-pyrrole), 3.22 (dt, 4H, $J_1=5.8$ Hz, $J_2=6.8$ Hz, CH_2NH), 1.46 (m, 4H, CH_2), 1.32 (m, 4H, CH_2), 0.90 (t, 6H, $J_1=7.2$ Hz, CH_3); ^{13}C NMR (50 MHz DMSO) $\delta=160.2$, 129.3, 111.8, 38.7, 31.7, 20.1, 14.2; HR ESI calcd for $C_{14}H_{23}N_3O_2Na$ $[M+Na]^+$: 288.1682 found: 288.1698; Anal. calcd for $C_{14}H_{23}N_3O_2$: C 63.37, H 8.74, N 15.84, found: C 63.55, H 8.40, N 15.81.

4.1.3. 1*H*-Pyrrole-2,5-dicarboxylic acid bis-phenylamide (2b). Acid chloride **9** was prepared as described for diamide **2a**, starting from 0.5 g (3.2 mmol) of acid **8**. After dissolving the acid chloride in dry dichloromethane (15 ml) and cooling it to 0 °C, the solution of aniline (1.4 ml, 16 mmol) in 2 ml CH_2Cl_2 was added with intensive stirring, and a precipitate appeared. The reaction was stirred overnight, and then the precipitate was filtered off and thoroughly washed with ether, 2 M HCl and water. The resulting amide **2b** was recrystallised from methanol/dichloromethane mixture. Yield 92%.

Colourless crystals, mp 248–286 °C; ^{1}H NMR (200 MHz DMSO) $\delta=12.26$ (s, 1H, N*H*-pyrrole), 10,12 (s, 2H, CON*H*), 7.75 (d, 4H, $J_1=7.6$ Hz, *o*-Ph), 7.37 (dd, 4H, $J_1=7.8$ Hz, $J_2=7.8$ Hz, *m*-Ph), 7.13–7.07 (m, 4H, *p*-Ph+ *H*-pyrrole); ^{13}C NMR (50 MHz DMSO) $\delta=158.6$, 139.4, 129.8, 129.2, 124.0, 120.5, 133.6; HR ESI calcd for $C_{18}H_{15}N_3O_2Na$ $[M+Na]^+$: 328.1056 found: 328.1074; Anal. calcd for $C_{18}H_{15}N_3O_2$: C 70.81, H 4.95, N 13.76, found: C 70.74, H 4.99, N 13.65.

4.1.4. 1*H*-Pyrrole-2,5-dicarbothioic acid bis-butylamide (3a). The 1*H*-pyrrole-2,5-dicarboxylic acid butylamide **2a** (265 mg, 1 mmol) and the Lawesson's reagent (0.8 g, 2 mmol) were suspended in dry THF (20 ml), and the mixture was refluxed for one day under argon. The solvent was evaporated in vacuo and the reaction product was purified by column chromatography on silica gel (CH_2Cl_2). The resulting crude product was recrystallised from $C_2H_4Cl_2$/pentane. Yield 90%.

Yellow crystals, mp 114–115 °C; ^{1}H NMR (200 MHz DMSO) $\delta=10.86$ (s, 1H, N*H*-pyrrole), 10.07 (t, 2H, $J_1=$ 5.6 Hz, CSN*H*), 6.96 (d, 2H, $J_1=2.4$ Hz, *H*-pyrrole), 3.68 (dt, 4H, $J_1=7.0$ Hz, $J_2=5.6$ Hz, CH_2NH), 1.64 (m, 4H, CH_2), 1.34 (m, 4H, CH_2), 0.91 (t, 6H, $J_1=7.2$ Hz, CH_3); ^{13}C NMR (50 MHz $CDCl_3$) $\delta=184.9$, 134.6, 106.0, 45.5, 30.4, 20.2, 13.7; HR EI calcd for $C_{14}H_{23}N_3S_2$ M^+: 297.1333 found: 297.1332; Anal. calcd for $C_{14}H_{23}N_3S_2$: C 56.53, H 7.79, N 14.12, S 21.56, found: C 56.74, H 7.75, N 14.15, S 21.51.

4.1.5. 1*H*-Pyrrole-2,5-dicarbothioic acid bis-phenylamide (3b). The 1*H*-pyrrole-2,5-dicarboxylic acid bisphenylamide **2b** (305 mg, 1 mmol) and Lawesson's reagent (0.8 g, 2 mmol) were suspended in dry THF (50 ml), and the mixture was refluxed over night under argon. The solvent was evaporated in vacuo. The residue was washed with CH_2Cl_2 and filtered off. The solid was purified by flash chromatography on silica gel using the following eluents: hexane/CH_2Cl_2 1:1 (150 ml), CH_2Cl_2 (150 ml), CH_2Cl_2/THF 1:1 (100 ml). The CH_2Cl_2/THF fraction gave crude thioamide **3b** which was recrystallised from THF/hexane. Yield 80%.

Yellow crystals, mp 242–244 °C; ^{1}H NMR (200 MHz DMSO) $\delta=11.52$ (s, 2H, CSN*H*), 11.13 (s, 1H, N*H*-pyrrole), 7.71 (d, 4H, $J_1=7.6$ Hz, *o*-Ph), 7.46 (dd, 4H, $J_1=$ 7.9 Hz, $J_2=7.9$ Hz, *m*-Ph), 7.33–7.25 (m, 4H, *p*-Ph+*H*-pyrrole); ^{13}C NMR (50 MHz $CDCl_3$) $\delta=183.8$, 139.6, 135.8, 129.0, 126.9, 125.5, 112.0; HR EI calcd for $C_{18}H_{15}N_3S_2$ M^+: 337.0707 found: 337.0702; Anal. calcd for $C_{18}H_{15}N_3S_2$: C 64.07, H 4.48, N 12.45, S 19.00, found: C 63.88, H 4.45, N 12.39, S 18.41.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.029.

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Silicon tetrachloride in organic synthesis: new applications for the vinylogous aldol reaction

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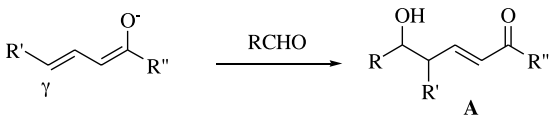
Abstract—This paper describes a novel and efficient methodology for vinylogous aldol reactions based on $SiCl_4$ catalysis. According to the nucleophilicity Mayr's scale, vinylogous aldol reaction of Chan's diene proved to be effective by using catalytic amount of $SiCl_4$, without any other promoter. On the contrary, the $SiCl_4$/Lewis base system has been conveniently exploited for the efficient and selective vinylogous reaction of less nucleophilic Danishefsky's diene and 2-trimethylsilyloxyfuran (TMSOF). Indeed, a number of Lewis bases, such as sulfoxides, formamides and phosphoramides have been successfully used as $SiCl_4$ promoters. TMSOF and silyloxydienes, resulting from 2,2,6-trimethyl-[1,3]-dioxin-4-one derivatives, required stoichiometric amount of $SiCl_4$, while vinylogous aldol reaction of Chan's and Danishefsky's dienes took satisfactorily place in the presence of catalytic or sub-stoichiometric amount of catalyst.

1. Introduction

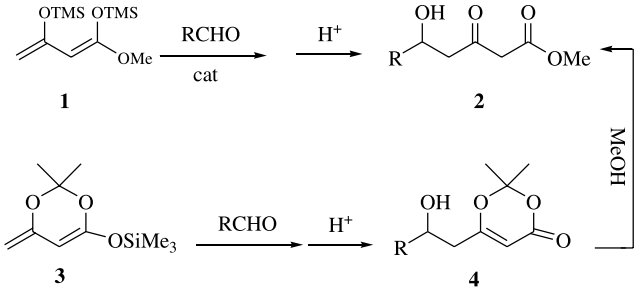
The vinylogous aldol reaction of α,β-unsaturated carbonyl compounds represents an extension of the classical aldol condensation particularly important both from a preparative and stereochemical point of view.[1] In fact, the choice of appropriate experimental conditions ensuring the γ-selectivity allows the formation of δ-hydroxy-α,β-unsaturated carbonyl derivatives of type **A** (Scheme 1) in racemic or enantioenriched form. For $R^1 \neq H$ two stereogenic centers would be generated in the desired configurations.[2] Still, thanks to the presence of an adjacent oxygenated function, the conjugate C=C double bond is susceptible to further elaboration.



Scheme 1.

In this context the use of enoxy silanes proved to be very advantageous in a variety of vinylogous additions to carbonyl compounds (aldehydes and ketones) as well as to carbonyl related electrophiles (acetals, orthoesters, imines, iminium ions and nitrones).[1,3]

In these last years, notable attention has been paid to the reactivity of acetoacetate ester dianion equivalents **1** and **3**: in fact, they have been widely used in the synthesis of enantiopure or racemic δ-hydroxy-β-keto esters **2**, key-intermediates in the preparation of many important bioactive compounds (Scheme 2).[4]



Scheme 2.

Most of the reported procedures, leading to *rac*-**2** and -**4** (starting, respectively, from **1** and **3**) in good yields, involved the use of $TiCl_4$, as catalyst of choice.[5–7] When an enantiopure aldehyde reacted with **1**, the stereochemical outcome was found to be highly dependent on the position of the stereogenic centre with respect to the carbonyl

Keywords: Vinilogous aldol reaction; Silicon tetrachloride; Organocatalyst.
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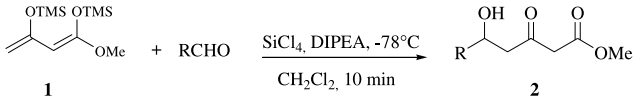
function and the substitution pattern. Furthermore, good efficiency and high levels of diastereoselectivity were often observed by using $TiCl_4$, $TiCl_2(OiPr)_2$, $Eu(fod)_3$, $BF_3 \cdot Et_2O$, as catalysts.[4]

Interestingly, Denmark[2] has recently reported that the vinylogous aldol reaction of silyl dienol ethers deriving from α,β-unsaturated esters (or 2,2,6-trimethyl-[1,3]-dioxin-4-one) can be carried out in very satisfactory way, as regards regio-, stereo- and enantioselectivity, by using an appropriate combination of $SiCl_4$ and chiral bis-phosphoramide. Because of the very mild Lewis acidic character of $SiCl_4$ the activation by the organocatalyst seemed to be a strict pre-requisite for the occurrence of the reaction.

According to the scale of nucleophilicity of silyl and alkyl enol ethers proposed by Mayr,[8] we envisaged that the overall presence of three silyloxy and alkoxy groups (+M effect) could attribute good nucleophilic properties to Chan's diene **1** and, therefore, the possibility of employment of $SiCl_4$, as exclusive catalyst, in a vinylogous aldol reaction was verified.



Scheme 3.

2. Vinylogous aldol reaction of Chan's diene 1

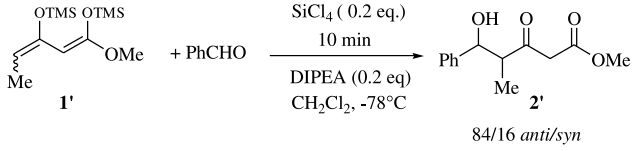
In a preliminary experiment, benzaldehyde, chosen as representative substrate, was submitted to treatment with **1** in the presence of $SiCl_4$ (1 equiv) under the conditions depicted in Scheme 3. As shown in Table 1 (entry 1), the very fast formation of the corresponding aldol **2** was achieved in quantitative yield and complete γ-regioselectivity.

More interestingly, from a preparative point of view, in spite of the well-known poor catalytic properties of $SiCl_4$, the drastic reduction of the catalyst loading (down to 0.05 equiv) did not cause any appreciable decrease of the level of efficiency and selectivity (entries 2 and 3). However, the employment of different aromatic, heteroaromatic, α,β-unsaturated aldehydes (entry 4–8) required at least 0.20 equiv of $SiCl_4$ to get comparable results. It has to be noted that a poor efficiency was observed in the case of an aliphatic aldehyde (entry 9).

Table 1. Vinylogous aldol reaction of Chan's diene **1** promoted by $SiCl_4$

Entry	R	$SiCl_4$ (equiv)	Product	Yield (%)[a]
1	Ph	1.00	**2a**	>99
2	Ph	0.20	**2a**	>99
3	Ph	0.05	**2a**	>99
4	*p*-$MeOC_6H_4$	0.20	**2b**	>99
5	*p*-$NO_2C_6H_4$	0.20	**2c**	63
6	2-Furyl	0.20	**2d**	>99
7	3-Furyl	0.20	**2e**	97
8	PhCH=CH	0.20	**2f**	97
9	*n*-C_9H_{19}	0.20	**2g**	27

[a] Yields refer to isolated, chromatographically pure compounds whose structures were confirmed by comparison with authentic samples.[9,10] In entries 2 and 4–9 the aldol reaction was performed on 1 mmol (RCHO) scale and 1/1.2/0.2/0.2 RCHO/Chan's diene/$SiCl_4$/DIPEA ratio was used.



Scheme 4.

With the aim to investigate the stereochemical aspects of the process, we have used, as nucleophile, the Chan's diene derivative **1′** (Scheme 4).[11,12] Under the standard conditions silyloxydiene **1′** was changed into aldol **2′** in satisfactory yield and good level of diastereoselectivity (64% yield, 84/16 *anti*/*syn* ratio). Since the starting material **1′** was used as a complex mixture of geometrical isomers (1/2/1/1 ratio according to ^1H NMR analysis), the stereochemical outcome has been tentatively explained by an open transition state with an antiperiplanar arrangement of the reagents: in agreement with previous reports,[13] the *anti*-diastereoselectivity was attributed to a steric interaction between the Me group and the Lewis acid coordinated to the carbonyl oxygen (Fig. 1).

It is noteworthy that an opposite diastereoselectivity was reported for the $TiCl_4$ catalysed conversion **1′**→**2′** (75/25 *syn*/*anti* ratio).[12] Furthermore, a different approach, involving a SmI_2-mediated bromo-ester-carbonyl compound

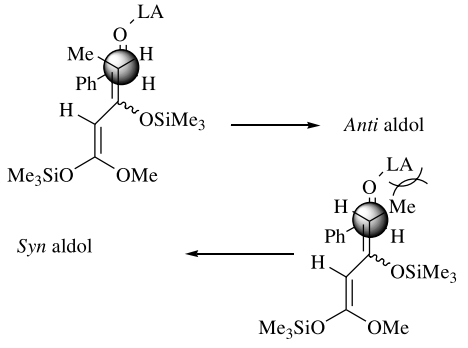
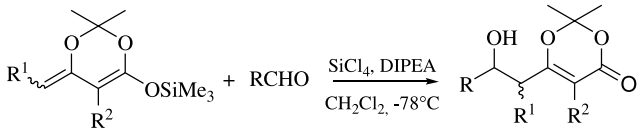


Figure 1.



3a-c **4aa-cc**

a: R^1= R^2= H
b: R^1= H; R^2= Me
c: R^1= Me; R^2= H

Scheme 5.

Rather surprisingly, in spite of the presence of a methyl group on the reaction site, no reaction at the α-position was found to take place and, furthermore, **3c** proved to be more reactive than **3b**.

2.2. Vinylogous aldol reaction of Danishefsky's diene 5

Hetero Diels–Alder (HDA) reaction of Danishefsky's diene **5** represents one of the powerful tools for the construction of pyran derivatives.[17] As is well documented, the conversion

Table 2. Vinylogous aldol reaction of **3a–c** promoted by $SiCl_4$

Entry	R	R^1	R^2	Time (h)	Product	Yield (%)[a]
1	Ph	H	H	5	**4aa**	27
2	Ph	H	H	1	**4aa**	72
3	2-Furyl	H	H	1	**4ab**	84
4	PhCH=CH	H	H	1	**4ac**	63
5	Ph	H	Me	5	**4ba**	72
6	2-Furyl	H	Me	4	**4bb**	71
7	*p*-$MeOC_6H_4$	H	Me	4	**4bc**	71
8	*o*-$MeOC_6H_4$	H	Me	4	**4bd**	78
9	*p*-$NO_2C_6H_4$	H	Me	4	**4be**	60
10	Ph	Me	H	2	**4ca**	65 (25/75)[b]
11	2-Furyl	Me	H	2	**4cb**	65 (34/66)[b]
12	PhCH=CH	Me	H	2	**4cc**	70 (13/87)[b]

[a] Yields refer to isolated, chromatographically pure compounds whose structures were confirmed by comparison with authentic samples.[14,15] With the exception of entry 1, in all entries 1/1.2/1/1 aldehyde/**3**/$SiCl_4$/DIPEA ratios were used.
[b] Values in parentheses refer to *syn*/*anti* diastereoisomeric ratios that were determined by ^{1}H NMR analysis performed on the crude products **4cc**.[15,16]

coupling afforded *syn*-aldol **2′** again as predominant diastereoisomer (75/25 *syn*/*anti* ratio).[14]

2.1. $SiCl_4$-catalysed vinylogous aldol reaction of masked acetoacetic esters 3

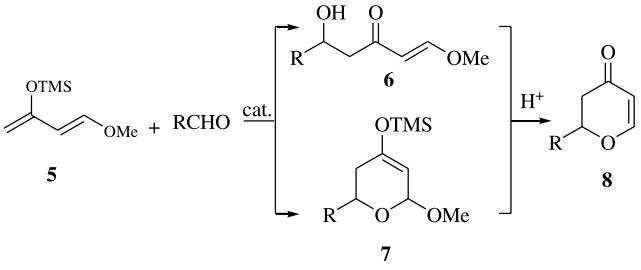
The structurally different masked acetoacetic ester **3a** was then used as nucleophile. A lower reactivity was observed so that when benzaldehyde was submitted to reaction in the presence of 0.1 equiv of $SiCl_4$ under the condition depicted in Scheme 5 and Table 2 (entry 1) the corresponding aldol **4a** could be isolated in only 27% yield. This result could be reasonably explained through the enhanced steric hindrance of **3a** in comparison with **1**.

However, the employment of 1 equiv of $SiCl_4$ proved to be successful in additional experiments affording the aldols **4aa–4ac**, as the exclusive products, with complete γ-regioselectivity and good to high yields (entries 2–4).

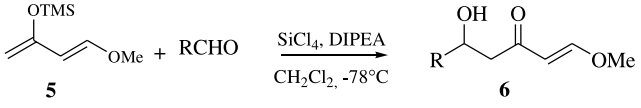
The presence of a methyl group in 5-position of the nucleophile caused only a further decrease of reactivity, but, in every case, the starting material **3b** was converted into the vinylogous aldols **4ba–be** in satisfactory way by prolonging the reaction times (entries 5–9).

The possibility to achieve a diastereoselective procedure was explored using the silyl dienol ether **3c**, easily accessible from 6-ethyl-2,2-dimethyl-dioxin-4-one as an inseparable mixture of *E* and *Z* geometrical isomers (3/5 *E*/*Z* ratio).[15] The usual treatment of **3c** in the presence of $SiCl_4$ (1 equiv) led to the γ-addition products **4ca–cc**, obtained in good yield as *syn*/*anti* diastereoisomeric mixture, resulting again the *anti*-aldol as the predominant diastereoisomer. **5→8** can take place through two different pathways (Scheme 6).

The Mukaiyama aldol type process, involving the formation of the intermediate **6**, was detected with catalysts based on Ti(IV),[18] B(III)[19] and Zr(IV)[20] complexes, while the traditional Diels–Alder reaction was found to occur in the presence of Eu(III),[21] Cr(VI)[22] and Zn(II)[23] complexes. The high efficiency previously pointed out by $SiCl_4$ in the promotion of aldol reaction of silyloxydiene **1** and **3** suggested the possibility to achieve a new procedure for the synthesis of pyran derivatives of type **8**, based on a vinylogous aldol condensation of Danishefsky's diene to give the intermediates **6**.



Scheme 6.



Scheme 7.

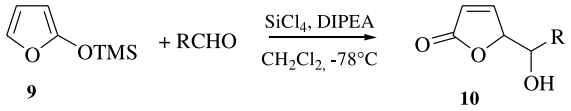
Table 3. Aldol reaction of Danishefsky's diene **5** promoted by $SiCl_4$

Entry	R	Lewis base (0.1 equiv)	$SiCl_4$ (equiv)	Time (h)	Product	Yield (%)[a]
1	Ph	—	1.0	0.75	**6a**	25
2	Ph	—	0.5	0.75	**6a**	30
3	Ph	—	0.5	4.0	**6a**	56
4	Ph	—	0.2	4.0	**6a**	NR
5	Ph	*p*-MeC_6H_4-SO–Me	0.5	0.75	**6a**	71
6	Ph	Py*N*-oxide	0.5	0.75	**6a**	74
7	Ph	DMF	0.5	1.0	**6a**	85
8	Ph	HMPA	0.5	2.5	**6a**	72
9	*p*-$NO_2C_6H_4$	*p*-MeC_6H_4-SO–Me	0.5	2.5	**6b**	57
10	2-Furyl	*p*-MeC_6H_4-SO–Me	0.5	1.5	**6c**	67
11	PhCH=CH	*p*-MeC_6H_4-SO–Me	0.5	2.0	**6d**	70
12	*o*-$MeOC_6H_4$	*p*-MeC_6H_4-SO–Me	0.5	1.5	**6e**	68

[a] All the yields refer to isolated chromatographically pure compounds, whose structures were confirmed by ^1H and ^{13}C NMR data. In all entries the reaction was performed on 1mmol (RCHO) scale. In entries 5–12 1/1.1/0.5/0.5/0.1 aldehyde/**5**/$SiCl_4$/DIPEA/Lewis base ratios were used. NR: no reaction.

Therefore, in preliminary experiments, benzaldehyde was submitted to reaction with **5** in the presence of different amounts of $SiCl_4$ under the conditions reported in Scheme 7 and Table 3 (entries 1–3).

Although yields were poor to moderate, depending on the catalyst loading and reaction times, the above reactions again led to the vinylogous aldols **6**, easily obtained as exclusive products, through an appropriate isolation and purification procedure. The lower reactivity of Danishefsky's diene **5**, in comparison with **1** and **3**, could be reasonably attributed to the presence of only two substituents at +M effect on the diene moiety. Taking in mind previous reports which pointed out the strong enhancement of the catalytic properties of $SiCl_4$ in related reactions through a beneficial interaction with a Lewis base,[24] further experiments were performed in the presence of suitable organocatalysts, such as methyl *p*-tolyl sulfoxide, HMPA, DMF and pyridine *N*-oxide.



Scheme 8.

In all entries 4–7, aldol **6a** could be obtained in significantly improved yield and in shorter reaction times.

It is notable that although the procedure proved to be unsuccessful with aliphatic aldehydes, satisfactory results have been obtained with other aromatic, heteroaromatic and α,β-unsaturated substrates (entries 8–11). This finding allows a new approach to pyran derivatives under non metallic catalysis, since the conversion **6**→**8** can be carried out in quantitative yield by a well-known acidic treatment.[25,26]

2.3. $SiCl_4$-catalysed vinylogous aldol reaction of TMSOF 9

To further broaden the scope of these $SiCl_4$-catalysed processes, we decided to investigate the reactivity of TMSOF **9**, a synthetic equivalent of 2(5*H*)-furanone anion.[27]

Benzaldehyde was therefore submitted to treatment with **9** in the presence of $SiCl_4$ (1 equiv) under the conditions reported in Scheme 8 and Table 4 (entry 1). The failure of the reaction could be reasonably explained on the ground of Mayr's scale, attributing much lower nucleophilic properties to **9** in comparison to Danishefsky's diene **5**.

Table 4. Vinylogous aldol reaction of TMSOF **9** promoted by $SiCl_4$

Entry	R	Lewis base	Time (h)	Product	Yield (%)[a]	dr
1	Ph	—	3	**10a**	NR	—
2	Ph	DMSO	2	**10a**	51	60/40[b]
3	Ph	Py*N*-oxide	2	**10a**	62	62/38[b]
4	Ph	DMF	2	**10a**	54	57/43[b]
5	Ph	HMPA	2	**10a**	57	75/25[b]
6	2-Furyl	DMSO	2	**10b**	52	60/40[c]
7	*p*-BrC_6H_4	DMSO	2	**10c**	61	60/40[c]
8	Ph–CH=CH	DMSO	1.5	**10d**	76	60/40[c]
9	Ph–CH=CH	HMPA	1.5	**10d**	54	73/27[c]
10	*p*-CNC_6H_4	DMSO	2	**10e**	44	40/60[c]
11	*p*-CNC_6H_4	Py*N*-oxide	2	**10e**	48	28/72[c]
12	*p*-MeO–C_6H_4	DMSO	2	**10f**	49	54/46[c]
13	2-Fu–CH=CH	DMSO	1.5	**10g**	64	55/45[c]
14	Ph_2C=CH	DMSO	1.2	**10h**	59	57/43[c]

[a] All the yields refer to isolated products **10**, obtained as diastereoisomeric mixtures after chromatographic purification. NR: no reaction.
[b] The reported values refer to *anti*/*syn* diastereoisomeric ratios, calculated according to previous reports.[28]
[c] The relative configurations of the products **10b–h** have been tentatively assigned according to Ref. 28.

The presence of a Lewis base again proved to be determining for the occurrence of the reaction (entries 2–5), although vinylogous aldol **10a**, isolated as exclusive product, was usually obtained in moderate yields. Comparable efficiency was observed with a variety of aromatic, heteroaromatic and α,β-unsaturated aldehydes (entries 6–14), while aliphatic aldehydes, such as decanale, were found to be completely unreactive under different experimental conditions. More interestingly from a stereochemical point of view, in several cases diastereoselectivity was found to depend on the organocatalyst employed, so that more satisfactory diastereoisomeric ratios could be afforded by its appropriate choice.

In conclusion, $SiCl_4$ has been conveniently used in new and efficient procedures for the highly regioselective vinylogous reaction of two synthetic equivalents of acetoacetate dianions. In both cases, a good level of *anti*-diastereoselectivity could be observed. In spite of the lower nucleophilicity of Danishefsky's diene and TMSOF, the activation of $SiCl_4$ by Lewis bases, such as sulfoxides, HMPA, DMF and PyN^+O^-, allowed the formation of the corresponding vinylogous aldols, again as exclusive products, in satisfactory yields.

3. Experimental

All the reactions were performed in a flame-dried glassware under an atmosphere of dry argon. All the solvents were of reagent grade and were dried and distilled immediately before use (CH_2Cl_2 from calcium hydride). Purifications of the products were performed by flash chromatography column (silica gel Merck). Starting materials and all the other reagents, unless otherwise indicated, were purchased from Aldrich or Fluka and used without further purification. The IR spectra were recorded by FT-IR instrument (Bruker Vector 22). The NMR spectra (Bruker DRX 400 (^{1}H 400 MHz; ^{13}C 100 MHz)),were performed in $CDCl_3$ solution and referenced to residual $CHCl_3$ (7.26 ppm (^{1}H); 77.23 ppm (^{13}C)). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet) q (quartet), m (multiplet) and brs (broad singlet). Coupling constants, *J*, are reported in Hz.

3.1. General procedure for the vinylogous addition of Chan's diene 1

In a typical experimental procedure, a well-stirred solution of DIPEA (35 μL, 0.20 mmol) in dry CH_2Cl_2 (3.5 mL) under argon was cooled at −78 °C and then aldehyde (1 mmol) and $SiCl_4$ (23 μL, 0.20 mmol) were added. After 10 min, the silyloxydiene **1**[12] (313 mg, 1.2 mmol) was added dropwise, followed by CH_2Cl_2 (0.5 mL). The progress of the reaction was monitored by TLC. Upon completion, a saturated aqueous $NaHCO_3$ solution (3.5 mL) was added and the whole was warmed at room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The resulting organic layer was dried over Na_2SO_4 and concentrated in vacuo affording a yellow oil. Purification by chromatography on silica gel using 9/1 $CHCl_3$/Et_2O afforded the aldol adducts **2** whose spectroscopic data matched those reported in the literature.[9,10]

3.2. General procedure for the vinylogous addition of dienes 3

In a flame-dried 2-neck round-bottom flask was added DIPEA (192 μL, 1.1 mmol) in 4 mL of CH_2Cl_2. The solution was cooled to −78 °C and then the aldehyde (1 mmol), $SiCl_4$ (127 μL, 1. mmol) and the diene **3** (1.2 mmol) were added. After 2 h at −78 °C, the solution was quenched by adding a saturated $NaHCO_3$ solution (3.5 mL) and extracted with Et_2O (3×15 mL). After drying over Na_2SO_4, the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel with 9/1 $CHCl_3$/Et_2O to afford the pure aldol adducts **4** whose spectroscopic and analytical data matched those reported in the literature.[15,16]

3.3. General procedure for the vinylogous addition of Danishefsky's diene 5

In a flame-dried 2-neck round-bottom flask, DIPEA (233 μL, 1.34 mmol), $SiCl_4$ (77 μL, 0.67 mmol) and the aldehyde (1.34 mmol) were successively added at −78 °C under argon to a solution of Lewis base (0.13 mmol) in dry CH_2Cl_2 (6 mL). Then, Danishefsky's diene (285 μL, 1.48 mmol) was slowly added over a period of 5 min. The reaction was stirred at −78 °C for the time reported in Table 3. At the end of the reaction, a mixture of 1/1 MeOH/Et_3N (0.6 mL) was added at −78 °C and the resulting mixture was allowed to stir at 0 °C till the formation of a precipitate. Then the mixture was filtered and the precipitate was washed with petroleum ether/AcOEt (8/2) (5 mL). The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel with petroleum ether/AcOEt (from 95/5 to 8/2) to afford the pure aldol adducts **6**.

3.3.1. (*E*)-5-Hydroxy-1-methoxy-5-phenylpent-1-en-3-one (6a). Viscous yellow oil. Anal. Calcd for: $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.99; H, 6.80. IR (ν_{max} (liquid film)) cm^{-1}: 3420, 2923, 1718, 1619, 1591, 1453, 1241, 1093, 760, 701. ^{1}H NMR ($CDCl_3$), δ: 7.63 (d, *J*=12.8 Hz, 1H); 7.28–7.42 (m, 5H); 5.59 (d, *J*=12.8 Hz, 1H); 5.2 (t, *J*=6.0 Hz, 1H); 3.72 (s, 3H); 2.87 (d, *J*=6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$), δ: 199.3; 163.8; 143.1; 128.4; 127.5, 125.7; 105.9; 70.2; 57.7; 49.0.

3.3.2. (*E*)-5-Hydroxy-1-methoxy-5-(4-nitrophenyl)pent-1-en-3-one (6b). Viscous yellow oil. Anal. Calcd for: $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.47; H, 5.29; N, 5.55. IR (ν_{max} (liquid film)) cm^{-1}: 3420, 2923, 1718, 1619, 1591, 1520, 1340, 1250, 1100, 830. 700. ^{1}H NMR ($CDCl_3$), δ: 8.21 (d, *J*=8.0 Hz, 2H); 7.64 (d, *J*=12.0 Hz, 1H); 7.56 (d, *J*=8.0 Hz, 2H); 5.59 (d, *J*=12.0 Hz, 1H); 5.25 (m, 1H); 4.0 (bs, 1H); 3.74 (s, 3H); 2.85 (m, 1H). ^{13}C NMR ($CDCl_3$), δ: 197.8; 163.4; 149.8; 146.4; 125.7; 122.9; 104.8; 68.6; 57.1; 47.8.

3.3.3. (*E*)-5-(Furan-2-yl)-5-hydroxy-1-methoxypent-1-en-3-one (6c). Viscous yellow oil. Anal. Calcd for: $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.33; H, 6.29. IR

(ν_{max} (liquid film)) cm^{-1}: 3401, 2924, 1715, 1676, 1620, 1589, 1437, 1247, 1011, 817, 743. ^1H NMR ($CDCl_3$), δ: 7.65 (d, $J=12.8$ Hz, 1H); 7.36 (bs, 1H); 6.33 (bd, $J=5.6$ Hz, 1H); 6.26 (d, 5.6 Hz, 1H); 5.61 (d, $J=12.8$ Hz, 1H); 5.24 (dd, $J_1=8.8$ Hz, $J_2=3.2$ Hz, 1H); 3.73 (s, 1H); 3.0 (dd, $J_1=17.2$ Hz, $J_2=8.8$ Hz, 1H); 2.96 (dd, $J_1=17.2$ Hz, $J_2=3.2$ Hz, 1H). ^{13}C NMR ($CDCl_3$), δ: 198.0; 163.0; 154.5; 141.2; 109.5; 105.4; 105.0; 63.5; 56.9; 44.3.

3.3.4. (1*E*,6*E*)-5-Hydroxy-1-methoxy-7-phenylhepta-1,6-dien-3-one (6d). Viscous yellow oil. Anal. Calcd for: $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.48; H, 6.86. IR (ν_{max} (liquid film)) cm^{-1}: 3421, 2927, 1718, 1617, 1590, 1494, 1449, 1241, 976, 750, 694. ^1H NMR ($CDCl_3$), δ: 7.64 (d, $J=13$ Hz, 1H); 7.30 (m, 5H); 6.64 (d, $J=16$ Hz, 1H); 6.22 (dd, $J=16$ Hz, 1H); 5.61 (d, $J=13$ Hz, 1H); 4.76 (m, 1H); 3.71 (s, 3H); 3.56 (br s, 1H); 2.77 (m, 2H). ^{13}C NMR ($CDCl_3$), δ: 199.0; 163.6; 136.6; 130.6; 130.0; 128.4; 127.5; 126.4; 105.9; 68.7; 57.5; 47.0.

3.3.5. (*E*)-5-Hydroxy-1-methoxy-5-(2-methoxyphenyl)-pent-1-en-3-one (6e). Viscous yellow oil. Anal. Calcd for: $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.00; H, 6.90. IR (ν_{max} (liquid film)) cm^{-1}: 3440, 2924, 1715, 1677, 1638, 1589, 1491, 1241, 757. ^1H NMR ($CDCl_3$), δ: 7.55 (d, $J=12.8$ Hz, 1H); 7.43 (bd, $J=7.6$ Hz, 1H); 7.17 (m, 1H); 6.91 (m, 1H); 6.78 (bd, $J=8.4$ Hz, 1H); 5.53 (d, $J=12.8$ Hz, 1H); 5.39 (bd, $J=9.2$ Hz, 1H); 4.00 (bs, 3H); 3.75 (s, 3H); 3.60 (s, 3H); 2.90 (bd, $J=16.4$ Hz, 1H); 2.68 (dd, $J=16.4$, $J=9.2$ Hz, 1H). ^{13}C NMR ($CDCl_3$), δ: 199.7; 163.6; 155.6; 131.4; 128.2; 126.3; 120.7; 110.1; 106.1; 65.6; 57.5; 55.2; 47.4.

3.4. General procedure for the vinylogous addition of TMSOF 9

To a flame-dried 2-neck round-bottom flask, were added the aldehyde (1 mmol), CH_2Cl_2 (2 mL) and DIPEA (209 mL, 1.2 mmol). The solution was cooled at −78 °C whereupon $SiCl_4$ (115 μL, 1 mmol) and TMSOF (168 μL, 1 mmol) were added. To the resulting solution was added the promoter (0.1 mmol in 2 mL of CH_2Cl_2) over a period of 5 min and the mixture was stirred at −78 °C for the time reported in Table 4. The reaction was then quenched with $NaHCO_3$ saturated solution (2 mL) and extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography (flash silica gel, 2/1 hexane/EtOAc) to afford the pure aldol adducts **10**.

Isolated products. The product **10a** gave spectral and analytical data according to the literature.[26]

3.4.1. 5-((Furan-2-yl)(hydroxy)methyl)furan-2(5*H*)-one (10b). Mixture of diastereoisomers. Viscous yellow oil. Anal. Calcd for: $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.13; H, 4.59. IR (ν_{max} (liquid film)) cm^{-1}: 3382; 2922; 2850; 1755; 1682; 1013.

Spectroscopic data selected for the anti diastereoisomer. ^1H NMR ($CDCl_3$) δ: 5.03 (d, 1H, $J=4.8$ Hz); 5.30–5.33 (m, 1H); 6.19 (dd, 1H, $J_1=1.6$ Hz, $J_2=5.6$ Hz); 6.38–6.41 (m, 2H); 7.42 (s, 1H); 7.56 (dd, 1H, $J_1=1.6$ Hz, $J_2=5.2$ Hz). ^{13}C NMR ($CDCl_3$) δ: 67.8; 84.5; 108.6; 110.8; 123.3; 142.9; 151.5; 153.4; 173.1.

3.4.2. 5-((4-Bromophenyl)(hydroxy)methyl)furan-2(5*H*)-one (10c). Mixture of diastereoisomers. Viscous yellow oil. Anal. Calcd for: $C_{11}H_9BrO_3$: C, 49.10; H, 3.37; Br, 29.69. Found: C, 49.19; H, 3.42, Br, 29.62. IR (ν_{max} (liquid film)) cm^{-1}: 3421; 2921; 1751; 1734; 1594; 1487; 1071.

anti Isomer. ^1H NMR ($CDCl_3$) δ: 7.52 (d, 2H, $J=8.4$ Hz); 7.30 (dd, 1H, $J_1=1.6$ Hz; $J_2=6.0$ Hz); 7.26 (d, 2H, $J=8.4$ Hz); 6.15 (dd, 1H, $J_1=1.6$ Hz; $J_2=6.0$ Hz); 5.13–5.12 (m, 1H); 5.03 (d, 1H, $J=4.0$ Hz). ^{13}C NMR ($CDCl_3$) δ: 173.1; 152.7; 137.4; 131.9 (2C); 127.9 (2C); 123.4; 122.5; 86.4; 72.4.

syn Isomer. ^1H NMR ($CDCl_3$) δ: 7.40 (d, 2H, $J=8.4$ Hz); 7.21 (dd, 1H, $J_1=1.6$ Hz; $J_2=5.8$ Hz); 7.15 (d, 2H, $J=8.4$ Hz); 6.00 (dd, 1H, $J_1=2.4$ Hz; $J_2=5.8$ Hz); 5.10 (dd, 1H, $J_1=1.6$ Hz; $J_2=6.4$ Hz); 4.69 (d, 1H, $J=6.4$ Hz). ^{13}C NMR ($CDCl_3$) δ: 173.2; 153.7; 137.3; 131.4 (2C); 128.2 (2C); 122.6; 122.5; 86.5; 73.5.

3.4.3. 5-((*E*)-1-Hydroxy-3-phenylallyl)furan-2(5*H*)-one (10d). Mixture of diastereoisomers. Viscous yellow oil. Anal. Calcd for: $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.28; H, 5.50. IR (ν_{max} (liquid film)) cm^{-1}: 3413; 3026; 2921; 1751; 1734; 1598; 1165; 1092.

Spectroscopic data selected for the anti isomer. ^1H NMR ($CDCl_3$) δ: 7.54 (d, 1H, $J=5.8$ Hz); 7.41–7.28 (m, 5H); 6.27–6.21 (m, 1H); 5.13–5.11 (m, 1H); 4.67–4.63 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 173.0; 153.1; 135.7; 133.4; 128.7 (2C); 128.4; 128.1 (2C); 125.3; 123.3; 85.6; 72.1.

3.4.4. 5-((4-Cyanophenyl)(hydroxy)methyl)furan-2(5*H*)-one (10e). Mixture of diastereoisomers. Viscous yellow oil. Anal. Calcd for: $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 67.05; H, 4.15; N, 6.43. IR (ν_{max} (liquid film)) cm^{-1}: 3447; 2922; 2229; 1752; 1609; 1166; 1102; 1042.

Spectroscopic data selected for the anti diastereoisomer. ^1H NMR ($CDCl_3$) δ: 7.65 (d, 2H, $J=7.9$ Hz); 7.49 (d, 2H, $J=7.9$ Hz); 6.11 (dd, 1H, $J_1=1.6$ Hz; $J_2=5.6$ Hz); 5.21–5.19 (m, 1H); 4.93 (d, 1H, $J=5.9$ Hz). ^{13}C NMR ($CDCl_3$) δ: 172.2; 152.6; 143.7; 132.3 (2C); 127.5 (2C); 123.4; 118.3; 112.5; 85.9; 73.8.

3.4.5. 5-(Hydroxy(4-methoxyphenyl)methyl)furan-2(5*H*)-one (10f). Mixture of diastereoisomers. Viscous yellow oil. Anal. Calcd for: $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.37; H, 5.41. IR (ν_{max} (liquid film)) cm^{-1}: 3404; 2923; 1751; 1611; 1584; 1102; 1084.

anti Isomer. ^1H NMR ($CDCl_3$) δ: 7.37 (dd, 1H, $J_1=1.6$ Hz; $J_2=5.6$ Hz); 7.29 (d, 2H, $J=8.4$ Hz); 6.91 (d, 2H, $J=8.4$ Hz); 6.14 (dd, 1H, $J_1=2.0$ Hz; $J_2=5.6$ Hz); 5.13 (dd, 1H, $J_1=1.6$ Hz; $J_2=4.4$ Hz); 4.98 (d, 1H, $J=4.4$ Hz); 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 173.0; 159.7; 153.0; 130.4; 127.3 (2C); 123.2; 114.1 (2C); 86.6; 72.9; 55.3.

syn Isomer. ^1H NMR ($CDCl_3$) δ: 7.29 (d, 2H, $J=8.4$ Hz); 7.16 (dd, 1H, $J_1=1.2$ Hz; $J_2=5.6$ Hz); 6.90 (d, 2H,

$J=8.4$ Hz); 6.11 (dd, 1H, $J_1=2.4$ Hz; $J_2=5.6$ Hz); 5.14 (dt, 1H, $J_1=1.2$ Hz; $J_2=6.8$ Hz); 4.65 (d, 1H, $J=6.8$ Hz); 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 173.2; 159.8; 153.2; 130.5; 127.5 (2C); 123.2; 114.3 (2C); 86.8; 73.0; 55.4.

3.4.6. 5-((*E*)-3-(Furan-2-yl)-1-hydroxyallyl)furan-2(5*H*)-one (10g). Mixture of diastereoisomers. Viscous yellow oil. Anal. Calcd for: $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.16; H, 4.81. IR (ν_{max} (liquid film)) cm^{-1}: 3400; 2921; 1751; 1165; 1092.

anti Isomer. ^{1}H NMR ($CDCl_3$) δ: 7.51 (dd, 1H, $J_1=1.6$ Hz; $J_2=5.6$ Hz); 7.36 (bs, 1H); 6.58 (dd, 1H, $J_1=1.6$ Hz; $J_2=15.8$ Hz); 6.38 (dd, 1H, $J_1=1.6$ Hz; $J_2=3.0$ Hz); 6.28 (d, 1H, $J=3.0$ Hz); 6.22–6.14 (m, 2H); 5.10–5.08 (m, 1H); 4.64–4.61 (m, 1H). ^{13}C NMR ($CDCl_3$) δ: 172.6; 153.0; 151.6; 142.5; 123.5; 123.3; 121.3; 111.5; 109.4; 85.5; 71.4.

syn Isomer. ^{1}H NMR ($CDCl_3$) δ: 7.49 (dd, 1H, $J_1=1.6$ Hz; $J_2=5.6$ Hz); 7.36 (bs, 1H); 6.54 (d, 1H, $J=15.6$ Hz); 6.38 (dd, 1H, $J_1=2$ Hz; $J_2=6.4$ Hz); 6.29 (d, 1H, $J=3.6$ Hz); 6.20 (dd, 1H, $J_1=2.0$ Hz; $J_2=5.6$ Hz); 6.11 (dd, 1H, $J_1=6.4$ Hz; $J_2=15.6$ Hz); 5.07–5.05 (m, 1H); 4.39 (t, 1H, $J=6.4$ Hz). ^{13}C NMR ($CDCl_3$) δ: 172.5; 153.1; 151.4; 142.6; 123.2; 123.1; 122.1; 111.5; 109.6; 85.9; 73.0.

3.4.7. 5-(1-Hydroxy-3,3-diphenylallyl)furan-2(5*H*)-one (10h). Mixture of diastereoisomers. Viscous yellow oil. Anal. Calcd for: $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.18; H, 5.46. IR (ν_{max} (liquid film)) cm^{-1}: 3412; 3056; 2921; 1751; 1598; 1162; 1102; 1038.

Spectroscopic data selected for the anti isomer. ^{1}H NMR ($CDCl_3$) δ: 4.46 (dd, 1H, $J_1=4.4$ Hz, $J_2=9.2$ Hz); 5.06–5.08 (m, 1H); 6.03 (d, 1H, $J=9.6$ Hz); 6.15–6.20 (m, 1H); 7.19–7.48 (m, 11H). ^{13}C NMR ($CDCl_3$) δ: 64.1; 85.8; 122.3; 124.3; 127.3–129.3 (9 C); 138.3; 140.8; 146.6; 149.9; 153.7; 173.1.

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26. As a demonstration, for example, **6a** (0.36 mmol) submitted to treatment with TFA (0.65 mmol, 50 μL) in CH_2Cl_2 (5 mL), afforded the corresponding HDA adduct of type **8** in >99% yield, after 2 h at 0 °C.
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28. (a) Szlosek, M.; Figadere, B. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1799–1801. (b) Matsuoka, Y.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, *32*, 584–585.

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New synthetic approach to substituted isoindolo[2,1-*a*]quinoline carboxylic acids via intramolecular Diels–Alder reaction of 4-(*N*-furyl-2)-4-arylaminobutenes-1 with maleic anhydride

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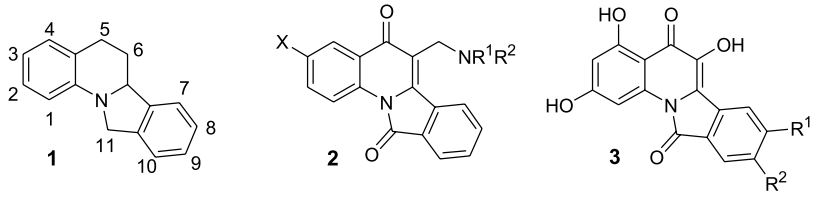
Abstract—Acylation of substituted 4-(furyl-2)-4-arylaminobut-1-enes with maleic anhydride provided 2-allyl-6-carboxy-4-oxo-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes in high yield under mild reaction conditions. The Diels–Alder adducts are formed via an initial amide formation followed by a stereoselective intramolecular [4+2] *exo*-cycloaddition reaction. Treatment of the tricyclic compounds with phosphoric acid at high temperatures (70–120 °C) promoted cyclic ether opening, intramolecular cyclization and aromatization to give the corresponding tetracyclic compounds, 5,6,6a,11-tetrahydro-10-carboxyisoindolo[2,1-*a*]quinolines, in moderate yields. The influence of the acid and the reaction temperature on the cyclization reactions are also discussed.

1. Introduction

Polycyclic nitrogen heterocycles with an isoindolo[2,1-*a*]-quinoline motif (**1**) have been shown to possess important biological properties. For example, compounds **2** and **3** (Scheme 1), analogs of berberine alkaloids, have been shown to have effect against N_2-induced hypoxia and inhibit human topoisomerase II, respectively.[1,2]

Considering the important pharmacological properties displayed by compounds with isoindolo[2,1-*a*]quinoline cores, several synthetic approaches have been reported[1–11] and reviewed.[8] Phthalimides,[1,11] derivatives of anthranilic acid,[2,4,6,10] benzanilide[3] and quinoline derivatives[5,7] have been used to prepare isoindolo[2,1-*a*]quinoline cores.

Most of these approaches were reported in the last 10 years. One of the earliest and shortest routes[7] for the preparation of the nitro substituted isoindolo[2,1-*a*]quinoline was the interaction between quinoline salt and picryl chloride in the presence of a base.



Scheme 1.

Keywords: Homoallylamines (4-(furyl-2)-4-*N*-arylaminobut-1-enes); Intramolecular furan Diels–Alder reaction (IMDAF); Isoindolo[2,1-*a*]quinolines; 3-Aza-10-oxatricyclo[5.2.1.0^{1,5}]decenes; Intramolecular Friedel–Crafts alkylation.
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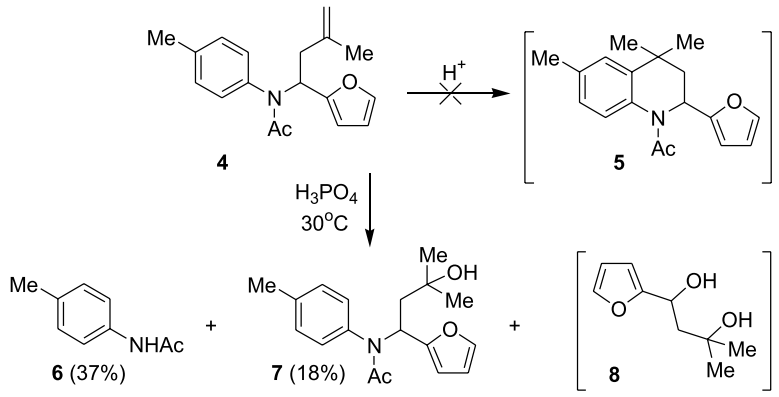
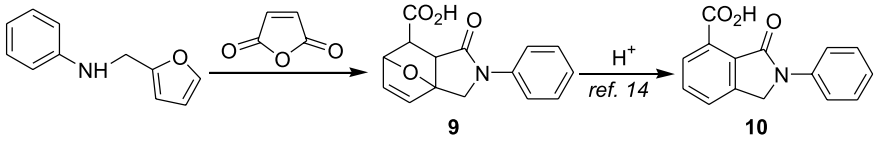


Scheme 2.

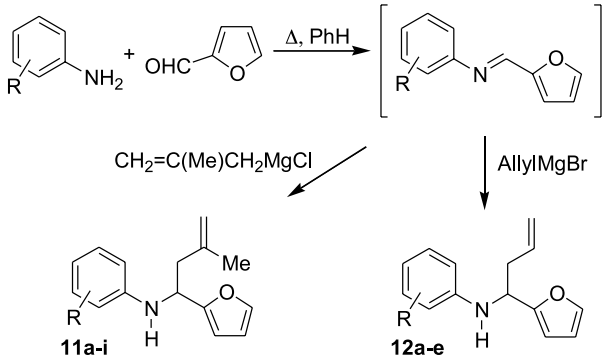
As part of our research program directed towards the preparation of polycyclic nitrogen heterocycles using homoallylamines as starting compounds, we were interested in developing a route to isoindolo[2,1-*a*]quinoline via an intramolecular Diels–Alder cycloaddition/cyclic ether opening–aromatization/cyclization sequence. Herein we disclose our initial results on this study.

We recently reported the preparation of 1,2,3,4-tetrahydroquinolines[12] from 4-alkyl- and 4-pyridylsubstituted 4-(*N*-aryl)aminobut-1-enes via an acid promoted intramolecular cyclization. It was established that Friedel–Crafts alkylation proceeded only under strong mineral acids (H_3PO_4 or H_2SO_4) treatment at 65–85 °C. An initial attempt to utilize this route to prepare 2-furyl substituted tetrahydroquinolines, a potential precursor to isoindolo[2,1-*a*]quinolines **1**, from 4-(2′-furyl)-4-(*N*-aryl)aminobut-1-enes failed due to the acid lability of the furfuryl moiety and the deactivating influence of the ammonium cation formed upon protonation. Acylation of the secondary amine would be expected to avoid decomposition of the furan ring under acidic conditions and to yield the desired cyclized product.

To study the influence of the acetyl group on the cyclization reaction, amide **4** was chosen as the substrate (Scheme 2). It was then subjected to various reaction conditions to promote the intramolecular cyclization reaction. Heating the amide **4** with $BF_3 \cdot OEt_2$ in ether or $AlCl_3$ in boiling hexane promoted polymerization and no tetrahydroquinoline **5** formation was observed. Heating compound **4** in 85% *ortho*-phosphoric acid at 30 °C promoted decomposition of amide **4** and provided *N*-acetyltoluidine **6**, alcohol **7** and diol **8** as the fragmentation products. *N*-Acetyltoluidine **6** and the hydration product **7** were isolated from the reaction mixture; the formation of compound **8** was confirmed by LCMS. We would like to note that isolation of *N*-alkyl substituted acetanilide as the fragmentation product under harsh conditions has been described in the previous publication.[13]



Scheme 3.



	a	b	c	d	e	f	g	h	i
11	H	2-Me	4-Me	2-Et	2-OMe	4-OMe	2-Bn	2-Me, 4-Me	4-*i*-Pr
Yield, %	*76*	*66*	*75*	*85*	*46*	*75*	*79*	*50*	*57*
12	H	2-Me	2-OMe	4-OMe	2-Me, 3-Me				
Yield, %	*76*	*78*	*63*	*66*	*76*				

Scheme 4.

It is also known that under acidic conditions (H_3PO_4 or H_2SO_4, 65–85 °C) 3a,6-epoxyisoindolones **9** undergoes cyclic ether opening and aromatization reaction sequence to give isoindolones **10** (Scheme 3).[14]

In this paper an alternative way of synthesizing tetracycles **1** from homoallylamines based on the acid catalyzed 3-aza-10-oxatricyclo[5.2.1.$0^{1,5}$]dec-8-enes[15] cyclization is presented.

2. Results and discussion

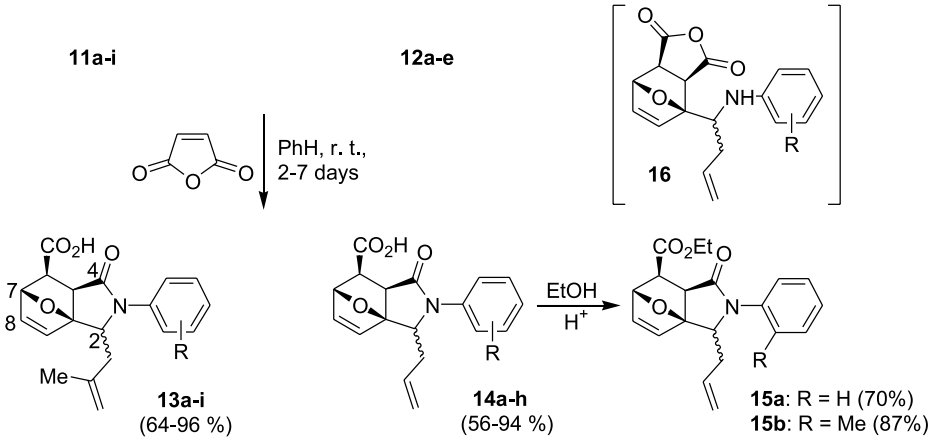
The required precursors for our study **11a–i** and **12a–e** were readily synthesized via a two-step process.[16] Condensation of the aniline and furfural gave the imine, which was then treated with the Grignard reagent to give amines **11**, **12** in moderate to good yields (Scheme 4).

The reaction of homoallylamines **11a–i**, **12a–e** with maleic anhydride[14a,b,17–23] was carried out at room temperature (2–4 days) and the products **13** and **14** were isolated in high yields. In the case of amines with an *ortho*-substituent (**11b**,**d**,**e**,**h** and **12b**,**c**,**e**) the reaction rate was slow (3–4 days) compared to the unsubstituted amines. The 2-benzyl derivative **11g** required longer reaction time (>7 days) to drive the reaction to complete (Scheme 5).

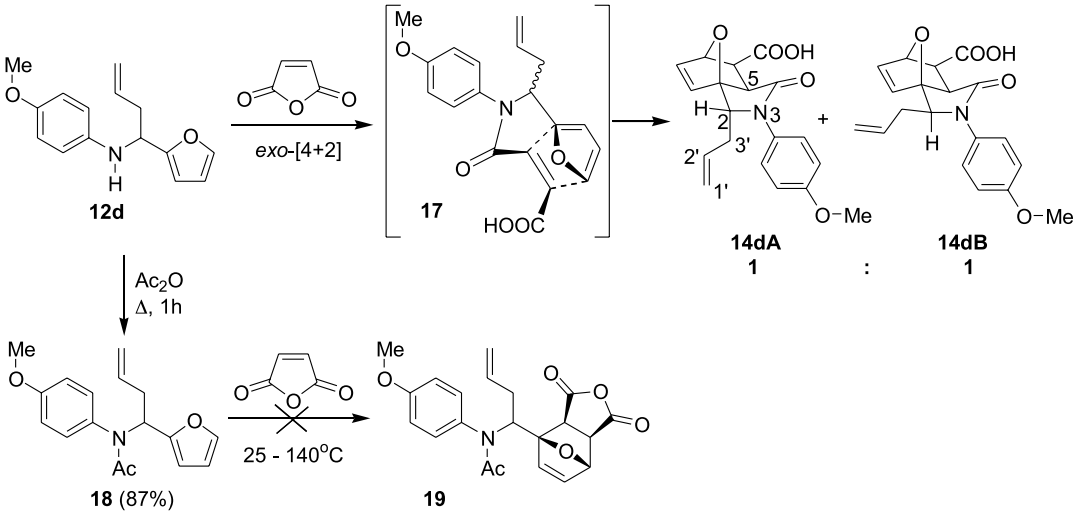
The cycloaddition reaction was highly stereoselective and only the *exo*-adducts **13**, **14** were formed as confirmed by the ^{1}H NMR spectra of the crude reaction mixtures (in the case of *endo*-orientation of carboxyl group in the 6-position in the tricycles **13**, **14** $J_{6\text{-}exo,7}$ would be around 5.0 Hz).[14b]

The possible formation of cycloaddition products **16** has been proposed in the literature.[24] The preparation of monoesters **15**, from adducts **14a**,**b** unambiguously confirms that no intermediate anhydride **16** was isolated (Scheme 5).

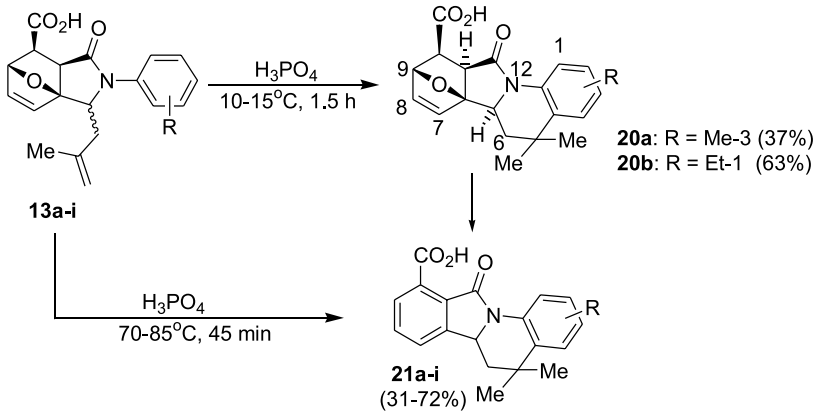
Exo-3-aza-10-oxatricyclo[5.2.1.$0^{1,5}$]dec-8-enes **13** and **14** were isolated as mixtures of isomers (**A** and **B**) based on the orientation of the methallyl (for **13**) or allyl (for **14**) groups relative to the 1,7-epoxy-bridge (Scheme 6). The isomer ratio varied from 2.5:1 to 1:3 depending on the position and nature of the substituent. Isomers of compounds **13** and **14** could not be separated due to poor solubility in commonly used organic solvents (chloroform, alcohol, ethyl acetate). However, we were able to separate isomers of compound **14d** using fractional crystallization from *i*-PrOH–DMF.



Scheme 5.



Scheme 6.



Scheme 7.

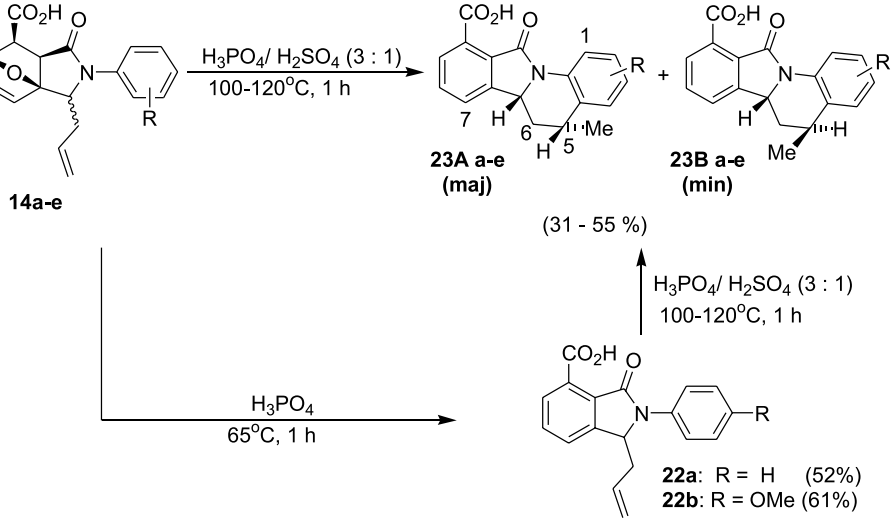
The relative configuration of the isomers **14dA** and **14dB** was established basing on ^{1}H NMR NOE values indicating the increase of H_i intensity when the H_j signal was saturated ($\eta_{Hi}\{H_j\}$). The comparison of the NOE values for 2-H, 5-H, and 2′-H in two isomers of **14d** ($\eta_{5\text{-H}}\{2'\text{-H}\}$, $\eta_{3'\text{-H}}\{5\text{-H}\} \approx 3\%$ in **14dA**, and $<1\%$ in **14dB**; $\eta_{2\text{-H}}\{5\text{-H}\} \approx \eta_{5\text{-H}}\{2\text{-H}\} < 1\%$ in **14dA**, and $\approx 2.5\%$ in **14dB**) demonstrated that the allyl substituent was *cis* to 5-H in **14dA**, and *trans* to 5-H in **14dB**.

Acylation of furfurylamines **11** and **12** with maleic anhydride initially gave the maleinamide intermediate **17**, which immediately underwent [4+2] cycloaddition to give cycloadducts **13** and **14**. Treatment of *N*-acetylallylamines **4** and **18** with maleic anhydride did not produce any of the addition products **19** even in boiling *o*-xylene (Scheme 6). That is why the alternative reaction, when an anhydride similar to **16** could be initially formed (Scheme 5), is hardly possible. It is notable that the adducts **13** and **14** did not undergo thermal *exo-endo*-isomerisation in boiling xylene as described for similar compounds types.[14b]

The rate of the intramolecular cyclization of 2-methallyl-substituted 3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **13c**,**d** (possessing an electron rich aromatic ring) was very fast and the reaction proceeded even at 10 °C in the presence of *ortho*-phosphoric acid. The products—6b,9-epoxyisoindolo[2,1-*a*]quinolines **20a**,**b** were isolated in 37 and 63% yields, respectively (Scheme 7).

According to NMR spectroscopic data, the crude product **20a** exists in the form of two isomers with relative ratio ~93:7. In the predominant isomer **20a** (isolated by recrystallization) 6a-H and 10a-H were in the same *cis*-orientation as 2-H and 5-H in the isomer **14dB** of compound **14d** (see above). The conclusion followed from comparison of the NOE values for 6a-H and 10a-H in this isomer of **20a** ($\eta_{6a\text{-H}}\{10a\text{-H}\}=2.4\%$, $\eta_{10a\text{-H}}\{6a\text{-H}\}=4\%$) with the NOE values for 2-H and 5-H in both isomers of **14d**. The stereochemistry of product **20b** was established by analogy with **20a**.

Heating compounds **13** at 70–85 °C in the presence of phosphoric acid promoted cyclization, cyclic ether opening followed by aromatization to give isoindolo[2,1-*a*]quinolines **21a–i** in 31–72% yields (Scheme 7). Heating pentacyclic compounds **20a**,**b** at 65 °C in the presence of PPA readily initiated the cyclic ether opening and aromatization reaction sequence to give the isoindoloquinolines **21d**,**c** in good yields.



Scheme 8.

Intramolecular cyclization of 2-allylsubstituted 3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-enes **14a–e** required more severe reaction conditions compared to their methallyl substituted analogs **13** (Scheme 8). It can be explained by poor stability of the intermediate secondary carbocation formed by protonation of the allyl fragment, compared to the tertiary one formed from the methallyl fragment. Accordingly, heating compounds **14a**,**b** in phosphoric acid at 65 °C initiated the cyclic ether opening and aromatization reaction sequence to give 3-allylisoindolones **22a**,**b**. However heating 3-allylisoindolones **22a–e** in the presence of phosphoric acid at 130–150 °C, polyphosphoric acid or mixture of H_3PO_4/H_2SO_4 (3:1, in volume) at 100–120 °C promoted cyclization to give compounds **23a–e**. The best results were obtained by using the latter conditions to yield compounds **23a–e** in 31–55%.

In contrast to the 5,5-dimethylisoindolo[2,1-*a*]quinolines **21**, their 5-monosubstituted homologues **23** are formed as a mixture of two diastereomeres **23A** and **23B** according to the orientation of the hydrogen atoms at the C_5 and C_{6a} positions (Scheme 8). The ratio of the isomers **23A/23B** varies from 3.5:1 to 12:1. Isomer **23A** with the 5-methyl group in a pseudo-equatorial orientation (and with a *cis*-orientation of the protons 5-H and 6a-H) predominates in all cases.

The relative stereochemistry of **23A a–e** and **23B a–e** was determined based on the *J* values between protons 5-H and 6-H. Thus, for the major isomer **23A** with an axial orientation of the proton 5-H, the coupling constants were $J_{5ax,6ax}=11.0$–13.5 and $J_{5ax,6eq}=5.8$–6.6 Hz, while for the minor isomer **23B** with an equatorial orientation of the proton 5-H, the constants were much smaller: $J_{5eq,6ax}=5.8$ and $J_{5eq,6eq}=1.2$ Hz. In both isomers of the tetracyclic acids **23** and also in their 5,5-dimethylanalogues **20**, **21** the proton 6a-H has the axial orientation confirmed by the values of the spin–spin coupling constants ($J_{6a\text{-}ax,6ax}=9.7$–12.9, $J_{6a\text{-}ax,6eq}=2.0$–4.9 Hz).

In conclusion, this work demonstrates a new two-step approach to 10-carboxy-11-oxa-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]-quinolines from readily available 4-(furyl-2)-4-*N*-arylaminobut-1-enes which generates the final products in up to 60% overall yield.

3. Experimental

All reagents were purchased from Acros Chemical Co. All solvents were used without further purification. Melting points were determined using a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained in KBr pellets for solids or in thin film for oils. NMR spectra ^{1}H (200 or 400 MHz) and ^{13}C (100.6 MHz) were recorded for solutions (2–5%) in deuteriochloroform or DMSO-d_6 at 30 °C and traces of chloroform (^{1}H NMR δ 7.26 ppm) or DMSO-d_5H (^{1}H NMR δ 2.49 ppm and ^{13}C NMR 39.43 ppm) were used as the internal standard. Mass spectra were obtained by electron ionization at 70 eV on a Varian MAT-112 spectrometer or Finnegan MAT95XL chromatomass spectrometer. The purity of the obtained substances and the composition of the reaction mixtures were controlled by TLC silufol UV_{254} plates. The separation of the final products was carried out by column chromatography on Al_2O_3 (activated, neutral, 50–200 mm) or by fractional crystallization.

3.1. 4-(2′-Furyl)-4-*N*-arylaminobutenes-1 (11a–i, 12a–e). Typical procedure

The corresponding aldimine (0.30 mol) was slowly added drop-wise at reflux to a stirred solution of allylmagnesium bromide, prepared from allyl bromide (39 mL, 0.45 mol) and magnesium turnings (22.0 g, 0.90 mol) in ether (300 mL) (for amines **12**), or to a solution of methallylmagnesium chloride, prepared from methallyl chloride (41 mL, 0.45 mol) and magnesium turnings (22.0 g, 0.90 mol) in mixture THF–ether (1:1, 300 mL) (for amines **11**). After the addition of the Schiff base, the reaction mixture was stirred for 1 h at room temperature. The cooled reaction mixture was poured into saturated aqueous NH_4Cl solution (300 mL) under ice cooling and extracted with ether (3×100 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was distilled in vacuo to give the products **11a–i** or **12a–e** as colourless oils.

3.1.1. 2-Methyl-4-*N*-phenylamino-4-(2′-furyl)butene-1 (11a). Yield 51.76 g (76%); bp 130–133 °C/3 mmHg; n_D^{25} 1.5578; IR 3390 (NH), and 1645 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.74 (br s, 3H, Me-2), 2.54 (dd, 1H, $J=14.0$, 8.2 Hz, H-3A), 2.66 (dd, 1H, $J=14.0$, 6.1 Hz, H-3B), 3.95 (br s, 1H, NH), 4.58 (dd, 1H, $J=8.2$, 6.1 Hz, H-4), 4.81 (br s, 1H, H-1A), 4.87 (br s, 1H, H-1B), 6.16 (dd, 1H, $J=3.2$, 0.9 Hz, H-3′), 6.27 (dd, 1H, $J=3.2$, 1.8 Hz, H-4′), 6.60 (m, 2H, H-Ph), 6.69 (m, 1H, H-Ph), 7.13 (m, 2H, H-Ph), 7.33 (dd, 1H, $J=1.8$, 0.9 Hz, H-5′). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.29; H, 7.49; N, 6.17. Found: C, 79.27; H, 7.48; N, 6.16.

3.1.2. 2-Methyl-4-*N*-(2″-methylphenyl)amino-4-(2′-furyl)butene-1 (11b). Yield 47.72 g (66%); bp 131–134 °C/1.5 mmHg; n_D^{23} 1.5521; IR 3421 (NH), and 1641 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68 (br s, 3H, Me-2), 2.15 (s, 3H, Me-2″), 2.60 (dd, 1H, $J=13.9$, 8.6 Hz, H-3A), 2.69 (dd, 1H, $J=13.9$, 5.4 Hz, H-3B), 3.93 (br s, 1H, NH), 4.58 (dd, 1H, $J=8.6$, 5.4 Hz, H-4), 4.85 (br s, 1H, H-1A), 4.89 (br s, 1H, H-1B), 6.16 (dd, 1H, $J=3.2$, 0.8 Hz, H-3′), 6.27 (dd, 1H, $J=3.2$, 1.8 Hz, H-4′), 6.53 (d, 1H, $J=7.7$ Hz, H-Ph), 6.64 (dt, 1H, $J=7.7$, 1.0 Hz, H-Ph), 7.04–7.02 (m, 2H, H-Ph), 7.34 (dd, 1H, $J=1.8$, 0.8 Hz, H-5′). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.65; H, 7.88; N, 5.84.

3.1.3. 2-Methyl-4-*N*-(4″-methylphenyl)amino-4-(2′-furyl)butene-1 (11c). Yield 54.23 g (75%); bp 138–140 °C/2.5 mmHg; n_D^{22} 1.5536; IR 3393 (NH), and 1650 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.71 (br s, 3H, Me-2), 2.30 (s, 3H, Me-4″), 2.63 (dd, 1H, $J=14.3$, 8.1 Hz, H-3A), 2.74 (dd, 1H, $J=14.3$, 6.1, H-3B), 3.90 (br s, 1H, NH), 4.64 (dd, 1H, $J=8.1$, 6.1 Hz, H-4), 4.89 (br s, 1H, H-1A), 4.95 (br s, 1H, H-1B), 6.24 (dd, 1H, $J=3.2$, 0.5 Hz, H-3′), 6.35 (dd, 1H, $J=3.2$, 1.8 Hz, H-4′), 6.61 (m, 2H, H-Ph), 7.03 (m, 2H, H-Ph), 7.41 (dd, 1H, $J=1.8$, 0.5 Hz, H-5′). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.69; H, 7.85; N, 5.83.

3.1.4. 2-Methyl-4-*N*-(2″-ethylphenyl)amino-4-(2′-furyl)-butene-1 (11d). Yield 65.03 g (85%); bp 141–143 °C/4 mmHg; n_D^{22} 1.5502; IR 3417 (NH), and 1651 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (t, 3H, J=7.5 Hz, CH_2Me), 1.80 (br s, 3H, Me-2), 2.63 (q, 2H, J=7.5 Hz, CH_2Me), 2.72 (dd, 1H, J=13.9, 8.7 Hz, H-3A), 2.82 (dd, 1H, J=13.9, 5.2 Hz, H-3B), 4.14 (br s, 1H, NH), 4.73 (dd, 1H, J=8.7, 5.2 Hz, H-4), 4.98 (br s, 1H, H-1A), 5.01 (br s, 1H, H-1B), 6.26 (dd, 1H, J=3.2, 0.8 Hz, H-3′), 6.38 (dd, 1H, J=3.2, 1.7 Hz, H-4′), 6.66 (d, 1H, J=7.8 Hz, H-Ph), 6.80 (t, 1H, J=7.8 Hz, H-Ph), 7.15 (t, 1H, J=7.8 Hz, H-Ph), 7.17 (d, 1H, J=7.8 Hz, H-Ph), 7.44 (dd, 1H, J=1.7, 0.8 Hz, H-5′). Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.23; N, 5.49. Found: C, 80.21; H, 8.25; N, 5.39.

3.1.5. 2-Methyl-4-*N*-(2″-methoxyphenyl)amino-4-(2′-furyl)butene-1 (11e). Yield 35.47 g (46%); bp 153–154 °C/3 mmHg; n_D^{22} 1.5578; IR 3411 (NH), and 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.75 (br s, 3H, Me-2), 2.66 (dd, 1H, J=14.0, 8.0 Hz, H-3A), 2.73 (dd, 1H, J=14.0, 5.9 Hz, H-3B), 3.88 (s, 3H, OMe), 4.63 (dd, 1H, J=8.0, 5.9 Hz, H-4), 4.68 (br s, 1H, NH), 4.87 (br s, 1H, H-1A), 4.91 (br s, 1H, H-1B), 6.22 (d, 1H, J=3.1 Hz, H-3′), 6.32 (dd, 1H, J=3.1, 1.7 Hz, H-4′), 6.61 (dd, 1H, J=7.8, 1.4 Hz, H-Ph), 6.71 (dt, 1H, J=7.8, 1.4 Hz, H-Ph), 6.81 (dd, 1H, J=7.8, 1.4 Hz, H-Ph), 6.84 (dt, 1H, J=7.8, 1.4 Hz, H-Ph), 7.38 (d, 1H, J=1.7 Hz, H-5′). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.71; H, 7.39; N, 5.45. Found: C, 74.75; H, 7.36; N, 5.42.

3.1.6. 2-Methyl-4-*N*-(4″-methoxyphenyl)amino-4-(2′-furyl)butene-1 (11f). Yield 57.83 g (75%); bp 156–158 °C/2 mmHg; n_D^{23} 1.5566; IR 3374 (NH), and 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.71 (br s, 3H, Me-2), 2.56 (dd, 1H, J=13.8, 8.1 Hz, H-3A), 2.66 (dd, 1H, J=13.8, 6.0 Hz, H-3B), 3.74 (s, 3H, OMe), 4.51 (dd, 1H, J=8.1, 6.0 Hz, H-4), 4.83 (br s, 1H, H-1A), 4.89 (br s, 1H, H-1B), 6.18 (d, 1H, J=3.2 Hz, H-3′), 6.30 (dd, 1H, J=3.2, 1.8 Hz, H-4′), 6.59 (m, 2H, H-Ph), 6.76 (m, 2H, H-Ph), 7.36 (d, 1H, J=1.8 Hz, H-5′). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.71; H, 7.39; N, 5.45. Found: C, 74.73; H, 7.39; N, 5.46.

3.1.7. 2-Methyl-4-*N*-(2″-benzylphenyl)amino-4-(2′-furyl)butene-1 (11g). Yield 75.13 g (79%); bp 185–195 °C/2.5 mmHg; n_D^{20} 1.5833; IR 3398 (NH), and 1650 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.64 (br s, 3H, Me-2), 2.50 (dd, 1H, J=13.9, 8.4 Hz, H-3A), 2.64 (dd, 1H, J=13.9, 5.4 Hz, H-3B), 4.01 (br s, 2H, CH_2Ph), 4.66 (dd, 1H, J=8.4, 5.4 Hz, H-4), 4.72 (br s, 1H, H-1A), 4.75 (m, 1H, H-1B), 5.99 (d, 1H, J=3.2 Hz, H-3′), 6.30 (dd, 1H, J=3.2, 1.8 Hz, H-4′), 6.66 (dd, 1H, J=7.5, 1.2 Hz, H-Ph), 6.81 (dt, 1H, J=7.5, 1.2 Hz, H-Ph), 7.15 (dd, 1H, J=7.5, 1.2 Hz, H-Ph), 7.19 (dt, 1H, J=7.5, 1.2 Hz, H-Ph), 7.37 (d, 1H, J=1.8 Hz Hz, H-5′), 7.25–7.39 (m, 5H, H-Ph). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.28; H, 7.26; N, 4.42. Found: C, 83.29; H, 7.30; N, 4.45.

3.1.8. 2-Methyl-4-*N*-(2′,4′-dimethylphenyl)amino-4-(2′-furyl)butene-1 (11h). Yield 38.25 g (50%); bp 142–145 °C/3 mmHg; n_D^{21} 1.5500; IR 3417 (NH), and 1620 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.67 (br s, 3H, Me-2), 2.12 (s, 3H, Me-Ar), 2.19 (s, 3H, Me-Ar), 2.58 (dd, 1H, J=13.8, 8.7 Hz, H-3A), 2.67 (dd, 1H, J=13.8, 5.3 Hz, H-3B), 3.78 (br s, 1H, NH), 4.54 (dd, 1H, J=8.7, 5.3 Hz, H-4), 4.84 (br s, 1H, H-1A), 4.88 (br s, 1H, H-1B), 6.15 (d, 1H, J=3.1 Hz, H-3′), 6.26 (dd, 1H, J=3.1, 1.8 Hz, H-4′), 6.43 (d, 1H, J=7.9 Hz, H-6″), 6.83 (br d, 1H, J=7.9 Hz, H-5″), 6.86 (br s, 1H, H-3″), 7.33 (d, 1H, J=1.8 Hz, H-5′). Anal. Calcd for $C_{17}H_{21}NO$: C, 80.00; H, 8.23; N, 5.49. Found: C, 80.20; H, 8.27; N, 5.52.

3.1.9. 2-Methyl-4-*N*-(4″-isopropylphenyl)amino-4-(2′-furyl)butene-1 (11i). Yield 45.99 g (57%); bp 150–151 °C/1 mmHg; n_D^{22} 1.5435; IR 3390 (NH), and 1635 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, 6H, J=7.0 Hz, $CHMe_2$), 1.73 (br s, 3H Hz, Me-2), 2.58 (dd, 1H, J=14.1, 8.7 Hz, H-3A), 2.68 (dd, 1H, J=14.1, 5.7 Hz, H-3B), 2.82 (sept, 1H, J=7.0 Hz, $CHMe_2$), 2.92 (br s, 1H, NH), 4.58 (dd, 1H, J=8.7, 5.7 Hz, H-4), 4.85 (br d, 1H, J=0.7 Hz, H-1A), 4.90 (br d, 1H, J=0.7 Hz, H-1B), 6.22 (dd, 1H, J=3.0, 0.7 Hz, H-3′), 6.32 (dd, 1H, J=3.0, 1.7 Hz, H-4′), 6.59 (BB′, 2H, H-Ph), 7.04 (AA′, 2H, H-Ph), 7.37 (dd, 1H, J=1.7, 0.7 Hz, H-5′). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.30; H, 8.55; N, 5.20. Found: C, 80.32; H, 8.66; N, 5.42.

3.1.10. 4-*N*-Phenylamino-4-(2′-furyl)butene-1 (12a). Yield 48.56 g (76%); bp 155–156 °C/7 mmHg; n_D^{20} 1.5640; IR 3398 (NH), and 1630 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.75 (t, 2H, J=6.4 Hz, H-3), 4.04 (br s, 1H, NH), 4.65 (t, 1H, J=6.4 Hz, H-4), 5.24 (dd, 1H, J=17.4, 1.2 Hz, H-1*trans*), 5.26 (dd, 1H, J=10.0, 1.2 Hz, H-1*cis*), 5.85 (ddt, 1H, J=17.4, 10.0, 6.4 Hz, H-2), 6.24 (dd, 1H, J=3.1, 0.8 Hz, H-3′), 6.35 (dd, 1H, J=3.1, 1.8 Hz, H-4′), 6.69 (d, 2H, J=7.5 Hz, H-Ph), 6.78 (t, 1H, J=7.5 Hz, H-Ph), 7.23 (t, 2H, J=7.5 Hz, H-Ph), 7.41 (dd, 1H, J=1.8, 0.8 Hz, H-5′). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.87; H, 7.04; N, 6.57. Found: C, 78.89; H, 7.06; N, 6.57.

3.1.11. 4-*N*-(2″-Methylphenyl)amino-4-(2′-furyl)butene-1 (12b). Yield 53.12 g (78%); bp 140–142 °C/4 mmHg; n_D^{20} 1.5576; IR 3419 (NH), and 1628 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 3H, Me-2″), 2.71 (dd, 2H, J=7.1, 6.1 Hz, H-3), 3.95 (br s, 1H, NH), 4.62 (t, 1H, J=6.1 Hz, H-4), 5.20 (dd, 1H, J=10.4, 1.8 Hz, H-1*cis*), 5.24 (dd, 1H, J=17.1, 1.8 Hz, H-1*trans*), 5.82 (ddt, 1H, J=17.1, 10.4, 7.1 Hz, H-2), 6.19 (d, 1H, J=3.1 Hz, H-3′), 6.33 (dd, 1H, J=3.1, 1.8 Hz, H-4′), 6.60 (d, 1H, J=8.4 Hz, H-Ph), 6.70 (t, 1H, J=8.4 Hz, H-Ph), 7.09 (d, 1H, J=8.4 Hz, H-Ph), 7.10 (t, 1H, J=8.4 Hz, H-Ph), 7.39 (d, 1H, J=1.8 Hz, H-5′). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.30; H, 7.49; N, 6.17. Found: C, 79.30; H, 7.51; N, 6.19.

3.1.12. 4-*N*-(2″-Methoxyphenyl)amino-4-(2′-furyl)-butene-1 (12c). Yield 45.93 g (63%); bp 156–158 °C/2 mmHg; n_D^{23} 1.5636; IR 3407 (NH), and 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.72 (t, 2H, J=7.0 Hz, H-3), 3.88 (s, 3H, OMe), 4.58 (t, 1H, J=7.0 Hz, H-4), 4.66 (br s, 1H, NH), 5.15 (dd, 1H, J=10.1, 1.3 Hz, H-1*cis*), 5.20 (dd, 1H, J=17.1, 1.3 Hz, H-1*trans*), 5.81 (ddt, 1H, J=17.1, 10.1, 7.0 Hz, H-2), 6.20 (br d, 1H, J=3.0 Hz, H-3′), 6.31 (dd, 1H, J=3.0, 1.7 Hz, H-4′), 6.60 (dd, 1H, J=7.7, 1.5 Hz, H-Ph), 6.70 (dt, 1H, J=7.7, 1.5 Hz, H-Ph), 6.80 (dd, 1H, J=7.7, 1.5 Hz, H-Ph), 6.84 (dt, 1H, J=7.7, 1.5 Hz, H-Ph), 7.37 (dd, 1H, J=1.7, 0.7 Hz, H-5′). Anal. Calcd for

$C_{15}H_{17}NO_2$: C, 74.07; H, 6.99; N, 5.76. Found: C, 74.09; H, 7.00; N, 5.76.

3.1.13. 4-*N*-(4″-Methoxyphenyl)amino-4-(2′-furyl)-butene-1 (12d). Yield 48.11 g (66%); bp 158–160 °C/4 mmHg; n_D^{23} 1.6210; IR 3391 (NH), and 1619 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.62 (t, 2H, J=6.7 Hz, H-3), 3.68 (s, 3H, OMe), 3.71 (br s, 1H, NH), 4.45 (t, 1H, J=6.7 Hz, H-4), 5.10 (dd, 1H, J=17.1, 1.9 Hz, H-1*trans*), 5.13 (dd, 1H, J=10.1, 1.9 Hz, H-1*cis*), 5.74 (ddt, 1H, J=17.1, 10.1, 6.7 Hz, H-2), 6.12 (dd, J=3.4, 0.9 Hz, H-3′), 6.25 (dd, 1H, J=3.4, 1.8 Hz, H-4′), 6.55 (m, 2H, H-Ph), 6.72 (m, 2H, H-Ph), 7.31 (dd, 1H, J=1.8, 0.9 Hz, H-5′). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.07; H, 6.99; N, 5.76. Found: C, 74.11; H, 6.97; N, 5.75.

3.1.14. 4-*N*-(2″,3″-Dimethylphenyl)amino-4-(2′-furyl)-butene-1 (12e). Yield 54.95 g (76%); bp 168–171 °C/4 mmHg; n_D^{23} 1.5571; IR 3421 (NH), and 1629 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.17 (s, 3H, Me-Ar), 2.37 (s, 3H, Me-Ar), 2.79 (t, 2H, J=6.3 Hz, H-3), 4.66 (t, 1H, J=6.3 Hz, H-4), 5.23 (dd, 1H, J=10.0, 2.0 Hz, H-1*cis*), 5.29 (dd, 1H, J=17.1, 2.0 Hz, H-1*trans*), 5.88 (ddt, 1H, J=17.1, 10.0, 6.2 Hz, H-2), 6.23 (d, 1H, J=3.2 Hz, H-3′), 6.36 (dd, 1H, J=3.2, 1.8 Hz, H-4′), 6.55 (d, 1H, J=8.1 Hz, H-Ph), 6.67 (d, 1H, J=7.5 Hz, H-Ph), 7.04 (dd, 1H, J=8.1, 7.5 Hz, H-Ph), 7.43 (d, 1H, J=1.8 Hz, H-5′). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.67; N, 7.88; H, 5.81. Found: C, 79.69; N, 7.90; H, 5.80.

3.2. *N*-Acetyl-4-*N*-arylamino-4-(2′-furyl)butene-1 (4, 18). Typical procedure

Homoallylamine **11c** or **12d** (0.10 mol) was refluxed in 10-fold molar excess of acetic anhydride (~100 mL) for 1 h. An excess of the anhydride was removed in vacuo. The residue was diluted with water (200 mL), and the solution was basified with sodium carbonate to pH 9–10. The mixture was extracted with ether (3×70 mL), and dried over $MgSO_4$. After solvent distillation, the residue was purified on Al_2O_3 (3×10 cm, ethyl acetate–hexane) in case of **4** or by recrystallization in case of **18**.

3.2.1. *N*-Acetyl-2-methyl-4-*N*-(4″-methylphenyl)amino-4-(2′-furyl)butene-1 (4). Colorless oil; yield 25.19 g (89%); R_f (20% ethyl acetate–hexane) 0.58; n_D^{24} 1.5400; IR 1656 (N–C=O, and C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 323 (100), 306 (26), 279 (85), 249 (23), 234 (19), 220 (14), 204 (13), 191 (9), 165 (5), 153 (6), 132 (5), 103 (5), 77 (9), 36 (6), 28 (10); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.77 (s, 3H, Me), 1.78 (s, 3H, Me), 2.34 (s, 3H, Me-4″), 2.40 (dd, 1H, J=15.0, 7.7 Hz, H-3A), 2.51 (dd, 1H, J=15.0, 7.7 Hz, H-3B), 4.81 (br s, 1H, H-1A), 4.86 (br s, 1H, H-1B), 6.07 (d, 1H, J=3.2 Hz, H-3′), 6.25 (dd, 1H, J=3.2, 1.9 Hz, H-4′), 6.36 (t, 1H, J=7.7 Hz, H-4), 6.67 (m, 2H, H-Ph), 7.08 (m, 2H, H-Ph), 7.33 (d, 1H, J=1.9 Hz, H-5′). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.32; H, 7.42; N, 4.95. Found: C, 76.30; H, 7.42; N, 4.98.

3.2.2. *N*-Acetyl-4-*N*-(4″-methoxyphenyl)amino-4-(2′-furyl)butene-1 (18). Colorless needle like crystals; yield 22.19 g (87%); mp 40.5–41.5 °C; IR 1656 (N–C=O, and C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 283 (11), 228 (39), 186 (100), 135 (24), 117 (12), 107 (14), 91 (21), 79 (7), 65 (6), 55 (6), 43 (9), 39 (5); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.77 (s, 3H, Ac), 2.42–2.58 (m, 2H, H-3), 3.79 (s, 3H, OMe); 5.10 (dq, 1H, J=10.3, 1.5 Hz, H-1*cis*), 5.14 (dq, 1H, J=17.3, 1.7 Hz, H-1*trans*), 5.83 (dddd, 1H, J=17.3, 10.3, 7.1, 5.9 Hz, H-2), 6.02 (dd, 1H, J=3.1, 0.8 Hz, H-3′), 6.20 (t, 1H, J=7.9 Hz, H-4); 6.24 (dd, 1H, J=3.1, 1.8 Hz, H-4′), 6.79 (br s, 4H, H-Ph), 7.33 (dd, 1H, J=1.8, 0.8 Hz, H-5′). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49. Found: C, 75.31; H, 6.69; N, 5.52.

3.3. *N-p*-Tolylacetamide (6) and *N*-acetyl-2-methyl-4-*N*-(4″-methylphenyl)amino-4-(2′-furyl)butanol-2 (7)

A mixture of 3.30 g (11.66 mmol) of *N*-acetyl derivative **4** and 15 mL of 85% H_3PO_4 was stirred at 30 °C for 1 h. Then it was diluted with water (200 mL) and basified with 25% aqueous ammonia to pH 9–10. The mixture was extracted with ethyl acetate (3×50 mL) and the extract was dried over Na_2SO_4. The crude crystalline product obtained after evaporation of the solvent was chromatographed on Al_2O_3 (1.5×10 cm, hexane–ether–ethyl acetate) to give compounds **6** and **7** as white crystals.

3.3.1. Compound 6. Yield 37%; mp 149 °C.

3.3.2. Compound 7. White crystals; yield 0.60 g (17%); R_f (20% ethyl acetate–hexane) 0.42; IR 3320 (OH), and 1700 (N–C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 3H, Me), 1.51 (s, 3H, Me), 1.90 (s, 3H, Me), 2.20 (s, 3H, Me-4″), 2.28 (dd, 1H, J=14.8, 7.5 Hz, H-3A), 2.34 (dd, 1H, J=14.8, 5.5 Hz, H-3B), 4.00 (br s, 1H, OH), 4.61 (dd, 1H, J=7.5, 5.5 Hz, H-4), 6.13 (d, 1H, J=3.2 Hz, H-3′), 6.25 (dd, 1H, J=3.2, 1.8 Hz, H-4′), 6.50 (m, 2H, H-Ph), 6.94 (m, 2H, H-Ph), 7.31 (d, 1H, J=1.8 Hz, H-5′). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.76; H, 7.64; N, 4.65. Found: C, 71.78; H, 7.69; N, 4.65.

3.4. 4-Oxo-3-aza-10-oxatricyclo[5.2.1.$0^{1,5}$]dec-8-ene-6-carboxylic acids 13a–i and 14a–e. Typical procedure

Corresponding amine **11**, **12** (0.10 mol) was dissolved in 250 mL of benzene. Then an equimolar amount of maleic anhydride (0.10 mol, 9.80 g) was added in one portion to the solution. The reaction mixture was stirred for 1–7 days at room temperature. Then the crystalline product was filtered off, washed with benzene (2×100 mL) and ether (2×80 mL) and dried at 100 °C to give desired products **13**, **14** as white solids.

3.4.1. 4-Oxo-3-phenyl-2-methallyl-3-aza-10-oxatricyclo[5.2.1.$0^{1,5}$]dec-8-ene-6-carboxylic acid (13a). Ratio of isomers **A**/**B** ~ 1/1; yield 31.20 g (96%); mp 185.5 °C; IR 1738 (COOH), and 1672 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 325 (4), 270 (18), 240 (3), 226 (11), 172 (100), 170 (12), 135 (10), 117 (9), 99 (9), 91 (10), 77 (17), 44 (6); ^1H NMR (DMSO-d_6, 200 MHz) isomer **A** δ 1.71 (br s, 3H), 2.18–2.23 (m, 2H), 2.56 (d, 1H, J=9.2 Hz), 2.94 (d, 1H, J=9.2 Hz), 4.78 (br s, 1H), 4.85 (br s, 1H), 5.01 (dd, 1H, J=8.4, 6.0 Hz), 5.08 (d, 1H, J=1.5 Hz), 6.37 (dd, 1H, J=5.8, 1.5 Hz), 6.59 (d, J=5.8 Hz), 7.05–7.60 (m, 5H), 11.50 (br s, 1H); isomer **B** δ 1.70 (br s, 3H), 2.18–2.23 (m, 2H), 2.57 (d, 1H, J=9.2 Hz), 3.20 (d, 1H, J=9.2 Hz),

4.75 (br d, 1H, J=4.4 Hz), 4.78 (br s, 1H), 4.85 (br s, 1H), 5.01 (d, 1H, J=1.5 Hz), 6.48 (dd, 1H, J=5.8, 1.5 Hz), 6.54 (d, J=5.8 Hz), 7.05–7.60 (m, 5H), 11.50 (br s, 1H). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.15; H, 5.85; N, 4.31. Found: C, 70.16; H, 5.83; N, 4.29.

3.4.2. 4-Oxo-3-(2″-methylphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13b). Ratio of isomers **A/B** ~ 1.7/1; yield 27.46 g (81%); mp 231–234 °C (decomp.); IR 1744 (COOH), and 1672 (N–C=O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 339 (2), 284 (24), 254 (2), 240 (7), 224 (4), 187 (14), 186 (100), 184 (8), 156 (98), 135 (8), 130 (12), 118 (14), 107 (6), 91 (19), 79 (5), 65 (7); ^{1}H NMR (DMSO-d_6, 400 MHz) isomer **A** δ 1.64 (s, 3H); 1.88 (dd, 1H, J=14.2, 3.6 Hz), 2.10 (s, 3H), 2.55 (d, 1H, J=9.1 Hz), 2.69 (dd, 1H, J=14.2, 10.2 Hz), 2.92 (d, 1H, J=9.1 Hz), 4.66 (br s, 1H), 4.70 (br s, 1H), 4.95 (dd, 1H, J=10.2, 3.6 Hz), 5.09 (d, 1H, J=0.9 Hz), 6.37 (dd, 1H, J=5.7, 0.9 Hz), 6.54 (d, 1H, J=5.7 Hz), 7.16–7.31 (m, 4H), 12.18 (br s, 1H); isomer **B** δ 1.57 (s, 3H), 2.16 (s, 3H), 2.24 (m, 1H), 2.41 (m, 1H), 2.53 (d, 1H, J=8.7 Hz), 3.19 (br d, 1H, J=8.7 Hz), 4.75 (t, 1H, J=5.5 Hz), 4.76 (br s, 1H), 4.77 (br s, 1H), 5.04 (d, 1H, J=1.0 Hz), 6.46 (dd, 1H, J=5.7, 1.0 Hz), 6.57 (d, 1H, J=5.7 Hz), 7.16–7.31 (m, 4H) 12.18 (br s, 1H). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 70.85; H, 6.17; N, 4.10.

3.4.3. 4-Oxo-3-(4″-methylphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13c). Ratio of isomers **A/B** ~ 1/2; yield 32.21 g (95%); mp 191.5–192.5 °C; IR 1747 (COOH), and 1680 (N–C=O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 339 (6), 323 (5), 282 (12), 254 (2), 240 (6), 186 (100), 160 (3), 145 (5), 135 (8), 118 (15), 99 (13), 91 (37), 77 (16), 71 (5), 65 (9), 55 (9); ^{1}H NMR (DMSO-d_6, 200 MHz) isomer **B** δ 1.72 (br s, 3H), 2.15–2.24 (m, 2H), 2.31 (s, 3H), 2.56 (d, 1H, J=9.2 Hz), 2.92 (d, 1H, J=9.2 Hz), 4.76 (br s, 1H), 4.85 (br s, 1H), 4.97 (dd, 1H, J=8.1, 5.8 Hz), 5.07 (d, 1H, J=1.5 Hz), 6.36 (dd, 1H, J=5.8, 1.5 Hz), 6.53 (d, 1H, J=5.8 Hz), 7.14 (BB′, 2H), 7.23 (AA′, 2H), 11.50 (br s, 1H); isomer **A** δ 1.70 (br s, 3H), 2.15–2.24 (m, 2H), 2.29 (s, 3H) 2.55 (d, 1H, J=9.2 Hz), 3.17 (d, 1H, J=9.2 Hz), 4.69 (dd, 1H, J=9.5, 3.9 Hz), 4.76 (br s, 2H), 5.00 (d, 1H, J=1.5 Hz), 6.47 (dd, 1H, J=5.8, 1.5 Hz), 6.58 (d, 1H, J=5.8 Hz), 7.19 (BB′, 2H), 7.40 (AA′, 2H), 11.50 (br s, 1H). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found; C, 70.78; H, 6.16; N, 4.13.

3.4.4. 4-Oxo-3-(2″-ethylphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13d). Ratio of isomers **A/B** ~ 1.5/1; yield 22.59 (64%); mp 225 °C; IR 1737 (COOH, and N–C=O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 353 (1), 218 (20), 182 (7), 172 (7), 144 (30), 132 (18), 120 (15), 105 (8), 99 (24), 91 (20), 77 (20), 65 (7); ^{1}H NMR (DMSO-d_6, 200 MHz) isomer **A** δ 1.11 (t, 3H, J=7.6 Hz), 1.58 (s, 3H), 1.87 (dd, 1H, J=12.5, 4.0 Hz), 2.28 (dd, 1H, J=12.5, 10.4 Hz), 2.50 (d, 1H, J=9.2 Hz), 2.54 (q, 2H, J=7.6 Hz), 2.91 (d, 1H, J=9.2 Hz), 4.77 (br s, 2H), 4.91 (dd, 1H, J=10.4, 4.0 Hz), 5.06 (d, 1H, J=1.8 Hz), 6.46 (dd, 1H, J=5.8, 1.8 Hz), 6.58 (d, 1H, J=5.8 Hz), 7.15–7.35 (m, 4H); isomer **B** δ 1.09 (t, 3H, J=7.6 Hz), 1.63 (br s, 3H), 2.45–2.60 (m, 5H), 3.16 (d, 1H, J=9.5 Hz), 4.65 (br s, 1H), 4.70 (br s, 1H), 5.08 (dd, 1H, J=6.0, 8.7 Hz), 5.10 (d, 1H, J=1.8 Hz), 6.37 (dd, 1H, J=5.8, 1.8 Hz), 6.54 (d, 1H, J=5.8 Hz), 7.15–7.35 (m, 4H). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.51; N, 3.97. Found: C, 71.37; H, 6.55; N, 3.95.

3.4.5. 4-Oxo-3-(2″-methoxyphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13e). Ratio of isomers **A/B** ~ 1.6/1; yield 23.78 (67%); mp 172–174 °C; IR 1742 (COOH), and 1658 (N–C=O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 355 (7), 301 (5), 300 (27), 270 (2), 256 (8), 221 (5), 203 (14), 202 (100), 187 (4), 135 (13), 134 (11), 123 (6), 117 (9), 107 (5), 94 (6), 91 (12), 79 (7), 77 (9); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.69 (s, 3H), 2.03 (dd, 1H, J=13.2, 3.8 Hz), 2.39 (dd, 1H, J=13.2, 10.9 Hz), 2.84 (d, 1H, J=9.1 Hz), 3.07 (d, 1H, J=9.1 Hz), 3.86 (s, 3H), 4.70 (br s, 1H), 4.76 (br s, 1H), 4.92 (dd, 1H, J=10.9, 3.8 Hz), 5.25 (d, 1H, J=1.6 Hz), 6.33 (dd, 1H, J=5.7, 1.6 Hz), 6.47 (d, 1H, J=5.7 Hz), 6.90–7.00 (m, 2H), 7.20–7.35 (m, 2H); isomer **B** δ 1.64 (s, 3H), 2.44 (m, 2H, J=9.2, 5.6 Hz), 2.84 (d, 1H, J=9.1 Hz), 3.17 (d, 1H, J=9.1 Hz), 3.81 (s, 3H), 4.64 (dd, 1H, J=9.2, 5.6 Hz), 4.76 (br s, 1H), 4.81 (br s, 1H), 5.27 (d, 1H, J=1.7 Hz), 6.40 (dd, 1H, J=5.7, 1.7 Hz), 6.57 (d, 1H, J=5.7 Hz), 6.90–7.00 (m, 2H), 7.20–7.35 (m, 2H). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.60; H, 5.92; N, 3.94. Found: C, 67.60; H, 5.95; N, 3.93.

3.4.6. 4-Oxo-3-(4″-methoxyphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13f). Ratio of isomers **A/B** ~ 1.3/1; yield 29.11 g (82%); mp 187–188.5 °C; IR 1745 (COOH), and 1672 (N–C=O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 355 (12), 337 (5), 311 (2), 300 (26), 256 (11), 221 (39), 202 (100), 186 (21), 161 (9), 149 (5), 135 (37), 117 (19), 107 (10), 91 (16), 77 (12), 55 (14), 44 (9); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.71 (br s, 3H), 2.25 (dd, 1H, J=13.5, 3.7 Hz), 2.43 (dd, 1H, J=13.5, 10.8 Hz), 2.85 (d, 1H, J=9.0 Hz), 3.02 (d, 1H, J=9.0 Hz), 3.81 (s, 3H), 4.69 (dd, 1H, J=10.8, 3.7 Hz), 4.77 (br s, 1H), 4.82 (br s, 1H), 5.31 (d, 1H, J=1.7 Hz), 5.35 (dd, 1H, J=5.7, 1.7 Hz), 6.44 (d, 1H, J=5.7 Hz), 6.92 (BB′, 2H), 7.15 (AA′, 2H), 11.50 (br s, 1H); isomer **B** δ 1.71 (br s, 3H), 2.37 (dd, 1H, J=15.9, 10.4 Hz), 2.56 (dd, 1H, J=15.9, 3.7 Hz), 2.85 (d, 1H, J=9.0 Hz), 3.15 (d, 1H, J=9.0 Hz), 3.80 (s, 3H), 4.61 (dd, 1H, J=10.4, 3.7 Hz), 4.81 (br s, 1H), 4.90 (br s, 1H), 5.26 (d, 1H, J=1.7 Hz), 6.42 (dd, 1H, J=5.7, 1.7 Hz), 6.57 (d, 1H, J=5.7 Hz), 6.90 (BB′, 2H), 7.31 (AA′, 2H), 11.50 (br s, 1H). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.60; H, 5.92; N, 3.94. Found: C, 67.60; H, 5.90; N, 3.98.

3.4.7. 4-Oxo-3-(2″-benzylphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13g). Ratio of isomers **A/B** ~ 1/4; yield 34.44 g (83%); mp 202–203 °C; IR 1738 (COOH), and 1675 (N–C=O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 415 (11), 360 (30), 316 (8), 280 (35), 262 (100), 206 (9), 194 (15), 184 (8), 180 (17), 165 (18), 135 (11), 117 (10), 105 (5), 99 (11), 91 (29), 77 (6); ^{1}H NMR (DMSO-d_6, 400 MHz) isomer **B** δ 1.58 (br s, 3H), 1.75 (dd, 1H, J=13.3, 3.3 Hz), 2.05 (dd, 1H, J=13.3, 10.8 Hz), 2.59 (d, 1H, J=9.1 Hz), 2.94 (d, 1H, J=9.1 Hz), 3.71 (d, 1H, J=15.5 Hz), 3.92 (d, 1H, J=15.5 Hz), 4.58 (br s, 1H), 4.67 (br s, 1H), 4.98 (dd, 1H, J=10.8,

3.3 Hz), 5.11 (s, 1H), 6.36 (d, 1H, J=5.7 Hz), 6.53 (d, 1H, J=5.7 Hz), 7.05 (d, 1H, J=7.6 Hz), 7.13–7.34 (m, 8H), 12.26 (br s, 1H); isomer **A** δ 1.46 (br s, 3H), 1.79 (dd, 1H, J=13.2, 4.0 Hz), 2.24 (dd, 1H, J=13.2, 11.1 Hz), 2.51 (d, 1H, J=9.1 Hz), 2.94 (d, 1H, J=9.1 Hz), 3.90 (m, 2H), 4.16 (dd, 1H, J=11.1, 4.0 Hz), 4.48 (br s, 1H), 4.63 (br s, 1H), 5.05 (br s, 1H), 6.32 (dd, 1H, J=6.0, 1.6 Hz), 6.36 (d, 1H, J=6.0 Hz), 6.94 (d, 1H, J=7.9 Hz), 7.13–7.34 (m, 8H), 12.26 (br s, 1H). Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.18; H, 6.02; N, 3.37. Found: C, 75.20; H, 6.00; N, 3.38.

3.4.8. 4-Oxo-3-(2″,4″-dimethylphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13h). Ratio of isomers **A/B**∼1/1; yield 25.42 g (72%); mp 235–236 °C; IR 1720 (COOH), and 1674 (N–C═O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 353 (2), 335 (2), 321 (7), 298 (10), 254 (5), 238 (5), 200 (100), 170 (9), 144 (22), 132 (12), 117 (10), 99 (12), 91 (14), 77 (9); ^{1}H NMR (DMSO-d_6, 200 MHz) isomer **A** δ 1.62 (br s, 3H), 1.89 (dd, 1H, J=12.8, 4.0 Hz), 2.05 (s, 3H), 2.27 (s, 3H), 2.45 (dd, 1H, J=12.8, 10.7 Hz), 2.52 (d, 1H, J=9.2 Hz), 2.89 (d, 1H, J=9.2 Hz), 4.70 (br s, 1H), 4.77 (br s, 1H), 4.87 (dd, 1H, J=10.7, 4.0 Hz), 5.08 (d, 1H, J=1.5 Hz), 6.36 (dd, 1H, J=5.8, 1.5 Hz), 6.53 (d, 1H, J=5.8 Hz), 7.02–7.15 (m, 3H); isomer **B** δ 1.60 (br s, 3H), 2.12 (s, 3H), 2.27 (br s, 3H), 2.50 (m, 2H), 2.55 (d, 1H, J=9.2 Hz), 3.13 (d, 1H, J=9.2 Hz), 4.24 (dd, 1H, J=9.2, 4.3 Hz), 4.66 (br s, 1H), 4.77 (br s, 1H), 5.03 (d, 1H, J=1.5 Hz), 6.44 (dd, 1H, J=5.8, 1.5 Hz), 6.57 (d, 1H, J=5.8 Hz), 7.02–7.15 (m, 3H). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.51; N, 3.97. Found: C, 71.39; H, 6.52; N, 4.00.

3.4.9. 4-Oxo-3-(4″-isopropylphenyl)-2-methallyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (13i). Ratio of isomers **A/B**∼1/2.5; yield 30.09 g (82%); mp 174–174.5 °C; IR 1725 (COOH), and 1675 (N–C═O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 367 (22), 312 (21), 268 (8), 214 (100), 198 (11), 172 (11), 146 (12), 135 (29), 117 (21), 99 (18), 91 (22), 77 (15), 65 (9), 55 (22), 19 (41); ^{1}H NMR (DMSO-d_6, 200 MHz) isomer **B** δ 1.19 (d, 6H, J=6.7 Hz), 1.70 (s, 3H), 2.17 (d, 2H, J=7.9 Hz), 2.55 (d, 1H, J=9.2 Hz), 2.88 (sept, 1H, J=6.7 Hz), 2.93 (d, 1H, J=9.2 Hz), 4.67 (m, 1H), 4.74 (m, 2H), 4.99 (m, 1H), 5.05 (d, 1H, J=1.6 Hz), 6.35 (dd, 1H, J=5.6, 1.6 Hz), 6.51 (d, 1H, J=5.6 Hz), 7.16 (BB′, 2H), 7.28 (AA′, 2H); isomer **A** δ 1.18 (d, 6H, J=6.6 Hz), 1.70 (s, 3H), 2.37 (m, 1H), 2.51 (m, 1H), 2.53 (d, 1H, J=9.2 Hz), 2.88 (sept, 1H, J=6.6 Hz), 3.20 (d, 1H, J=9.2 Hz), 4.85 (m, 1H), 4.99 (m, 2H), 4.99 (d, 1H, J=1.6 Hz), 6.45 (dd, 1H, J=5.8, 1.6 Hz), 6.55 (d, 1H, J=5.8 Hz), 7.24 (BB′, 2H), 7. 43 (AA′, 2H). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.94; H, 6.81; N, 3.82. Found: C, 71.96; H, 6.80; N, 3.84.

3.4.10. 4-Oxo-3-phenyl-2-allyl-3-aza-10-oxatricyclo-[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (14a). Ratio of isomers **A/B**∼1/1; yield 27.06 g (87%); mp 180–182 °C; IR 1749 (COOH), and 1670 (N–C═O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 311 (8), 293 (5), 270 (20), 226 (12), 212 (23), 173 (15), 172 (100) 170 (16) 145 (6), 121 (13), 104 (13), 103 (16), 99 (12), 93 (13), 91 (21), 77 (36); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 2.41 (m, 2H), 2.84 (d, 1H, J=9.2 Hz), 3.02 (d, 1H, J=9.2 Hz), 4.59 (dd, 1H, J=9.8, 5.2 Hz), 5.07 (dd, 1H, J=18.5, 1.3 Hz), 5.09 (dd, 1H, J=10.4, 1.3 Hz), 5.27 (d, 1H, J=1.8 Hz), 5.71 (dd, 1H, J=18.5, 10.4 Hz), 6.39 (dd, 1H, J=5.8, 1.8 Hz), 6.47 (d, 1H, J=5.8 Hz), 7.20–7.45 (m, 5H), 10.06 (br s, 1H); isomer **B** δ 2.62 (m, 2H), 2.86 (d, 1H, J=9.2 Hz), 3.10 (d, 1H, J=9.2 Hz), 4.63 (t, 1H, J=4.8 Hz), 5.17 (dd, 1H, J=18.0, 1.3 Hz), 5.19 (dd, 1H, J=9.3, 1.3 Hz), 5.33 (d, 1H, J=1.8 Hz), 5.77 (dd, 1H, J=18.0, 9.3 Hz), 6.49 (dd, 1H, J=5.8, 1.8 Hz), 6.62 (d, 1H, J=5.8 Hz), 7.20–7.45 (m, 5H), 10.06 (br s, 1H). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.45; H, 5.47; N, 4.50. Found: C, 69.49; H, 5.46; N, 4.54.

3.4.11. 4-Oxo-3-(2″-methylphenyl)-2-allyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (14b). Ratio of isomers **A/B**∼2/1; yield 27.30 g (84%); mp 211.5–212 °C; IR 1744 (COOH), and 1673 (N–C═O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 325 (2), 307 (2), 284 (7), 253 (3), 226 (6), 195 (7), 186 (100), 118 (24), 99 (13), 91 (47), 77 (24), 65 (32), 55 (22); ^{1}H NMR (DMSO-d_6, 400 MHz) isomer **A** δ 1.99 (m, 1H), 2.14 (s, 3H), 2.55 (d, 1H, J=9.1 Hz), 2.59 (m, 1H), 2.94 (d, 1H, J=9.1 Hz), 4.75 (dd, 1H, J=10.6, 4.4 Hz), 4.93 (dd, 1H, J=10.1, 1.7 Hz), 4.96 (dd, 1H, J=17.0, 1.7 Hz), 5.04 (d, 1H, J=1.7 Hz), 5.63 (ddt, 1H, J=17.0, 10.1, 7.1 Hz), 6.41 (dd, 1H, J=5.7, 1.7 Hz), 6.56 (d, 1H, J=5.7 Hz), 7.20–7.29 (m, 4H). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.41; H, 5.96; N, 4.24.

3.4.12. 4-Oxo-3-(2″-methoxyphenyl)-2-allyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (14c). Ratio of isomers **A/B**∼1.5/1; yield 19.10 g (56%); mp 152–153 °C; IR 1755 (COOH), 1684 (N–C═O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 341 (12), 300 (16), 282 (4), 256 (5), 242 (7), 202 (100), 186 (8), 134 (9), 121 (16), 99 (12), 91 (21), 81 (12), 77 (30), 65 (15); ^{1}H NMR ($CDCl_3$, 200 MHz) isomer **A** δ 2.18 (m, 1H), 2.57 (m, 1H), 2.91 (d, 1H, J=9.2 Hz), 3.03 (d, 1H, J=9.2 Hz), 3.84 (s, 3H), 4.70 (dd, 1H, J=10.4, 4.6 Hz), 5.00 (br d, 1H, J=10.4 Hz), 5.02 (br d, 1H, J=17.1 Hz), 5.41 (d, 1H, J=1.5 Hz), 5.68 (m, 1H), 6.45 (dd, 1H, J=5.8, 1.5 Hz), 6.47 (d, 1H, J=5.8 Hz), 6.95–7.05 (m, 2H), 7.20–7.40 (m, 2H); isomer **B** δ 2.40 (m, 1H), 2.57 (m, 1H), 2.91 (d, 1H, J=9.2 Hz), 3.02 (d, 1H, J=9.2 Hz), 3.87 (s, 3H), 4.53 (t, 1H, J=5.2 Hz), 5.19 (br d, 1H, J=9.2 Hz), 5.21 (br d, 1H, J=18.0 Hz), 5.41 (d, 1H, J=1.5 Hz), 5.89 (m, 1H), 6.52 (dd, 1H, J=6.1, 1.5 Hz), 6.63 (d, 1H, J=6.1 Hz), 6.95–7.05 (m, 2H), 7.20–7.40 (m, 2H). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.10. Found: C, 66.86; H, 5.56; N, 4.10.

3.4.13. 4-Oxo-3-(4″-methoxyphenyl)-2-allyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (14d). Ratio of isomers **A/B**∼1/1; yield 32.05 g (94%).

Isomer **A** mp 67.5–69.5 °C; IR 1720 (COOH), and 1685 (N–C═O) cm^{-1}; EI-MS (70 eV) m/z (rel intensity): M$^+$ 341 (22), 300 (24), 256 (12), 242 (12), 221 (63), 202 (100), 186 (17), 161 (7), 134 (11), 123 (20), 121 (37), 103 (23); 93 (14), 77 (20), 55 (11). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.24 (ddd, 2H, J=9.2, 6.8, 5.5 Hz), 2.57 (d, 1H, J=9.2 Hz), 2.93 (d, 1H, J=9.2 Hz), 3.77 (s, 3H), 4.73 (dd, 1H, J=9.2, 5.5 Hz), 4.98 (dd, 1H, J=10.1, 1.5 Hz), 5.03 (dd, 1H, J=18.0, 1.5 Hz), 5.08 (d, 1H, J=1.5 Hz), 5.72 (ddt, 1H, J=18.0, 10.1, 6.8 Hz), 6.41 (dd, 1H, J=5.8, 1.5 Hz), 6.55 (d, 1H, J=5.8 Hz), 6.96 (BB′, 2H), 7.17 (AA′, 2H), 11.50

(br s, 1H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.99 (m, 2H, CH_2-3′), 2.79 (d, 1H, J=9.2 Hz, H-6), 3.02 (d, 1H, J=9.2 Hz, H-5), 3.04 (s, 3H, MeO-4″), 4.47 (t, 1H, J=5.0 Hz, H-2), 5.15 (m, 1H, H-1′A), 5.17 (m, 1H, H-1′B), 5.23 (d, 1H, J=1.8 Hz, H-7), 5.74 (ddt, 1H, J=16.8, 10.5, 7.0 Hz, H-2′), 6.45 (dd, 1H, J=5.9, 1.8 Hz, H-8), 6.57 (d, 1H, J=5.9 Hz, H-9), 6.88 (m, 2H, H-3″ and H-5″), 7.27 (m, 2H, H-2″ and H-6″); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.6 (t, J=128.0 Hz, $C_{3'}$), 46.2 (d, J=138.2 Hz, C_6), 50.5 (d, J=139.3 Hz, C_5), 55.3 (q, J=144.2 Hz, MeO), 61.6 (d, J=146.3 Hz, C_2), 81.5 (d, J=169.0 Hz, C_7), 91.3 (s, C_1), 114.3 (d, J=160.8 Hz, $C_{3''}$ and $C_{5''}$), 119.9 (dd, J=154.0, 159.5 Hz, $C_{1'}$), 126.1 (d, J=161.0 Hz, $C_{2''}$ and $C_{6''}$), 129.3 (s, $C_{1''}$), 131.4 (d, J=152.8 Hz, $C_{2'}$), 133.4 (d, J=178.0 Hz, C_9), 137.2 (d, J=177.5 Hz, C_8), 158.0 (s, $C_{4''}$), 171.5 (s, COOH), 173.5 (s, C_4). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.10. Found: C, 66.88; H, 5.60; N, 4.10.

Isomer **B** mp 117.5–118 °C; IR 1740 (COOH), and 1675 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M$^+$ 341 (29), 300 (30), 256 (15), 242 (14), 221 (78), 202 (100), 186 (22), 161 (10), 134 (14), 123 (27), 121 (46), 108 (11), 103 (29); 93 (18), 77 (26), 55 (14). ^{1}H NMR (DMSO-d_6, 200 MHz) δ 2.48–2.59 (m, 2H), 2.55 (d, 1H, J=9.2 Hz), 3.01 (d, 1H, J=9.2 Hz), 3.76 (s, 3H), 4.57 (t, 1H, J=5.5 Hz), 5.01 (d, 1H, J=1.5 Hz), 5.12 (br dd, 1H, J=9.2, 1.5 Hz), 5.14 (dd, 1H, J=18.3, 1.5 Hz), 5.82 (ddt, 1H, J=18.3, 9.2, 6.7 Hz), 6.52 (dd, 1H, J=5.8, 1.5 Hz), 6.73 (d, 1H, J=5.8 Hz), 6.95 (BB′, 2H), 7.41 (AA′, 2H), 11.57 (br s, 1H); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (dddt, 1H, J=13.4, 7.7, 1.1 Hz, H-3′A), 2.41 (dddt, 1H, J=13.4, 10.8, 6.6, 1.1 Hz, H-3′B), 2.82 (d, 1H, J=9.1 Hz, H-6), 3.00 (d, 1H, J=9.1 Hz, H-5), 3.11 (s, 3H, MeO-4″), 4.50 (dd, 1H, J=10.8, 4.5 Hz, H-2), 5.01 (m, 1H, H-1′A), 5.04 (m, 1H, H-1′B), 5.27 (d, 1H, J=1.8 Hz, H-7), 5.68 (dddd, 1H, J=17.0, 10.2, 7.7, 6.6 Hz, H-2′), 6.38 (dd, 1H, J=5.7, 1.8 Hz, H-8), 6.46 (d, 1H, J=5.7 Hz, H-9), 6.89 (m, 2H, H-3″ and H-5″), 7.14 (m, 2H, H-2″ and H-6″); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.6 (t, J=131.5 Hz, $C_{3'}$), 46.1 (d, J=140.0 Hz, C_6), 50.6 (d, J=140.0 Hz, C_5), 55.3 (q, J=144.2 Hz, MeO), 60.1 (d, J=141.7 Hz, C_2), 81.6 (d, J=169.0 Hz, C_7), 90.4 (s, C_1), 114.2 (d, J=160.0 Hz, $C_{3''}$ and $C_{5''}$), 118.8 (dd, J=154.5, 158.5 Hz, $C_{1'}$), 127.3 (d, J=160.5 Hz, $C_{2''}$ and $C_{6''}$), 128.6 (s, $C_{1''}$), 132.3 (d, J=154.8 Hz, $C_{2'}$), 135.6 (d, J=177.8 Hz, C_8), 135.8 (d, J=177.8 Hz, C_9), 158.4 (s, $C_{4''}$), 172.2 (s, COOH), 173.4 (s, C_4). Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.10. Found: C, 66.86; H, 5.58; N, 4.12.

3.4.14. 4-Oxo-3-(2″,3″-dimethylphenyl)-2-allyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid (14e). Ratio of isomers **A/B** ~2.5/1; yield 25.76 g (76%); mp 227 °C; IR 1747 (COOH), and 1672 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M$^+$ 339 (4), 321 (2), 299 (5), 298 (27), 254 (9), 240 (14), 201 (16), 200 (100), 198 (11), 170 (6), 159 (7), 132 (13), 130 (10), 121 (16), 120 (8), 105 (8), 103 (14), 99 (9), 91 (16), 77 (17); ^{1}H NMR (DMSO-d_6, 200 MHz) isomer **A** δ 2.12 (s, 3H), 2.29 (s, 3H), 2.65 (m, 2H), 2.85 (d, 1H, J=10.0 Hz), 3.03 (d, 1H, J=10.0 Hz), 4.49 (dd, 1H, J=8.9, 5.0 Hz), 5.25 (dd, 2H, J=16.8, 10.1 Hz), 5.33 (d, 1H, J=1.5 Hz), 5.89 (dd, 1H, J=16.8, 10.1 Hz), 6.50 (dd, 1H, J=5.5, 1.5 Hz), 6.70 (br d, 1H, J=5.5 Hz), 6.95–7.00 (m, 1H), 7.05–7.25 (m, 2H), 12.00 (br s, 1H); isomer **B** δ 2.12 (s, 3H), 2.29 (s, 3H), 2.65 (m, 2H), 2.84 (d, 1H, J=10.0 Hz), 2.98 (d, 1H, J=10.0 Hz), 4.13 (dd, 1H, J=5.8, 4.6 Hz), 5.01 (m, 1H, J=10.7 Hz), 5.03 (m, 1H, J=17.1 Hz), 5.38 (d, 1H, J=1.5 Hz), 5.65 (m, 1H, J=16.8, 10.1 Hz), 6.39 (dd, 1H, J=5.5, 1.5 Hz), 6.57 (br d, 1H, J=5.5 Hz), 6.95–7.00 (m, 1H), 7.05–7.25 (m, 2H), 12.00 (br s, 1H). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 70.83; H, 6.17; N, 4.13.

3.5. 6-Ethoxycarbonyl-4-oxo-3-aza-10-oxatricyclo-[5.2.1.0^{1,5}]dec-8-enes (15a,b). Typical procedure

Adduct **14a**,**b** (0.01 mol) was refluxed in ethanol (20 mL) for 2 h in the presence of catalytic amounts of H_2SO_4 (concd). Then the reaction mixture was poured into 150 mL of water and extracted with ethyl acetate (4×60 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude product was recrystallized from mixture of hexane–ethyl acetate to give esters **15a**,**b** as white solids.

3.5.1. 6-Ethoxycarbonyl-4-oxo-3-phenyl-2-allyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene (15a). Ratio of isomers **A/B** ~1.2/1; yield 2.37 g (70%); mp 74.5–76 °C; IR 1786 (COOEt), 1695 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M$^+$ 339 (23), 298 (31), 270 (1), 212 (26), 200 (5), 172 (100), 127 (80), 121 (27), 104 (15), 99 (80), 91 (14), 77 (37), 65 (8); ^{1}H NMR (DMSO-d_6, 200 MHz) isomer **A** δ 1.22 (t, 3H, J=7.2 Hz), 2.25 (m, 2H), 2.68 (d, 1H, J=9.2 Hz), 3.02 (d, 1H, J=9.2 Hz), 4.10 (d, 2H, J=7.2 Hz), 4.85 (dd, 1H, J=10.1, 4.6 Hz), 4.95–5.20 (m, 2H), 5.13 (d, 1H, J=1.5 Hz), 5.78 (m, 1H), 6.42 (dd, 1H, J=5.8, 1.5 Hz), 6.57 (d, 1H, J=5.8 Hz), 7.10–7.60 (m, 5H); isomer **B** δ 1.17 (t, 3H, J=7.2 Hz), 2.59 (m, 2H), 2.68 (d, 1H, J=9.2 Hz), 3.13 (d, 1H, J=9.2 Hz), 4.02 (q, 2H, J=7.2 Hz), 4.71 (dd, 1H, J=5.5, 4.6 Hz), 4.95–5.20 (m, 2H), 5.05 (d, 1H, J=1.5 Hz), 5.78 (m, 1H), 6.52 (dd, 1H, J=5.8, 1.5 Hz), 6.75 (d, 1H, J=5.8 Hz), 7.10–7.60 (m, 5H). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 70.83; H, 6.17; N, 4.12.

3.5.2. 6-Ethoxycarbonyl-4-oxo-3-(2′-methylphenyl)-2-allyl-3-aza-10-oxatricyclo[5.2.1.0^{1,5}]dec-8-ene (15b). Ratio of isomers **A/B** ~3/1; yield 3.07 g (87%); mp 115–116.5 °C; IR 1724 (COOEt), and 1697 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M$^+$ 353 (10), 312 (34), 307 (7), 232 (9), 226 (43), 210 (11), 186 (100), 156 (15), 144 (11), 127 (57), 121 (28), 99 (80), 91 (38), 65 (15), 39 (11); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.30 (t, 3H, J=7.1 Hz), 2.05–2.19 (m, 1H), 2.24 (s, 3H), 2.44–2.57 (m, 1H), 2.78 (d, 1H, J=9.1 Hz), 2.93 (d, 1H, J=9.1 Hz), 4.15–4.37 (m, 2H), 4.51 (dd, 1H, J=10.8, 4.5 Hz), 5.01 (dd, 1H, J=10.0, 7.0 Hz), 5.04 (dd, 1H, J=17.0, 7.0 Hz), 5.25 (d, 1H, J=1.6 Hz), 5.60–5.74 (m, 1H), 6.41 (dd, 1H, J=5.7, 1.7 Hz), 6.52 (dd, 1H, J=5.7, 1.3 Hz), 7.20–7.28 (m, 4H). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.39; H, 6.51; N, 3.97. Found: C, 71.42; H, 6.50; N, 3.40.

3.6. 11-Oxo-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic acids (20a,b). Typical procedure

A mixture of the corresponding adduct **13c**,**d** (0.01 mol) and 85% H_3PO_4 (30 mL) was stirred at 10–15 °C for 1.5 h

(monitoring by TLC). At the end of the reaction, the mixture was diluted with water (150 mL). The obtained precipitate was filtered off, washed with cold water (5×80 mL) and dried in air. Then the crude product was recrystallized to give the desired product **20** as colorless crystals.

3.6.1. 3,5,5-Trimethyl-11-oxo-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic acid (20a). *Major isomer*. Yield 1.25 g (37%); mp 215.5–217 °C decomp. (chloroform); IR 1746 (COOH), and 1672 (N–C=O, and C=C) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 339 (11), 321 (4), 294 (3), 240 (100), 224 (18), 196 (8), 181 (7), 158 (13), 144 (8), 115 (7), 91 (7), 81 (4); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.29 (s, 3H, Me-5), 1.35 (s, 3H, Me-5), 1.77 (dd, 1H, J=13.5, 3.4 Hz, H-6A), 1.83 (dd, 1H, J=13.5, 11.8 Hz, H-6B), 2.25 (s, 3H, Me-3), 2.56 (d, 1H, J=9.1 Hz, H-10), 3.06 (d, 1H, J=9.1 Hz, H-10a), 4.62 (dd, 1H, J=11.8, 3.4 Hz, H-6a), 5.02 (d, 1H, J=1.7 Hz, H-9), 6.49 (dd, 1H, J=5.7, 1.7 Hz, H-8), 6.61 (d, 1H, J=5.7 Hz, H-7), 6.95 (dd, 1H, J=8.5, 2.0 Hz, H-2), 7.24 (d, 1H, J=2.0 Hz, H-4), 8.47 (d, 1H, J=8.5 Hz, H-1), 12.19 (br s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 173.2 (s), and 169.5 (s) (COOH, and C_{12}), 137.6 (d, J=177.5 Hz, C_8), 134.7 (d, J=178.5 Hz, C_7), 134.4, 133.1, and 132.1 (s, C_{4a}, C_3, C_{12a}), 127.2 (d, J=154.0 Hz, C_4), 126.9 (d, J=157.5 Hz, C_2), 118.0 (d, J=163.5 Hz, C_1), 89.8 (s, C_{6b}), 81.0 (d, J=168.5 Hz, C_9), 52.5 (d, J=142.5 Hz, C_{6a}), 51.0 (d, J=141.0 Hz, C_{10a}), 45.1 (d, J=138.5 Hz, C_{10}), 37.1 (t, J=131.5 Hz, C_6), 32.6 (s, C_5), 32.2 (q, J=126.0 Hz, Me-5), 30.5 (q, J=126.0 Hz, Me-5), 20.7 (q, J=126.5 Hz, Me-3). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.80; H, 6.19; N, 4.13. Found: C, 70.82; H, 6.23; N, 4.17. *Minor isomer* (has not been isolated). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.33 (s, 3H, Me-5), 1.37 (s, 3H, Me-5), 1.95 (t, 1H, J=13.1 Hz, H-6A), 2.12 (dd, 1H, J=13.1, 2.1 Hz, H-6B), 2.25 (s, 3H, Me-3), 2.57 (d, 1H, J=9.1 Hz, H-10), 3.02 (d, 1H, J=9.1 Hz, H-10a), 4.05 (dd, 1H, J=13.1, 2.1 Hz, H-6a), 5.08 (d, 1H, J=1.7 Hz, H-9), 6.50 (dd, 1H, J=5.7, 1.7 Hz, H-8), 6.71 (d, 1H, J=5.7 Hz, H-7), 6.97 (dd, 1H, J=8.2, 2.0 Hz, H-2), 7.27 (d, 1H, J=2.0 Hz, H-4), 7.61 (d, 1H, J=8.2 Hz, H-1), 12.19 (br s, 1H, COOH).

3.6.2. 1-Ethyl-5,5-dimethyl-11-oxo-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic acid (20b). Yield 2.22 g (63%); mp 150–151 °C (heptane–chloroform); IR 1700 (COOH), and 1617 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 353 (4), 309 (2), 280 (4), 254 (100), 240 (16), 212 (12), 186 (13), 172 (13), 160 (16), 144 (12), 130 (10), 115 (11), 99 (20), 91 (7), 77 (4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, 3H, J=7.7 Hz), 1.36 (s, 3H), 1.44 (s, 3H), 1.91 (t, 1H, J=12.8 Hz), 2.13 (dd, 1H, J=12.9, 2.7 Hz), 2.75 (d, 2H, J=7.7 Hz), 2.83 (d, 1H, J=8.8 Hz), 2.92 (d, 1H, J=8.8 Hz), 4.23 (dd, 1H, J=12.7, 2.7 Hz), 5.28 (d, 1H, J=1.5 Hz), 6.49 (dd, 1H, J=6.0, 1.5 Hz), 6.62 (d, 1H, J=6.0 Hz), 7.12 (dd, 1H, J=7.4, 2.4 Hz), 7.15 (t, 1H, J=7.4 Hz), 7.19 (dd, 1H, J=7.4, 2.4 Hz), 7.40 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 172.8 (s); 169.1 (s) (COOH and N–C=O); 139.0 (s); 138.8 (s); 132.4 (s); 136.8 (d) and 134.4 (d) (C_7 and C_8); 126.3 (d); 125.8 (d); 124.1 (d); 90.6 (s, C_{6b}); 81.7 (d, C_9); 55.2 (d, C_{6a}); 49.4 (d, C_{10a}); 45.1 (d, C_{10}); 40.6 (t, C_6); 34.0 (s, C_5); 33.2 (q) and 31.6 (q) (Me-5); 24.5 (t, CH_2CH_3); 14.3 (q, CH_2CH_3). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.20; H, 6.29; N, 4.15.

3.7. 5,5-Dimethyl-10-carboxyisoindolo[2,1-*a*]quinoline-11-ones (21a–i). Typical procedure

A mixture of corresponding adduct **13** (0.01 mol) and 85% H_3PO_4 (40 mL) was stirred at 70–85 °C for 45 min (monitoring by TLC). At the end of the reaction, the mixture was diluted with water (200 mL). The obtained precipitate was filtered off, washed with cold water (5× 80 mL) and dried in air. Then the crude product was recrystallized to give desired isoindoloquinolines **21** as colorless crystals.

3.7.1. 5,5-Dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21a). Yield 2.09 g (68%); mp 237.5–240 °C (heptane–chloroform); IR 1727 (COOH), and 1617 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 307 (92), 292 (65), 264 (21), 263 (100), 248 (18), 232 (11), 218 (15), 204 (12), 115 (9), 102 (7), 91 (6); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 3H, Me-5), 1.54 (s, 3H, Me-5), 1.72 (t, 1H, J=12.7 Hz, H-6*ax*), 2.41 (dd, 1H, J=12.7, 2.6 Hz, H-6*eq*), 4.97 (dd, 1H, J=12.7, 2.6 Hz, H-6a), 7.23–7.39 (m, 2H, H-Ar), 7.48 (dd, 1H, J=7.3, 1.8 Hz, H-Ar), 7.76–7.86 (m, 2H, H-Ar), 8.38 (dd, 1H, J=7.9, 1.5 Hz, H-1), 8.50 (dd, 1H, J=7.9, 1.5 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.2 (s), and 165.3 (s) (COOH, and N–C=O), 146.4 (s), 136.6 (s), 133.1 (s), 129.5 (s), 128.9 (s), 132.9 (d, C_8), 131.7 (d, C_9), 127.4 (d), 126.6 (d), 126.5 (d), 125.6 (d), 120.4 (d), 56.5 (d, C_{6a}), 41.9 (t, C_6), 33.6 (s, C_5), 31.7 (q), and 30.6 (q) (Me-5). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.22; H, 5.57; N, 4.59.

3.7.2. 1,5,5-Trimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21b). Yield 1.00 g (31%); mp 209.5–210 °C (*i*-PrOH–DMF); IR 1728 (COOH), and 1619 (N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 321 (79), 306 (12), 288 (13), 275 (100), 262 (12), 245 (4), 221 (12), 130 (14), 115 (25), 91 (15), 77 (18), 65 (12), 51 (13); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H, Me-5), 1.44 (s, 3H, Me-5), 1.72 (dd, 1H, J=13.4, 10.3 Hz, H-6*ax*), 2.39 (s, 3H, Me-1), 2.42 (dd, 1H, J=13.4, 4.7 Hz, H-6*eq*), 4.98 (dd, 1H, J=10.3, 4.7 Hz, H-6a), 7.20–7.30 (m, 3H, H-Ar), 7.77–7.79 (m, 2H, H-Ar), 8.45 (dd, 1H, J=5.8, 2.1, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.6 (s), and 165.4 (s) (COOH, and N–C=O), 148.7 (s), 139.5 (s), 132.7 (s), 131.7 (s), 129.8 (s), 128.5 (s), 133.0 (d, C_8), 131.4 (d, C_9), 129.2 (d), 126.81 (d), 126.80 (d), 124.1 (d), 57.3 (d, C_{6a}), 45.2 (t, C_6), 33.2 (s, C_5), 32.2 (q), and 30.2 (q) (Me-5), 20.0 (q, Me-1). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; N, 5.92; H, 4.36. Found: C, 74.80; N, 5.96; H, 4.32.

3.7.3. 3,5,5-Trimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21c). Yield 1.61 g (50%); mp 222–230 °C decomposition (heptane–chloroform); IR 1708 (COOH, and N–C=O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 321 (1), 277 (66), 262 (100), 246 (14), 232 (17), 218 (3), 124 (6), 115 (9), 91 (4), 77 (7); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 3H, Me-5), 1.52 (s, 3H, Me-5), 1.69 (t, 1H, J=13.0 Hz, H-6*ax*), 2.38 (s, 3H, Me-3), 2.38 (dd, 1H, J=13.0, 2.7 Hz, H-6*eq*), 4.92 (dd, 1H,

J=13.0, 2.7 Hz, H-6a), 7.13 (dd, 1H, J=8.5, 1.5 Hz, H-2), 7.25 (d, 1H, J=1.5 Hz, H-4), 7.74 (d, 1H, J=8.5 Hz, H-1), 7.78 (t, 1H, J=7.4 Hz, H-8), 8.25 (dd, 1H, J=7.4, 1.1 Hz, H-7), 8.47 (dd, 1H, J=7.4, 1.1 Hz, H-9), 15.80 (br s, 1H, COOH), ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.1 (s), and 164.8 (s) (COOH, and N–C=O), 146.3 (s), 136.5 (s), 134.8 (s), 130.7 (s), 129.5 (s), 129.1 (s), 132.6 (d, C_8), 131.8 (d, C_9), 127.5 (d), 127.0 (d), 126.4 (d), 120.2 (d), 56.6 (d, C_{6a}), 42.4 (t, C_6), 33.4 (s, C_5), 31.6 (q), and 30.6 (q) (Me-5), 20.6 (q, Me-3). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.75; H, 5.92; N, 4.40.

3.7.4. 1-Ethyl-5,5-dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21d). Yield 1.51 g (45%); mp 199.5–200.5 °C (*i*-PrOH–DMF); IR 1744 (COOH), and 1639 (N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M$^+$ 335 (98), 318 (15), 302 (6), 289 (100), 232 (7), 204 (9), 128 (9), 115 (19), 102 (10), 91 (11), 77 (12), 65 (9), 51 (9); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.16 (s, 3H, Me-5), 1.18 (t, 3H, J=7.5 Hz, CH_2*Me*), 1.41 (s, 3H, Me-5), 1.74 (dd, 1H, J=13.4, 8.8 Hz, H-6*ax*), 2.46 (dd, 1H, J=13.4, 5.8 Hz, H-6*eq*), 2.74 (m, 2H, *C*H_2Me), 5.21 (dd, 1H, J=8.8, 5.8 Hz, H-6a), 7.28 (d, 1H, J=7.4 Hz, H-Ar), 7.33 (t, 1H, J=7.4 Hz, H-3), 7.38 (d, 1H, J=7.4 Hz, H-Ar), 7.88 (t, 1H, J=7.5 Hz, H-8), 8.00 (d, 1H, J=7.5 Hz, H-7), 8.14 (d, 1H, J=7.5 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.1 (s), and 165.3 (s) (COOH, and N–C=O), 149.0 (s), 140.0 (s), 138.6 (s), 131.1 (s), 129.7 (s), 128.2 (s), 133.0 (d, C_8), 131.4 (d, C_9), 127.2 (d), 126.9 (d), 126.8 (d), 123.8 (d), 57.5 (d, C_{6a}), 44.7 (t, C_6), 34.3 (s, C_5), 31.8 (q), and 29.9 (q) (Me-5), 24.8 (t, *C*H_2CH$_3$), 14.1 (q, CH$_2$*C*H$_3$). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.26; H, 6.28; N, 4.19.

3.7.5. 1-Methoxy-5,5-dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21e). Yield 1.15 g (34%); mp 248–250 °C (*i*-PrOH–DMF); IR 1723 (COOH), and 1628 (N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M$^+$ 337 (100), 302 (25), 304 (12), 293 (82), 278 (9), 263 (20), 248 (18), 135 (16), 220 (9), 204 (13), 152 (9), 139 (20), 102 (25), 91 (27), 73 (30), 65 (19); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.29 (s, 3H, Me-5), 1.38 (s, 3H, Me-5), 1.50 (dd, 1H, J=13.1, 11.7 Hz, H-6*ax*), 2.45 (dd, 1H, J=13.1, 3.3 Hz, H-6*eq*), 3.84 (s, 3H, OMe), 5.16 (dd, 1H, J=11.7, 3.3 Hz,-6a), 7.04 (d, 1H, J=7.7 Hz, H-Ar), 7.13 (d, 1H, J=7.7 Hz,-Ar), 7.29 (t, 1H, J=7.7 Hz, H-3), 7.85 (t, 1H, J=7.7 Hz, H-8), 8.01 (d, 1H, J=7.7 Hz, H-7), 8.13 (d, 1H, J=7.7 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.2 (s), and 165.1 (s) (COOH, and N–C=O), 152.7 (s), 148.2 (s), 140.2 (s), 129.4 (s), 128.8 (s), 121.8 (s), 132.8 (d, C_8), 131.9 (d, C_9), 127.6 (d), 127.1 (d), 118.5 (d), 110.7 (d), 56.8 (OMe-1), 56.0 (d, C_{6a}), 45.2 (t, C_6), 34.1 (s, C_5), 32.3 (q), and 30.1 (q) (Me-5). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.22; H, 5.64; N, 4.15. Found: C, 71.18; H, 5.69; N, 4.15.

3.7.6. 3-Methoxy-5,5-dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21f). Yield 2.43 g (72%); mp 228–229.5 °C (*i*-PrOH–DMF); IR 1732 (COOH), and 1627 (N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M$^+$ 337 (100), 322 (30), 304 (7), 293 (24), 278 (18), 262 (4), 205 (4), 191 (3), 139 (3), 115 (2), 102 (2), 91 (2); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.44 (s, 3H, Me-5), 1.51 (s, 3H, Me-5), 1.68 (dd, 1H, J=12.8, 13.4 Hz, H-6*ax*), 2.36 (dd, 1H, J=13.4, 2.8 Hz, H-6*eq*), 3.84 (s, 3H, OMe), 4.91 (dd, 1H, J=12.8, 2.8 Hz, H-6a), 6.88 (dd, 1H, J=8.9, 2.8 Hz, H-2), 6.97 (d, 1H, J=2.8 Hz, H-4), 7.73 (dd, 1H, J=7.5, 1.5 Hz, H-Ar), 7.79 (t, 1H, J=7.5 Hz, H-8), 8.32 (d, 1H, J=8.9 Hz, H-1), 8.48 (dd, 1H, J=7.3, 1.5 Hz, H-Ar); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.8 (s), and 165.2 (s) (COOH, and N–C=O), 157.0 (s), 146.3 (s), 138.5 (s), 129.23 (s), 129.16 (s), 126.4 (s), 132.8 (d), 132.0 (d), 126.8 (d), 121.6 (d), 112.7 (d), 112.0 (d), 56.6 (d, C_{6a}), 55.4 (q, OMe), 42.0 (t, C_6), 33.9 (s, C_5), 31.6 (q), and 30.6 (q) (Me-5). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.22; H, 5.64; N, 4.15. Found: C, 71.22; H, 5.62; N, 4.18.

3.7.7. 1-Benzyl-5,5-dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21g). Yield 1.28 g (32%); mp 168–169 °C (*i*-PrOH–DMF); IR 1726 (COOH), and 1617 (N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): 399 (4), 398 (22), 397 (M$^+$, 72), 380 (2), 354 (4), 353 (16), 352 (31), 351 (100), 338 (5), 336 (6), 322 (5), 308 (4), 306 (6), 292 (5), 204 (4), 165 (5), 91 (11); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.16 (s, 3H, Me-5), 1.37 (s, 3H, Me-5), 1.67 (dd, 1H, J=13.4, 9.4 Hz, H-6*ax*), 2.41 (dd, 1H, J=13.4, 5.4 Hz, H-6*eq*), 4.07 and 4.16 (AB, 2H, J=15.9 Hz, *C*H_2Ph), 4.91 (dd, 1H, J=9.4, 5.4 Hz, H-6a), 7.04–7.09 (m, 4H, H-Ar), 7.16 (t, 2H, J=7.4 Hz, H-Ar), 7.25 (t, 1H, J=7.6 Hz, H-Ar), 7.39 (br d, 1H, J=7.5 Hz, H-Ar), 7.83 (t, 1H, J=7.6 Hz, H-Ar), 7.94 (d, 1H, J=7.6 Hz, H-Ar), 8.06 (d, 1H, J=7.6 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.0 (s), and 165.7 (s) (COOH, and N–C=O), 148.8 (s), 140.8 (s), 140.4 (s), 136.6 (s), 133.0 (d), 131.5 (s), 131.3 (d), 130.1 (s), 128.9 (2C, d), 128.8 (d), 128.4 (2C, d), 128.2 (s), 127.1 (d), 126.7 (d), 126.1 (d), 124.4 (d), 57.4 (d, C_{6a}), 34.4 (s, C_5), 38.6 (t, *C*H_2Ph), 44.6 (t, C_6), 31.8 (q), and 30.0 (q) (Me-5). Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.59; H, 5.79; N, 3.53. Found: C, 78.63; H, 5.78; N, 3.56.

3.7.8. 1,3,5,5-Tetramethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21h). Yield 2.04 g (61%); mp 220–221 °C (*i*-PrOH–DMF); IR 1718 (COOH, and N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M$^+$ 335 (100), 320 (18), 302 (16), 289 (76), 276 (11), 246 (11), 235 (13), 218 (3), 204 (3), 172 (4), 137 (5), 128 (7), 115 (10), 91 (5); ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.29 (s, 3H, Me-5), 1.44 (s, 3H, Me-5), 1.73 (dd, 1H, J=13.3, 10.1 Hz, H-6*ax*), 2.36 (s, 3H, Me-Ar), 2.38 (s, 3H, Me-Ar), 2.40 (dd, 1H, J=13.3, 4.7 Hz, H-6*eq*), 4.94 (dd, 1H, J=10.1, 4.7 Hz, H-6a), 7.03 (br s, 1H, H-Ar), 7.09 (br s, 1H, H-Ar), 7.75–7.80 (m, 2H, H-Ar), 8.45 (dd, J=6.1, 2.5, H-Ar), 15.65 (br s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.6 (s), and 165.3 (s) (COOH, and N–C=O), 148.6 (s), 139.2 (s), 136.0 (s), 132.4 (s), 129.6 (s), 129.2 (s), 128.6 (s), 132.8 (d, C_8), 131.6 (d, C_9), 129.7 (d), 126.8 (d), 124.5 (d), 57.4 (d, C_{6a}), 45.2 (t, C_6), 34.0 (s, C_5), 32.1 (q), and 30.1 (q) (Me-5), 20.8 (q), and 19.8 (q) (Me-1 and Me-3). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.24; H, 6.23; N, 4.20.

3.7.9. 3-Isopropyl-5,5-dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (21i). Yield 2.34 g (67%); mp 223.5–224.5 °C (*i*-PrOH–DMF); IR 1708 (COOH, and N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z*

(rel intensity): M^+ 349 (92), 334 (100), 316 (8), 305 (40), 290 (11), 273 (5), 115 (6), 43 (11); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, 6H, J=6.9 Hz, CH*Me*$_2$), 1.37 (s, 3H, Me-5), 1.45 (s, 3H, Me-5), 1.57 (t, 1H, J=12.9 Hz, H-6*ax*), 2.49 (dd, 1H, J=13.1, 2.6 Hz, H-6*eq*), 2.90 (sept, 1H, J=6.9 Hz, *CH*Me$_2$), 5.15 (dd, 1H, J=12.7, 2.2 Hz, H-6a), 7.19 (dd, 1H, J=8.5, 1.8 Hz, H-2), 7.40 (d, 1H, J=1.8 Hz, H-4), 7.85 (t, 1H, J=7.6 Hz, H-8), 8.01 (br d, 1H, J=7.6 Hz, H-7), 8.11 (br d, 1H, J=7.6 Hz, H-9), 8.16 (d, 1H, J=8.5 Hz, H-1); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.1 (s), and 165.3 (s) (COOH, and N–C=O), 146.3 (s), 146.0 (s), 136.6 (s), 133.0 (d), 131.9 (d), 131.1 (s), 129.4 (s), 129.2 (s), 126.8 (d), 125.4 (d), 124.3 (d), 120.5 (d), 56.6 (d, C_{6a}), 33.7 (s, C_5), 42.2 (t, C_6), 33.4 (d, *C*HMe$_2$), 31.8 (q), and 30.8 (q) (Me-5), 24.1 (q), and 24.0 (q) (CH*Me*$_2$). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.65; H, 6.59; N, 4.01. Found: C, 75.68; H, 6.62; N, 4.03.

3.8. 1-Allyl-3-oxo-2-arylisoindolo-7-carboxylic acids (22a,b). Typical procedure

A mixture of corresponding adduct **14a**,**d** (0.01 mol) and 85% H_3PO_4 (40 mL) was stirred at 65 °C for 1.5 h (monitoring by TLC). At the end of the reaction, the mixture was diluted with water (200 mL). The obtained precipitate was filtered off, washed with cold water (5× 80 mL) and dried in air. Then the crude product was purified by recrystallization to give desired products **22a**,**b** as colorless crystals.

3.8.1. 1-Allyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-isoindole-4-carboxylic acid (22a). Yield 1.52 g (52%); mp 123–124 °C (ethyl acetate–hexane); IR 1782 (COOH), and 1652 (N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M^+ 293 (4), 252 (100), 209 (20), 180 (23), 152 (14), 104 (14), 89 (5), 77 (68), 57 (8), 51 (21), 40 (33); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.61 (ddd, 1H, J=14.3, 7.8, 6.2 Hz, H-3′A), 2.80 (ddd, 1H, J=14.8, 7.8, 3.3 Hz, H-3′B), 4.85 (dd, 1H, J=16.9, 1.0 Hz, H-1′*trans*), 5.00 (br d, 1H, J=10.1 Hz, H-1′*cis*), 5.26 (ddd, 1H, J=16.9, 10.1, 7.8 Hz, H-2′), 5.40 (dd, 1H, J=6.2, 3.3 Hz, H-3), 7.39 (m, 1H, H-Ar), 7.50–7.55 (m, 4H, H-Ar), 7.76–7.81 (m, 2H, H-Ar), 8.47 (dd, J=6.7, 2.0 Hz, H-Ar); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 167.8 (s), and 165.2 (s) (C=O), 146.0 (s), 135.4 (s), 133.1 (d), 131.8 (d), 130.5 (d), 129.27 (2C, d), 129.24 (s), 128.7 (s), 127.2 (d), 127.1 (d), 124.8 (2C, d), 119.9 (t, CH_2=), 61.2 (d, C_3), 34.0 (t, –CH_2–). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.72; H, 5.12; N, 4.78. Found: C, 73.75; H, 5.16; N, 4.81.

3.8.2. 1-Allyl-3-oxo-2-(4′-methoxyphenyl)-2,3-dihydro-1*H*-isoindole-4-carboxylic acid (22b). Yield 1.97 g (61%); mp 124.5–126 °C (ethyl acetate–chloroform); IR 1723 (COOH, and N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M^+ 323 (23), 282 (100), 264 (2), 238 (12), 210 (14), 195 (3), 167 (10), 141 (3), 128 (4), 92 (10), 77 (16); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (ddd, 1H, J=14.4, 8.0, 5.9 Hz, H-3′A), 2.77 (ddd, 1H, J=14.4, 6.0, 3.5 Hz, H-3′B), 3.84 (s, 3H, OMe), 4.85 (dd, 1H, J=16.8, 1.2 Hz, H-1′*trans*), 4.97 (br d, 1H, J=10.0 Hz, H-1′*cis*), 5.32 (dddd, 1H, J=16.8, 10.0, 8.0, 6.0 Hz, H-2′), 5.31 (dd, 1H, J=5.9, 3.5 Hz, H-3), 6.99 (d, 2H, J=8.9 Hz, H-Ar), 7.38 (d, 2H, J=8.9 Hz, H-Ar), 7.71–7.76 (m, 2H, H-Ar), 8.38 (dd, 1H, J=5.9, 2.7 Hz, H-Ar); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 167.9 (s), and 165.1 (s) (C=O), 158.2 (s), 146.0 (s), 132.9 (d), 132.1 (d), 130.6 (d), 129.0 (s), 128.8 (s), 127.9 (s), 127.4 (d), 126.5 (2C, d), 119.9 (t, CH_2=), 114.5 (2C, d), 61.7 (d, C_3), 55.5 (q, OMe), 34.0 (t, –CH_2–). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.59; H, 5.26; N, 4.33. Found: C, 70.62; H, 5.24; N, 4.30.

3.9. 5-Methyl-5,6-dihydro-10-carboxyisoindolo[2,1-*a*]-quinoline-11-ones (23a–e). Typical procedure

Corresponding adduct **14** (0.01 mol), the mixture of 85% H_3PO_4 and 96% H_2SO_4 (45 mL, 3:1 in volume) were stirred at 100–120 °C for 1 h (monitoring by TLC). At the end of the reaction, the mixture was diluted with water (200 mL). The obtained precipitate was filtered off, washed with cold water (5×80 mL) and dried in air. Then the crude product was purified by recrystallization to give desired isoindoloquinolines **23** as colorless crystals.

3.9.1. 5-Methyl-5,6,6a,11-tetrahydro-11-oxoisoindolo-[2,1-*a*]quinoline-10-carboxylic acid (23a). Ratio of isomers **A**/**B**~4/1; yield 1.52 g (52%); mp 185.5–186 °C (*i*-PrOH–DMF); IR 1728 (COOH), and 1623 (N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M^+ 293 (54), 278 (11), 264 (5), 250 (24), 249 (100), 234 (26), 232 (12), 220 (8), 234 (26), 232 (12), 217 (7), 204 (20), 131 (6), 117 (7), 102 (8), 91 (7), 77 (14); ^{1}H NMR ($CDCl_3$, 200 MHz) isomer **A** δ 1.53 (d, 3H, J=7.0 Hz, Me-5), 1.89 (dt, 1H, J=12.8, 5.8 Hz, H-6*ax*), 2.41 (ddd, 1H, J=12.8, 2.8, 1.2 Hz, H-6*eq*), 3.32 (ddd, 1H, J=7.0, 5.8, 1.2 Hz, H-5), 4.93 (dd, 1H, J=12.8, 2.8 Hz, H-6a), 7.15–7.50 (m, 3H, H-Ar), 7.70–7.85 (m, 2H, H-Ar), 8.35–8.55 (m, 2H, H-Ar); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.2 (s), and 165.4 (s) (COOH, and N–C=O), 146.1 (s), 134.2 (s), 132.3 (s), 129.5 (s), 128.8 (s), 133.0 (d, C_8), 131.6 (d, C_9), 127.8 (d), 126.6 (d), 126.5 (d), 125.4 (d), 120.2 (d), 59.4 (d, C_{6a}), 36.0 (t, C_6), 30.8 (d, C_5), 20.7 (q, Me-5); ^{1}H NMR ($CDCl_3$, 200 MHz) isomer **B** δ 1.47 (d, 3H, J=6.7 Hz, Me-5), 1.48 (ddd, 1H, J=13.2, 12.8, 11.0 Hz, H-6A), 2.73 (ddd, 1H, J=13.2, 5.8, 2.8 Hz, H-6B), 3.32 (ddd, 1H, J=11.0, 6.7, 5.8 Hz, H-5), 4.84 (dd, 1H, J=12.8, 2.8 Hz, H-6a), 7.15–7.50 (m, 3H, H-Ar), 7.70–7.85 (m, 2H, H-Ar), 8.35–8.55 (m, 2H, H-Ar); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.4 (s), and 165.4 (s) (COOH, and N–C=O), 146.5 (s), 134.0 (s), 132.9 (s), 129.5 (s), 128.9 (s), 133.0 (d, C_8), 131.5 (d, C_9), 129.8 (d), 126.6 (d), 126.5 (d), 125.3 (d), 120.1 (d), 55.2 (d, C_{6a}), 33.5 (t, C_6), 30.3 (d, C_5), 24.0 (q, Me-5). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.72; H, 4.78; N, 4.78. Found: C, 73.53; H, 5.00; N, 4.75.

3.9.2. 1,5-Dimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (23b). Ratio of isomers **A**/**B**~4.5/1; yield 1.50 g (49%); mp 142.5–143 °C (*i*-PrOH–DMF); IR 1723 (COOH, and N–C=O) cm^{-1}; EI-MS (70 eV) *m*/*z* (rel intensity): M^+ 307 (29), 289 (7), 278 (4), 266 (100), 261 (59), 222 (8), 165 (8), 128 (6), 118 (15), 91 (47), 77 (19), 65 (41); ^{1}H NMR ($CDCl_3$, 200 MHz) isomer **A** δ 1.31 (d, 3H, J=6.9 Hz, Me-5), 1.59 (dt, 1H, J=13.5, 9.9 Hz, H-6*ax*), 2.41 (s, 3H, Me-1), 2.77 (ddd, 1H, J=13.5, 6.6, 4.9 Hz, H-6*eq*), 3.28 (ddd, 1H, J=13.5, 6.9, 6.6 Hz, H-5), 4.94 (dd, 1H, J=9.9, 4.9 Hz, H-6a), 7.19–7.30 (m, 3H, H-Ar), 7.75–7.85 (m, 2H,

H-7 and H-8), 8.48 (m, 1H, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 167.5 (s), and 167.0 (s) (COOH, and N–C═O), 149.9 (s), 137.0 (s), 134.2 (d), 134.0 (s), 133.2 (s), 132.7 (d), 130.4 (s), 130.4 (d), 128.9 (s), 128.2 (d), 128.0 (d), 126.2 (d), 60.6 (d, C_{6a}), 38.2 (t, C_6), 32.1 (d, C_5), 22.5 (q, Me-5), 20.5 (q, Me-1). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.26; H, 4.56; N, 5.54. Found: C, 74.05; H, 5.63; N, 4.43.

3.9.3. 1-Methoxy-5-methyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (23c). Ratio of isomers **A/B** ~3.5/1; yield 1.03 g (32%); mp 207–209 °C (heptane–chloroform); IR 1723 (COOH), and 1628 (N–C═O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 323 (100), 306 (26), 279 (85), 249 (23), 234 (19), 220 (14), 204 (13), 191 (9), 165 (5), 153 (6), 132 (5), 103 (5), 77 (9), 36 (6), 28 (10); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.37 (d, 3H, J=6.9 Hz, Me-5), 1.44 (td, 1H, J=13.4, 11.3 Hz, H-6*ax*), 2.73 (ddd, 1H, J=13.4, 6.5, 3.8 Hz, H-6*eq*), 3.27 (ddq, 1H, J=11.3, 6.9, 6.5 Hz, H-5), 3.95 (s, 3H, OMe), 4.84 (dd, 1H, J=11.3, 3.8 Hz, H-6a), 6.96 (br d, 1H, J=8.0 Hz, H-2), 7.01 (dd, 1H, J=8.0, 1.0 Hz, H-4), 7.29 (t, 1H, J=8.0 Hz, H-3), 7.70–7.80 (m, 2H, H-Ar), 8.45 (dd, 1H, J=7.2, 1.5 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.3 (s), and 165.2 (s) (COOH, and N–C═O), 152.9 (s), 148.2 (s), 136.2 (s), 132.94 (d), 132.08 (d), 129.39 (s), 128.67 (s), 127.6 (d), 127.1 (d), 122.8 (s), 119.4 (d), 111.0 (d), 59.2 (d, C_{6a}), 56.1 (OMe), 38.8 (t, C_6), 30.8 (d, C_5), 21.3 (q, Me-5); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **B** δ 1.42 (d, 3H, J=7.0 Hz, Me-5), 2.04 (ddd, 1H, J=13.5, 8.4, 6.0 Hz, H6A), 2.29 (ddd, 1H, J=13.5, 6.0, 5.7 Hz, H-6B), 2.99 (ddq, 1H, J=7.0, 6.0, 5.7 Hz, H-5), 3.96 (s, 3H, OMe), 4.92 (dd, 1H, J=8.4, 6.0 Hz, H-6a), 6.92 (br d, 1H, J=7.8, H-2), 6.98 (br d, 1H, J=7.8 Hz, H-4), 7.30 (t, 1H, J=7.8 Hz, H-3), 7.70–7.80 (m, 2H, H-Ar), 8.45 (dd, 1H, J=7.2, 1.5 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.9 (s), and 165.2 (s) (COOH, and N–C═O), 152.9 (s), 148.5 (s), 138.0 (s), 133.06 (d), 131.98 (d), 129.34 (s), 128.83 (s), 127.8 (d), 127.3 (d), 122.8 (s), 119.6 (d), 110.9 (d), 56.4 (d, C_{6a}), 56.0 (OMe), 37.2 (t, C_6), 29.6 (d, C_5), 22.4 (q, Me-5). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.59; H, 5.26; N, 4.33. Found: C, 70.62; H, 5.27; N, 4.33.

3.9.4. 3-Methoxy-5-methyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (23d). Ratio of isomers **A/B** ~12/1; yield 1.00 g (31%); mp 221–222 °C (*i*-PrOH–DMF); IR 1707 (COOH), and 1615 (N–C═O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 323 (100), 308 (21), 290 (5), 279 (53), 264 (45), 250 (5), 236 (8), 221 (8), 204 (5), 191 (9), 166 (3), 104 (3), 91 (3), 77 (4); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.45 (d, 3H, J=6.7 Hz, Me-5), 1.47 (q, 1H, J=12.9, 12.4, 12.0 Hz, H-6*ax*), 2.71 (ddd, 1H, J=12.9, 5.7, 2.0 Hz, H-6*eq*), 3.28 (ddq, 1H, J=12.0, 6.7, 5.7 Hz, H-5), 3.82 (s, 3H, OMe), 4.83 (dd, 1H, J=12.4, 2.0 Hz, H-6a), 6.84 (dd, 1H, J=9.0, 1.6 Hz, H-2), 6.94 (d, 1H, J=1.6 Hz, H-4), 7.75–7.80 (m, 2H, H-Ar), 8.32 (d, 1H, J=9.0 Hz, H-1), 8.43 (dd, 1H, J=6.7, 0.9 Hz, H-9), 15.70 (br s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 165.7 (s), and 165.2 (s) (COOH, and N–C═O), 156.8 (s), 146.4 (s), 145.9 (s), 134.1 (s), 129.0 (s), 127.4 (s), 132.8 (d, C_8), 132.0 (d, C_9), 126.7 (d), 121.4 (d), 113.1 (d), 112.1 (d), 59.5 (MeO-3), 55.4 (d, C_{6a}), 36.0 (t, C_6), 31.0 (d, C_5), 20.7 (q, Me-5). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.59; H, 5.26; N, 4.33. Found: C, 70.60; H, 5.28; N, 4.37.

3.9.5. 1,2,5-Trimethyl-5,6,6a,11-tetrahydro-11-oxoisoindolo[2,1-*a*]quinoline-10-carboxylic acid (23e). Ratio of isomers **A/B** ~6/1; yield 1.77 g (55%); mp 220–222 °C (*i*-PrOH–DMF); IR 1715 (COOH, and N–C═O) cm^{-1}; EI-MS (70 eV) *m/z* (rel intensity): M^+ 321 (72), 304 (7), 275 (100), 262 (12), 246 (5), 232 (10), 204 (6), 158 (3), 115 (9), 91 (7); ^{1}H NMR ($CDCl_3$, 400 MHz) isomer **A** δ 1.27 (d, 3H, J=7.3 Hz, Me-5), 1.58 (ddd, 1H, J=13.5, 9.7, 9.2 Hz, H-6*ax*), 2.24 (s, 3H, *Me*-Ar), 2.35 (s, 3H, *Me*-Ar), 2.74 (ddd, 1H, J=13.5, 6.4, 5.1 Hz, H-6*eq*), 3.24 (ddd, 1H, J=9.2, 7.3, 6.4 Hz, H-5), 4.95 (dd, 1H, J=9.7, 5.1 Hz, H-6a), 7.15 (s, 2H, H-3 and H-4), 7.78–7.81 (m, 2H, H-8 and H-9), 8.46 (d, 1H, J=7.4 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 166.1 (s), and 165.4 (s) (COOH, and N–C═O), 148.9 (s), 135.8 (s), 133.2 (s), 133.0 (d), 132.5 (s), 131.9 (d), 131.5 (s), 129.8 (s), 128.3 (s), 128.2 (d), 126.8 (d), 124.5 (d), 59.6 (d, C_{6a}), 38.5 (t, C_6), 31.1 (d, C_5), 21.5 (q), 20.0 (q), 16.7 (q) (Me-5, Me-1, Me-2). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; N, 5.92; H, 4.36. Found: C, 74.75; N, 5.96; H, 4.39.

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Michael addition of chiral formaldehyde *N*,*N*-dialkylhydrazones to activated cyclic alkenes

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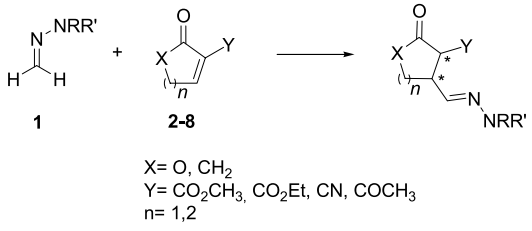
Abstract—The nucleophilic conjugate addition of chiral formaldehyde *N*,*N*-dialkylhydrazones **1** to doubly activated cyclic alkenes **2**–**8** proceeds smoothly to afford the corresponding Michael adducts **14**, **16**, **18**, **20**, **22**, **24**, and **25** in variable yields and selectivities. The reactions take place either spontaneously or in the presence of MgI_2 as a mild Lewis acid depending on the type of substrate. Release of the chiral auxiliary was achieved by transformation of the hydrazone moiety into acetals, dithioacetals or nitriles.

1. Introduction

The asymmetric Michael addition of carbon nucleophiles to conjugated carbonyl compounds is one of the most powerful methods for carbon–carbon bond formation. Due to the relevance of the resulting 1,5-dicarbonyl compounds, doubly activated cycloalkenes and related heterocycles have been frequently used as substrates for the asymmetric Michael addition of nucleophiles such as aza-enolates from hydrazones,[1] lithium derivatives of cyclic allylic sulfoxides,[2] lithium enolates from esters,[3] and ketene silyl acetals.[4] In a similar way, the asymmetric addition of acyl (formyl) anion equivalents would make available less accessible cyclic 1,4-dicarbonyl compounds. A few reports have been described for such a reaction in racemic fashion[5] but, to the best of our knowledge, the *asymmetric* nucleophilic acylation of those prochiral substrates has not been reported so far.

During the last years, we have exploited the nucleophilic reactivity of formaldehyde *N*,*N*-dialkylhydrazones **1** as neutral d^1 nucleophiles in several Michael type reactions.[6] Recently, we have discovered that the presence of two geminal carboxylate groups in alkylidene malonates allows to carry out such additions under very mild conditions.[7] We now wish to report on the extension of this methodology to the addition of chiral reagents **1** to cyclic alkenes **2**–**8** bearing two different electron-withdrawing groups on the same carbon atom (Scheme 1).



Scheme 1.

Compounds **2**–**8** were chosen as substrates taking into account that some of the expected addition products are precursors of natural carbocyclic compounds with important biological activity. Particularly interesting are cyclopentenone derivatives, as the resulting adducts posses substructures present in a large number of natural products of interest[8] including jasmonoids, prostaglandins, and cyclopentenoid antibiotics such as methylenomycin A,[9] methylenomycin B, xanthocydin,[10] cyclosarkomycin[11] and sarkomycin.[12] Additionally, compounds **2**–**8** have the practical advantage of a stable C=C configuration, which simplifies their synthesis and avoid considering eventual *E*/*Z* isomerizations.

2. Results and discussion

The cyclic alkenes used as substrates in our work include α-alkylidene-β-ketonitriles (**2**,**3**),[13] 2-methoxycarbonyl-

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cyclopent-2-enone (**4**),[14] five- and six-membered α-alkylidene-β-diketones (**5**,**6**)[15] and commercially available 3-acetylcumarine (**7**) and 3-ethoxycarbonylcumarine (**8**) (Fig. 1).

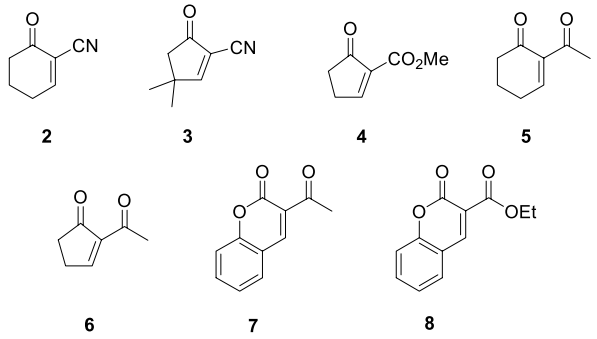
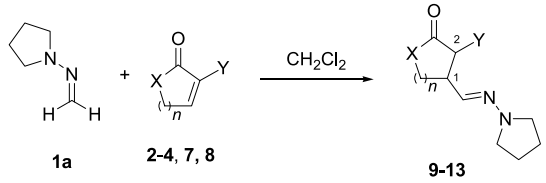


Figure 1. Doubly activated cyclic alkenes used as substrates.

Preliminary reactivity screenings indicated that, with the exception of **8**, reaction of these alkenes with hydrazones **1** proceeds spontaneously, without any need of promoter or catalyst. The influence of different factors in the yields and selectivities of the reactions were found to be dependent on the nature of the substrate. For this reason, the structure of the hydrazone **1** used as reagent, the solvent, the reaction temperature, and the presence or absence of MgI_2 as promoter or catalyst were considered and optimized for any type of cyclic alkenes used with the results described herein.

2.1. Addition of 1-methylenaminopyrrolidine (1a)

First experiments were carried out in the racemic version, using the highly reactive 1-methylenaminopyrrolidine (**1a**) as the nucleophile. Reactions were carried out in CH_2Cl_2, at room temperature, and using a 1:1.5 hydrazone/alkene ratio (Scheme 2).



Scheme 2.

The addition of hydrazone **1a** to compounds **2**, **3**, **4** and **7** takes place spontaneously to afford the expected adducts **9**–**12** in good yields (Table 1, entries 1–4). Products were isolated as *trans*/*cis* mixtures, obtained in variable ratios ranging from 3:1 in six-membered ketonitrile **9**, 10:1 and 12:1 in five-membered adducts **10** and **11**, respectively, to >99:1 for the less reactive cumarine derivative **12**. As expected, compound **7** showed lower reactivity and the reaction required 72 h to completion (entry 4). For alkenes **2**–**4**, addition of MgI_2 in either catalytic or stoichiometric amounts resulted in shorter reaction times, but there was no improvement of selectivity while yields dropped slightly. Attempts to accelerate the addition of **1a** to **7** by addition of MgI_2 failed due to extensive decomposition of the substrate.

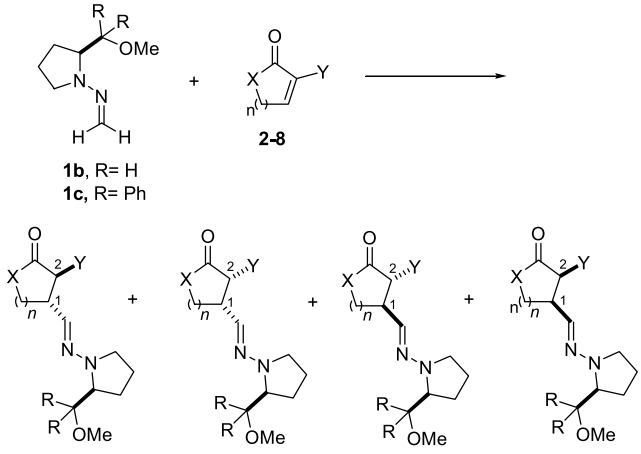
In sharp contrast, ethoxycarbonylcumarine **8** required external activation due to the poorer electron-withdrawing effect by carboxylate groups.[7] Fortunately, this compound tolerated the presence of MgI_2, which effectively catalysed the addition of **1a** to afford the desired adduct **13** in 80% yield as a 17:1 *trans*/*cis* mixture of isomers (entry 5).

The relative *trans* configuration of the major isomer in the mixtures was assigned mainly on the basis of ^1H NMR data. For instance, the high value of $J_{H\text{-}1,H\text{-}2}=11.4$ Hz in the spectrum of **9**, compared with the $J_{H\text{-}1,H\text{-}2}=4.7$ Hz value of the minor isomer confirms this assignment, in agreement with data reported for related structures.[16] The relative *trans* configuration in the major isomer of **10** was again assigned in view of the observed coupling constants ($J_{H\text{-}1,H\text{-}2}=12.0$, 8.9 Hz for the major and minor isomers, respectively).[16] In spite of the low values of the $J_{H\text{-}1,H\text{-}2}$ coupling constants for **12** and **13** ($J_{H\text{-}1,H\text{-}2}=2.3$, 4.5 Hz, respectively), the relative *trans* configuration was assigned to the major isomers by analogy with **9** and considering the absence of NOE effect between these protons.

The most relevant information derived from this preliminary study is the relative reactivity of the substrates object of study and the predominant formation of *trans* adducts. Due to the fact that in the asymmetric version two newly stereogenic centers would be formed, this is helpful information for the analysis of the reaction mixtures.

2.2. Addition of chiral hydrazones

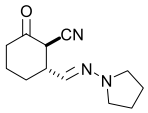
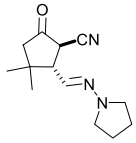
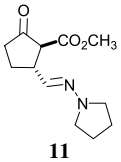
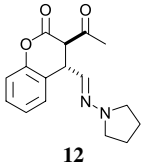
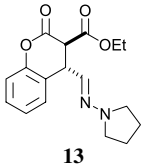
As in the precedent case, the asymmetric version of the methodology requires a specific optimization of the conditions for each type of cyclic alkene. The reactions create two new stereogenic centers and, therefore, four possible diastereomers can be formed (Scheme 3).



Scheme 3.

Some transformations were made in order to simplify the analysis of the mixtures during the optimization processes. These transformations were designed to eliminate the newly created stereogenic center at C-2. In this way the stereoselectivity in the formation of the new C–C bond at C-1 could be more easily determined. These transformations, explained in detail for each compound, were carried

Table 1. Addition of hydrazone **1a** to alkenes **2–4**, **7–8**

Entry	Alkene	Adduct	*t* (h)	Yield[a] (%)	*trans*:*cis*[b]
1	**2**	 **9**	3	78	3:1
2	**3**	 **10**	3	76	10:1
3	**4**	 **11**	2	50	12:1
4	**7**	 **12**	72	85	>99:1
5	**8**	 **13**	72	80[c]	17:1

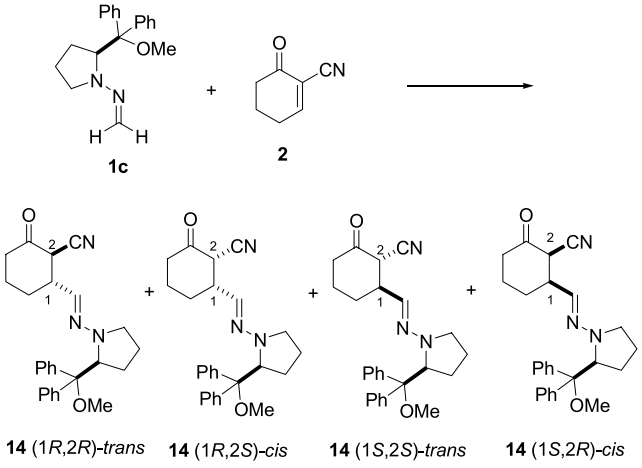
[a] Isolated yield after column chromatography.
[b] Determined by ^{1}H and ^{13}C NMR.
[c] 20% of MgI_2 added as catalyst.

out using mixtures of adducts with different diastereomeric ratios in order to guarantee that the reactions proceed without racemisation at C-1.

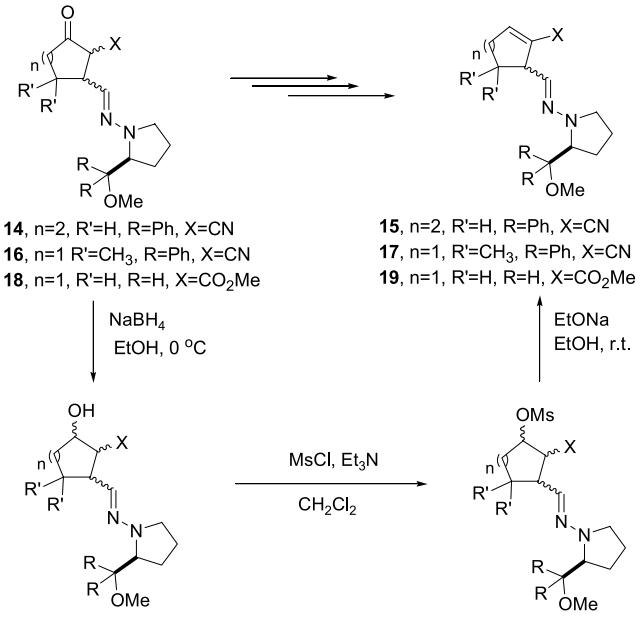
2.2.1. Addition of hydrazones 1b and 1c to 2-cyanocyclohex-2-enone 2. The first experiments of the asymmetric version were carried out using (*S*)-1-methyleneamino-2-(methoxymethyl)pyrrolidine **1b** as the reagent. The addition of formaldehyde SAMP hydrazone to **2**, performed in CH_2Cl_2 in the presence of 10% MgI_2, led to the formation of the four possible diastereomers in a 1:1:0.5:0.5 ratio. Reactions carried out at lower temperatures did not result in better yields and/or selectivities. Bearing in mind the better stereocontrol observed in the addition of bulkier hydrazone (*S*)-1-methyleneamino-2-(1,1-diphenyl-1-methoxymethyl)pyrrolidine **1c** to alkylidene malonates,[7] subsequent experiments were carried out using this reagent. Addition of **1c** in CH_2Cl_2 using 15% of MgI_2 as the catalyst afforded again a mixture of the four possible diastereomers of adduct **14** in a 1:0.3:0.5:0.15 ratio (Scheme 4).

Elimination of the stereogenic center in C-2 by reduction of the carbonyl group, mesylation of the resulting alcohol and subsequent elimination led to compound **15** (Scheme 5). Analysis of the crude mixture indicated a 1:0.5 diastereomeric ratio at the new stereogenic center at C-1.

This information, together with $^{3}J_{H\text{-}1,H\text{-}2}$ values (11.0 and 13.1 Hz)[16] and NOE experiments allowed the assignment of the relative 1,2-*trans* configuration to the two major isomers of **14**. Assuming that additions to cyclic compounds follow a similar reaction pathway to that described for alkylidene malonates,[7] we tentatively assigned the 1:0.3:0.5:0.15 ratio to the (1*R*)-*trans*/(1*R*)-*cis*/(1*S*)-*trans*/(1*S*)-*cis* isomers. In order to improve these results, a screening of different reaction conditions such as temperature, solvent and amount



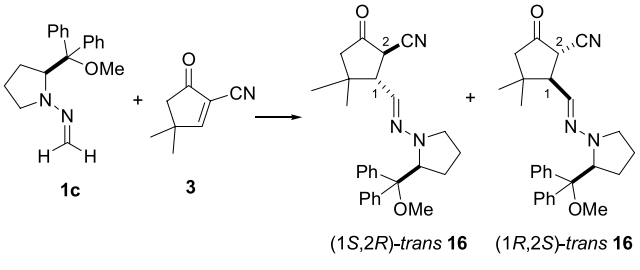
Scheme 4.



Scheme 5.

of promoter was made. As observed for **1a**, there is no effect of the temperature on the diastereomeric ratio. When reactions were performed with a stoichiometric amount of promoter, lower yields and selectivities were observed. A screening of different solvents (toluene, CH_2Cl_2, DMF, ether, THF and MeOH) revealed MeOH as the best option. Optimized conditions (MeOH, room temperature and 20% of MgI_2; Table 2, entry 1) afforded adduct **14** in an 83% yield and a 3.5:1 (*R*)/(*S*) diastereoselectivity at C-1. Medium pressure liquid chromatography allowed the isolation of the major isomer of tentative (*R*) configuration at C-1 as a 3:1 mixture of the corresponding *trans*/*cis* isomers.

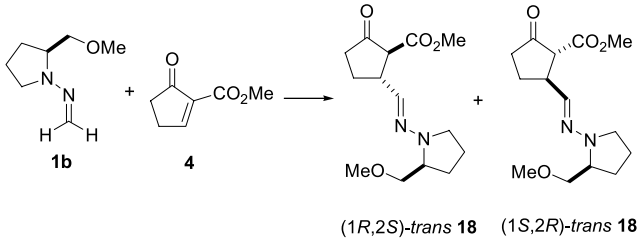
2.2.2. Addition of hydrazone 1c to 2-cyano-4,4-dimethylcyclopenten-2-one 3. Addition of hydrazone **1c** to 2-cyano-4,4-dimethylcyclopenten-2-one **3** afforded adduct **16** as a mixture of only two diastereoisomers under a variety of conditions. The elimination of the stereogenic center at C-2 following the procedure described previously (Scheme 5) was used again to determine that these compounds are isomers of opposite configuration at C-1. The high values of the coupling constant $J_{H\text{-}1,H\text{-}2}$ in both diastereoisomers (12.0 and 12.2 Hz) were used to assign the *trans* relative configuration in both compounds (Scheme 6).[17]



Scheme 6.

Although the reaction proceeds spontaneously in this case, addition of stoichiometric amounts of MgI_2 resulted in a significant improvement of yields and stereoselectivites. The reaction performed under optimized conditions (1 equiv of MgI_2, room temperature, and CH_2Cl_2 as the solvent) led to adduct **16** as a 5:1 mixture of the corresponding (1*S*)-*trans*/(1*R*)-*trans* diastereoisomers in 80% yield (Table 2, entry 2).

2.2.3. Addition of hydrazone 1b to 2-(methoxycarbonyl) cyclopenten-2-one 4. Preliminary experiments revealed that in this case use of the more hindered **1c** did not improve the diastereoisomeric ratio collected by the simplest **1b**. The addition of the latter to **4** was performed at 0 °C in CH_2Cl_2, in the presence of a catalytic amount of MgI_2 (5%). Under these optimized conditions, adduct **18** was obtained as a mixture of two isomers in a 3:1 (1*R*)-*trans*/(1*S*)-*trans* ratio in 75% yield (Scheme 7, Table 2, entry 3). No improvement was observed by use of higher amounts of MgI_2, lower temperatures or different solvents (MeOH, Et_2O).

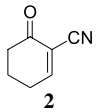
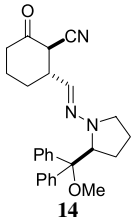
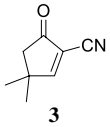
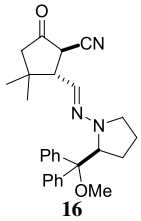
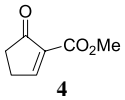
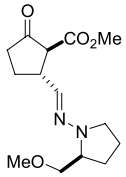
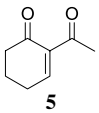
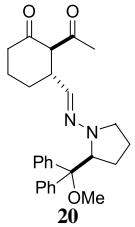
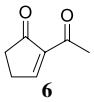
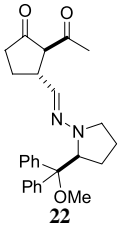
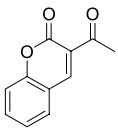
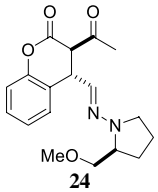
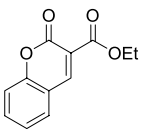
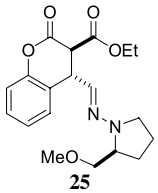


Scheme 7.

Again, removal of the stereogenic center at C-2 following the procedure described previously (Scheme 5) was required to determine the diastereomeric relationship. This procedure indicated that the products were isomers of opposite configurations at C-1. The *trans* relative configuration of both compounds was assigned with regard to the coupling constant $J_{H\text{-}1,H\text{-}2}$ (8.9 Hz for both isomers)[18] and NOE experiments.

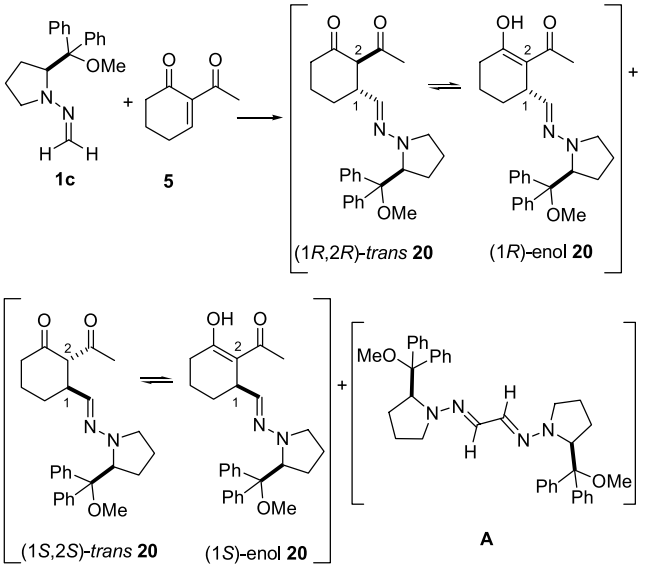
2.2.4. Addition of hydrazone 1c to 2-acetylcyclohex-2-enone 5. Addition of hydrazone **1c** to alkene **5** in CH_2Cl_2 at room temperature proceeds spontaneously to afford **20** in a 98% yield, although the diastereoselection values were disappointing. ^1H NMR experiments in $CDCl_3$ showed four groups of signals in 1:1:0.2:0.2 ratio. However, the presence of signals at 16.31 and 16.34 ppm corresponding to the two major products suggested a keto/enolic equilibrium of these products, with high predominance of the enolic form (1:5 keto/enol),[19] and the formation of the two possible diastereoisomers of opposite configuration at C-1 in a 1:1 ratio (Scheme 8). Additional evidence was provided by the ^1H NMR spectrum recorded in CD_3OD; as expected, there is a lower proportion of enolic forms in this solvent; the four groups of signals showed now a 1:1:0.3:0.3 ratio, corresponding to a 1:3 keto/enol ratio. This keto/enolic equilibrium was further demonstrated by reacting adduct **20** with hydrazine (Scheme 9). The resulting pyrazol **21** (lacking the stereogenic center at C-2) was obtained as a 1:1 mixture of diasteromers. Again, the analysis of the results obtained from mixtures of different diastereomeric ratios confirmed that the process proceeds without racemisation. The 1:1:0.3:0.3 ratio in compound **20** was therefore

Table 2. Synthesis of adducts **14**, **16**, **18**, **20**, **22**, **24** and **25**

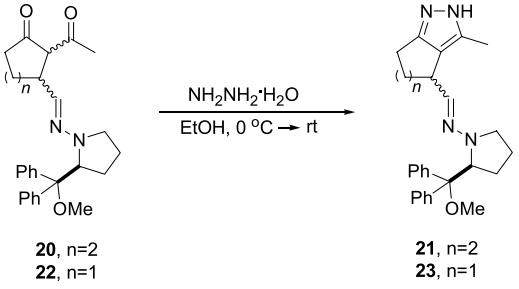
Entry	Alkene	**1**	MgI_2	Solvent	*T* (°C)	Adduct	Yield[a] (%)	d.r.[b]	*trans*/*cis*
1	 **2**	**1c**	20%	MeOH	r.t.	 **14**	97	3.5:1 (>98)	3:1
2	 **3**	**1c**	1 equiv.	CH_2Cl_2	r.t.	 **16**	80[c]	5:1	*trans*
3	 **4**	**1b**	5%	CH_2Cl_2	0	 **18**	75[c]	3:1	*trans*
4	 **5**	**1c**	20%	CH_2Cl_2	r.t.	 **20**	71[c]	2:1	—
5	 **6**	**1c**	5%	MeOH	r.t.	 **22**	80[c]	3.2:1	—
6	 **7**	**1b**	—	CH_2Cl_2	r.t.	 **24**	84	1.3:1 (>98)	*trans*
7	 **8**	**1b**	20%	CH_2Cl_2	r.t.	 **25**	75	1.3:1 (>98)	*trans*

[a] Global yield of adduct after column chromatography.
[b] Determined by ^1H NMR analysis of crude reaction mixtures; in brackets, d.e. of major isomer after column chromatography.
[c] Inseparable mixture of diastereoisomers.

assigned to the relation (1*R*)-enol/(1*S*)-enol/(1*R*)-keto/(1*S*)-keto.



Scheme 8.

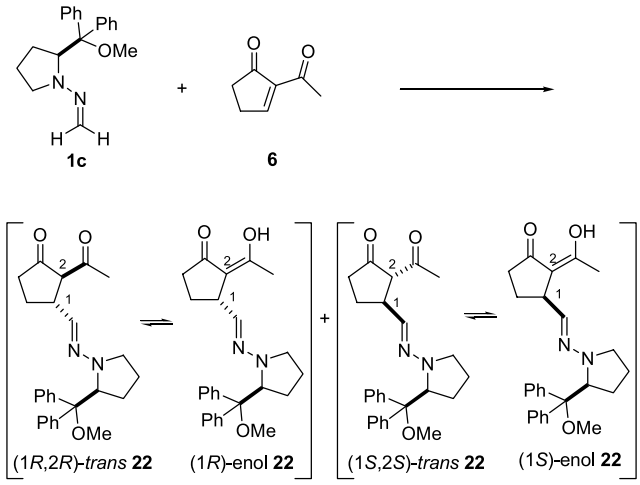


Scheme 9. Formation of pyrazols **21** and **23**.

The diastereoisomeric ratio was improved by addition of MgI_2 as catalyst: under optimized conditions (20% of MgI_2, room temperature and CH_2Cl_2 as solvent), the desired product was obtained in a 71% yield and a 2:1 (1*R*)/(1*S*) diastereoisomeric ratio (Table 2, entry 4). Using these conditions by-product **A** was isolated in 9% yield (Scheme 8).

According to the theoretical studies of Iglesias[20] and in agreement with different studies in related compounds,[21] we assigned the structure containing endocyclic C–C double bonds, as drawn in Scheme 8 to the enolic forms of **20**.

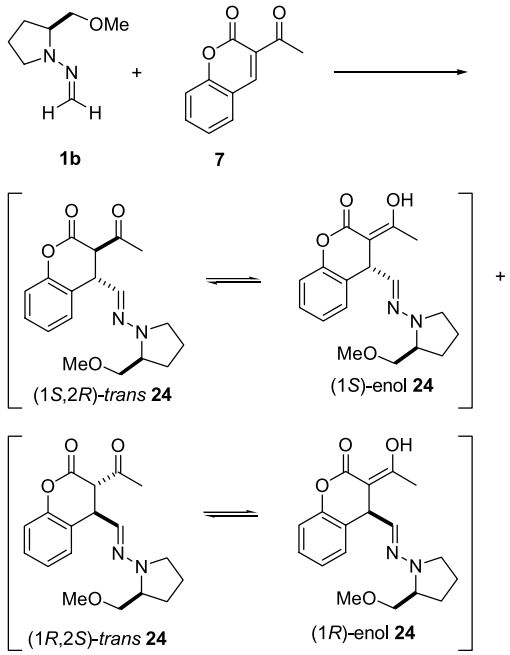
2.2.5. Addition of hydrazone 1c to 2-acetylcyclopent-2-enone 6. The results obtained with this alkene are similar to those observed with **5**. The reaction in CH_2Cl_2 proceeds at room temperature, without need of catalyst, to afford adduct **22** in 60% yield. The analysis of the ^1H NMR spectrum in $CDCl_3$ showed four isomers in a 1:0.5:0.5:0.2 ratio, indicating a 2:1 diastereoisomeric ratio and again a 1:2 keto/enol ratio. The spectrum recorded in CD_3OD indicated an inversion of the keto/enol ratio (2:1) in this solvent. Again, transformation of adduct **22** in the corresponding pyrazol **23** following the procedure described above (Scheme 9) confirmed these analysis. In the case of derivatives **22**, literature data[20,21] suggest to assign the structure with exocyclic C–C double bond to their enolic forms, as drawn in Scheme 10.



Scheme 10.

A substantial increase on the diastereomeric ratio was observed when the reaction was performed in MeOH, at room temperature and with catalytic amount (5%) of MgI_2. Under these optimized conditions, adduct **22** was obtained in 80% yield as a 3.2:1 (1*R*)-*trans*/(1*S*)-*trans* mixture (Table 2, entry 5).

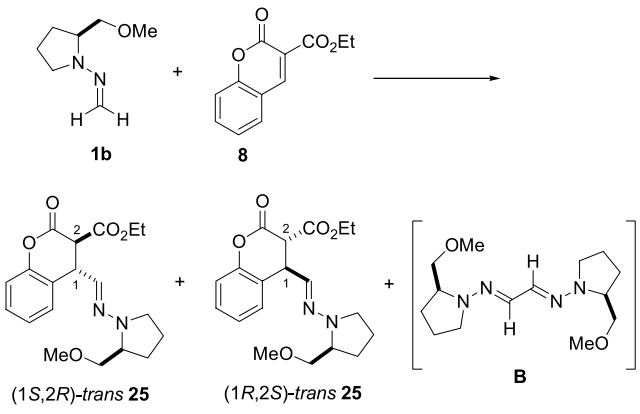
2.2.6. Addition of hydrazone 1b to alkene 7. As it was previously noted, polymerization of cumarine **7** in presence of MgI_2 did not allow its use as promoter. Fortunately, the reaction with hydrazone **1b** proceeded spontaneously in CH_2Cl_2 at room temperature (Scheme 11). The analysis of the ^1H NMR spectrum in $CDCl_3$ showed four isomers in a 1:1:0.8:0.8 ratio, indicating a 1.3:1 diastereoisomeric ratio



Scheme 11.

and 1:1 keto/enol ratio. Attempts to improve the selectivity using the hydrazone **1c** were unsuccessful because of the lack of reactivity of this reagent in the absence of catalysts. Under optimized conditions (CH_2Cl_2, room temperature), adduct **24** was obtained in 84% yield with a 1.3:1 (1*S*)-*trans*/(1*R*)-*trans* diastereoisomeric ratio (Table 2, entry 6). Separation by column chromatography afforded the isolation of pure diastereomers in this case.

2.2.7. Addition of hydrazone 1b to 2-ethoxycarbonylcumarine 8. 2-Ethoxycarbonylcumarine **8**, less reactive than ketoester **7**, gave the desired adduct using hydrazone **1b** in the presence of 20% of MgI_2 in CH_2Cl_2 at room temperature. Under these conditions, adduct **25** was obtained as a 1.3:1 mixture of two diastereoisomers in 75% yield and by-product **B** was isolated in 12% yield (Scheme 12). Different attempts to improve diastereoselectivites using equimolecular amounts of MgI_2 did not improve yield or selectivities, but led to 3.4:1 *trans*/*cis* mixtures instead. Experiments using hydrazone **1c** as the reagent were also unsuccessful due to the lack of reactivity observed, even in the presence of equimolecular amounts of MgI_2. In spite of the modest stereoselectivity, an easy chromatographic separation allowed to obtain both diastereomers as optically pure compounds.

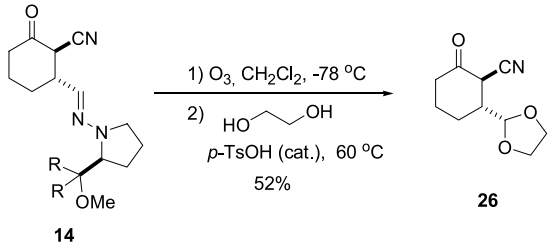


Scheme 12.

A summary of the best results in the addition reaction of chiral formaldehyde *N*,*N*-dialkylhydrazones **1b** or **1c** to alkenes **2**–**8** is collected in Table 2.

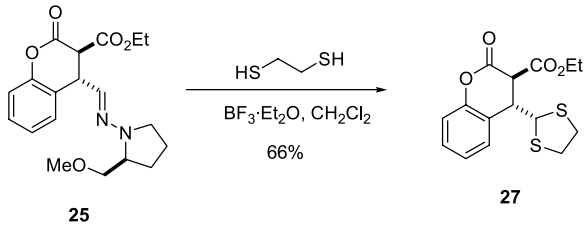
2.3. Deprotection of adducts

Treatment of compounds **14**, **16**, **18**, **20**, **22**, **24**, and **25** with ozone led to the corresponding pure aldehydes, according to the ^1H NMR analysis of the crude reaction mixtures. However, any attempt of purification of these compounds by column chromatography using either silica gel or florisil® led to extensive decomposition. Therefore, we decided to transform the crude aldehydes into the more stable carboxylic acids by oxidation with Jones reagent, but the resulting carboxylic acids were also unstable and did not resist chromatographic purification. Nevertheless, the crude aldehydes could be used in further reactions. For instance, nitrile **14**, in spite of its tendency to undergo β-elimination of hydrogen cyanide, has been successfully transformed into acetal **26** via the corresponding aldehyde and isolated after protection in a 52% yield over two steps (Scheme 13).



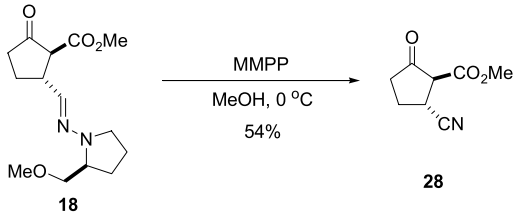
Scheme 13.

Other functional group transformations of *N*,*N*-dialkylhydrazones have been used to remove the chiral auxiliary, thereby illustrating the synthetic possibilities of the methodology. For instance, direct dithioacetalation of adduct **25** was achieved by reaction with ethanedithiol in the presence of an excess of $BF_3 \cdot Et_2O$[22] (2.5 mmol) to afford the desired dithioacetal **27** in 66% yield (Scheme 14).



Scheme 14.

Finally, adduct **18** was transformed into the corresponding nitrile **28**, obtained in 54% yield by treatment with magnesium monoperoxyphthalate (MMPP) (Scheme 15).[23]



Scheme 15.

The methyl 2-cyano-5-oxocyclopentanocarboxylate **28** is an interesting precursor of the cyclopentenoid antibiotic sarkomycin.[24]

3. Experimental

Et_2O, toluene and THF were distilled from sodium benzophenone ketyl and CH_2Cl_2 from calcium hydride immediately prior use; Et_3N from KOH. All other reagents and solvents were purified by standard procedures or were used as obtained from commercial sources as appropriate. Light petroleum ether used had a bp 40–65 °C. Aqueous solutions were all saturated, unless otherwise stated. Flash column chromatography was carried out using silica-gel

Merk 60 (0.063–0.200, 0.040–0.063 or 0.015–0.040 mm) or prepacked silica columns. Analytical thin layer chromatography was performed on precoated plates (Merk Kieselger 60 F254). Melting points were recorded using a Gallenkamp MFB-595 apparatus and are uncorrected. Optical rotations were measured using a Perkin Elmer 241 MC polarimeter. Infrared spectra were recorded on a FT-IR Bomen MB-120 spectrometer. Spectra were recorded for KBr pellets or films. Proton magnetic resonance spectra (^{1}H NMR) were recorded at 300 or 500 MHz on a Brucker AMX 300 or Brucker AMX 500 instruments respectively and are reported as follows: chemical shift δ in ppm, (multiplicity, number of protons, coupling constant J in Hz). Residual protic solvent was used as the internal reference. Carbon magnetic resonance spectra (^{13}C NMR) were recorded at 75.5 or 125.5 MHz on a Brucker AMX 300 or Brucker AMX 500 instruments, respectively. Chemical shifts are quoted in ppm and referenced to the appropriate solvent peak. Microanalyses were determined in microanalytical laboratories at the Instituto de Investigaciones Químicas Isla de la Cartuja (Seville). Mass spectra were obtained on a Kratos MS 80 RFA or Micromass AutoSpecQ spectrometers.

3.1. Addition of 1-methylenaminopyrrolidine 1a to compounds 2–4, 7, 8 (general procedure)

1-Methylenaminopyrrolidine **1a** (98 mg, 1 mmol) was added under an argon atmosphere to a solution of alkene (1.5 mmol) in dry CH_2Cl_2 and the mixture stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was concentrated and the residue purified by flash chromatography. Eluants, yields and spectral and analytical data for compounds **9**–**13** are as follows:

3.1.1. Synthesis of compound 9. From alkene **2** (182 mg, 1.5 mmol), flash chromatography (1:2:1 Et_2O–petroleum ether–CH_2Cl_2) gave 171 mg (78%) of **9** as an inseparable mixture of *trans* and *cis* adducts (3:1 *trans*/*cis* ratio). IR (film, cm^{-1}): 2945, 2872, 2249, 2201, 1726, 1659, 1595, 1452, 1379, 1337, 1096, 1028, 868; mass spectrum (CI) *m*/*z* (rel intensity) 220 (100%, $M^+ + 1$), 219 (13, M^+), 195 (15), 70 (22); *m*/*z* calcd for $C_{12}H_{18}N_3O$ 220.1450, found 220.1451. NMR data for *trans* **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56–1.85 (m, 2H), 1.87–1.94 (m, 4H), 2.09–2.17 (m, 2H), 2.27–2.42 (m, 1H), 2.56–2.64 (m, 1H), 2.85–2.95 (m, 1H), 3.12–3.20 (m, 4H), 3.72 (d, 1H, J=11.4 Hz), 6.47 (d, 1H, J=4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 23.1, 24.3, 29.9, 40.2, 45.6, 47.1, 50.9, 116.0, 131.2, 200.2. NMR data for *cis* **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56–1.85 (m, 1H), 1.87–1.94 (m, 4H), 1.95–2.06 (m, 2H), 2.09–2.17 (m, 1H), 2.27–2.42 (m, 1H), 2.66–2.78 (m, 1H), 3.01–3.08 (m, 1H), 3.22–3.27 (m, 4H), 3.59 (d, 1H, J=4.7 Hz), 6.34 (d, 1H, J=4.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 23.2, 23.4, 27.1, 39.0, 44.0, 46.6, 50.8, 115.9, 129.9, 199.9.

3.1.2. Synthesis of compound 10. From alkene **3** (203 mg, 1.5 mmol), flash chromatography (1:4:1 Et_2O–petroleum ether–CH_2Cl_2) gave 177 mg (76%) of **10** as an inseparable mixture of *trans* and *cis* adducts (10:1 *trans*/*cis* ratio). IR (film, cm^{-1}): 2963, 2239, 1753, 1397, 1092, 1026, 872, 801, 708; mass spectrum (EI) *m*/*z* (rel intensity): 234 (10%, $M^+ + 1$), 233 (61, M^+), 149 (100), 70 (93), 56 (66); *m*/*z* calcd for $C_{13}H_{19}N_3O$ 233.1528, found 233.1529. NMR data for *trans* **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 3H), 1.25 (s, 3H), 1.85–1.89 (m, 4H), 2.31–2.33 (m, 2H), 3.02 (dd, 1H, J=12.0, 4.3 Hz), 3.10–3.17 (m, 4H), 3.77 (d, 1H, J=12.0 Hz), 6.40 (d, 1H, J=4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 23.2, 27.7, 38.2, 41.4, 51.1, 53.0, 53.8, 116.6, 126.8, 205.3. NMR data for *cis* **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.18 (s, 3H), 1.85–1.89 (m, 4H), 2.22–2.24 (m, 2H), 2.97–3.05 (m, 1H), 3.10–3.17 (m, 4H), 3.59 (d, 1H, J=8.9 Hz), 6.40–6.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 24.2, 27.5, 39.1, 42.6, 51.0, 51.7, 52.6, 117.8, 128.5, 206.9.

3.1.3. Synthesis of compound 11. From alkene **4** (209 mg, 1.5 mmol), flash chromatography (1:4:1 Et_2O–petroleum ether–CH_2Cl_2) gave 119 mg (50%) of **4** as an inseparable mixture of *trans* and *cis* adducts (12:1 *trans*/*cis* ratio). IR (film, cm^{-1}): 2959, 2864, 1712, 1593, 1442, 1347, 1204, 1124, 900, 878, 728; mass spectrum (CI) *m*/*z* (rel intensity): 239 (34%, $M^+ + 1$), 238 (22, M^+), 237 (30), 141 (100), 99 (96); *m*/*z* calcd for $C_{12}H_{18}N_2O_3$ 238.1317, found 238.1319. NMR data for *trans* **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83–1.89 (m, 6H), 2.28–2.50 (m, 3H), 3.09–3.13 (m, 4H), 3.32–3.41 (m, 1H), 3.75 (s, 3H), 6.51 (d, 1H, J=4.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 26.3, 37.8, 43.6, 51.1, 52.3, 59.2, 134.0, 169.1, 210.8. NMR data for *cis* **11**: 1H NMR (300 MHz, $CDCl_3$) δ 1.83–1.89 (m, 6H), 2.28–2.50 (m, 3H), 3.09–3.13 (m, 4H), 3.32–3.41 (m, 1H), 3.85 (s, 3H), 6.47 (d, 1H, J=6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 26.3, 37.7, 43.6, 51.6, 52.8, 57.8, 133.4, 169.1, 210.8.

3.1.4. Synthesis of compound 12. From alkene **7** (283 mg, 1.5 mmol), flash chromatography (1:6:1 Et_2O–petroleum ether–CH_2Cl_2) gave 243 mg (85%) of *trans*-**12** (*cis* isomer was not observed by 1H NMR analysis of crude mixture). IR (film, cm^{-1}): 3051, 2966, 2874, 1599, 1479, 1395, 1093, 987, 866, 754; mass spectrum (EI) *m*/*z* (rel intensity): 286 (20%, M^+), 217 (33), 175 (56), 131 (21), 85 (25), 70 (100); *m*/*z* calcd for $C_{16}H_{18}N_2O_3$ 286.1317, found 286.1315; ^{1}H NMR (300 MHz, $CDCl_3$) (1.81–1.89 (m, 4H), 2.46 (s, 3H), 3.14–3.23 (m, 4H), 3.70 (d, 1H, J=2.3 Hz), 4.32 (dd, 1H, J=7.2, 2.3 Hz), 6.07 (d, 1H, J=7.2 Hz), 6.84–7.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) (23.3, 29.8, 39.6, 50.7, 62.3, 94.4, 110.7, 121.9, 124.3, 127.4, 129.5, 157.7, 166.5, 201.5.

3.1.5. Synthesis of compound 13. In this case, the general procedure was modified as follows: to a solution of alkene **8** (327 mg, 1.5 mmol) and MgI_2 (55.6 mg, 20 mol%) in dry CH_2Cl_2 (1 mL) was added 1-methylenpyrrolidine **1a** (98 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2×5 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (1:3 Et_2O–petroleum ether) gave 253 mg (80%) of **13** as an inseparable mixture of *trans* and *cis* adducts (17:1 *trans*/*cis* ratio). IR (film, cm^{-1}) 2974, 2874, 1780, 1738, 1588, 1487, 1458, 1339, 1223, 1161, 1028, 912, 874, 760; mass spectrum (FAB) *m*/*z* (rel intensity): 339 (100%, $M^+ + 23$), 316 (85, M^+), 314 (95), 243 (53), 147 (56); *m*/*z*

calcd for $C_{17}H_{20}N_2O_4$ 316.1423, found 316.1422. NMR data for *trans* **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, 3H, J=7.2 Hz), 1.82–1.86 (m, 4H), 3.05–3.15 (m, 4H), 4.08–4.14 (m, 3H), 4.24 (t, 1H, J=4.5 Hz), 6.36 (d, 1H, J=4.5 Hz), 7.04–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 23.2, 42.2, 50.0, 50.9, 61.9, 117.1, 122.4, 124.8, 128.0, 128.9, 129.1, 150.9, 164.2, 167.2. NMR data for *cis* **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, 3H, J=7.1 Hz), 1.82–1.86 (m, 4H), 3.05–3.15 (m, 4H), 4.08–4.14 (m, 4H), 6.52 (d, 1H, J=6.8 Hz), 7.04–7.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 23.2, 42.0, 50.0, 50.9, 61.7, 116.8, 122.4, 124.8, 127.2, 128.9, 129.1, 150.9, 164.2, 167.2.

3.2. Addition of hydrazones 1b and 1c to alkenes 2–8

3.2.1. Synthesis of compound 14. To a solution of alkene **2** (182 mg, 1.5 mmol) and MgI_2 (55.6 mg, 20 mol%) in dry MeOH (1 mL) was added **1c** (295 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was concentrated, the residue diluted with CH_2Cl_2 (10 mL) and washed with water (2×5 mL). The organic layer was dried ($MgSO_4$) and concentrated. The crude 1H NMR indicated a mixture of four possible diastereoisomers (1*R*,2*R*)-*trans*/(1*R*,2*S*)-*cis*/(1*S*,2*S*)-*trans*/(1*S*,2*R*)-*cis* in a 1:0.3:0.3:0.1 ratio. The residue was purified by medium pressure liquid chromatography (1:4 AcOEt–petroleum ether) and two fractions were obtained, 116 mg (28%) of major isomers (1*R*,2*R*)-*trans*/(1*R*,2*S*)-*cis* (3:1 ratio) and 228 mg (55%) of a mixture of all four stereoisomers. IR (film, cm^{-1}): 3065, 2944, 2824, 2259, 1735, 1598, 1453, 1356, 1219, 1090, 913, 768, 711; mass spectrum (IE) *m*/*z* (rel intensity): 415 (13%, M^+), 384 (34, M^+-OCH_3), 305 (25), 234 (100); *m*/*z* calcd for $C_{26}H_{29}N_3O_2$ 415.2260, found 415.2250. NMR data for (1*R*,2*R*)-*trans* **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10–0.28 (m, 1H), 1.37–1.45 (m, 1H), 1.47–1.54 (m, 1H), 1.60–1.72 (m, 1H), 1.88–2.07 (m, 4H), 2.16–2.24 (m, 1H), 2.51–2.54 (m, 1H), 2.58–2.65 (m, 1H), 2.70–2.84 (m, 2H), 2.96 (s, 3H), 3.12 (d, 1H, J=11.0 Hz), 4.69 (dd, 1H, J=8.8, 2.2 Hz), 6.34 (d, 1H, J=4.2 Hz), 7.23–7.51 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.3, 25.8, 30.2, 40.2, 45.0, 47.4, 48.9, 51.6, 68.0, 85.8, 116.4, 127.6, 126.9, 127.0, 127.1, 127.2, 129.6, 130.4, 138.8, 141.2, 200.7. NMR data for (1*R*,2*S*)-*cis* **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10–0.28 (m, 1H), 1.37–1.45 (m, 1H), 1.47–1.54 (m, 1H), 1.60–1.72 (m, 1H), 1.88–2.07 (m, 4H), 2.37–2.41 (m, 1H), 2.51–2.54 (m, 1H), 2.58–2.65 (m, 1H), 2.70–2.84 (m, 2H), 2.99 (s, 3H), 3.44 (d, 1H, J=3.9 Hz), 4.78–4.80 (m, 1H), 6.20 (d, 1H, J=3.1 Hz), 7.23–7.51 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 24.7, 25.9, 27.0, 39.0, 44.4, 46.4, 49.8, 51.5, 67.2, 85.7, 116.3, 127.4, 126.9, 127.0, 127.2, 130.4, 140.0, 141.3, 201.3. NMR data for (1*S*,2*S*)-*trans* **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10–0.28 (m, 1H), 1.37–1.45 (m, 1H), 1.47–1.54 (m, 1H), 1.60–1.72 (m, 1H), 1.88–2.07 (m, 4H), 2.16–2.24 (m, 1H), 2.51–2.54 (m, 1H), 2.58–2.65 (m, 1H), 2.70–2.84 (m, 2H), 2.97 (s, 3H), 3.23 (d, 1H, J=13.1 Hz), 4.76 (dd, 1H, J=8.8, 2.3 Hz), 6.29 (d, 1H, J=3.4 Hz), 6.29–7.53 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.3, 25.7, 30.8, 40.3, 45.3, 46.7, 48.7, 51.6, 67.9, 85.8, 116.5, 127.5, 126.9, 127.1, 129.5, 130.3, 139.1, 141.5, 201.1. NMR data for (1*S*,2*R*)-*cis* **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10–0.28 (m, 1H), 1.37–1.45 (m, 1H), 1.47–1.54 (m, 1H), 1.60–1.72 (m, 1H), 1.88–2.07 (m, 4H), 2.16–2.24 (m, 1H), 2.51–2.54 (m, 1H), 2.58–2.65 (m, 1H), 2.70–2.84 (m, 2H), 2.96 (s, 3H), 2.95–2.97 (m, 1H), 4.77–4.81 (m, 1H), 6.25 (d, 1H, J=4.2 Hz), 6.29–7.53 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 24.7, 27.0, 29.6, 39.2, 43.8, 47.0, 50.1, 51.4, 68.0, 85.8, 116.5, 127.3, 126.9, 127.1, 127.3, 130.3, 139.1, 141.5, 201.0.

3.2.2. Synthesis of compound 16. To a solution of alkene **3** (203 mg, 1.5 mmol) and MgI_2 (278 mg, 1 mmol) in dry CH_2Cl_2 (1 mL) was added **1c** (295 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2×5 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (1:4:1 Et_2O–petroleum ether–CH_2Cl_2) gave 343 mg (80%) of **16** as an inseparable mixture of major isomer (1*S*/2*R*)-*trans* **16** and minor isomer (1*R*,2*S*)-*trans* **16** (d.r. 5:1). IR (film, cm^{-1}): 3063, 2975, 2864, 2236, 1617, 1466, 1355, 1299, 1172, 1029, 926, 719; mass spectrum (FAB) *m*/*z* (rel intensity): 452 (5%, M^++23), 428 (5, M^+−1), 398 (19), 232 (90), 197 (100); *m*/*z* calcd for $C_{27}H_{31}N_3O_2$ 429.2416, found 429.2406. NMR data for (1*S*,2*R*)-*trans* **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05–0.17 (m, 1H), 0.55 (s, 3H), 1.21 (s, 3H), 1.39–1.48 (m, 1H), 1.90–2.10 (m, 2H), 2.21 (s, 2H), 2.59–2.68 (m, 1H), 2.76–2.81 (m, 1H), 2.91 (s, 3H), 2.89–2.94 (m, 1H), 3.20 (d, 1H, J=12.2 Hz), 4.74 (dd, 1H, J=7.7, 3.4 Hz), 6.20 (d, 1H, J=3.0 Hz), 7.20–7.51 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 22.2, 25.4, 27.8, 37.9, 40.4, 48.6, 51.6, 53.1, 53.5, 68.3, 85.7, 117.0, 122.2, 126.9, 127.0, 127.1, 127.2, 129.4, 130.2, 138.6, 140.7, 205.4. NMR data for (1*R*,2*S*)-*trans* **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05–0.17 (m, 1H), 0.84 (s, 3H), 1.20 (s, 3H), 1.39–1.48 (m, 1H), 1.90–2.10 (m, 2H), 2.25 (s, 2H), 2.59–2.68 (m, 1H), 2.76–2.81 (m, 1H), 2.89–2.94 (m, 1H), 2.95 (s, 3H), 3.30 (d, 1H, J=12.0 Hz), 4.68 (dd, 1H, J=8.3, 3.1 Hz), 6.26 (d, 1H, J=4.5 Hz), 7.20–7.51 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 23.1, 25.7, 29.3, 38.4, 40.6, 49.5, 51.4, 52.8, 53.3, 68.0, 85.7, 116.9, 123.8, 126.9, 127.0, 127.1, 127.2, 129.5, 129.9, 138.7, 140.8, 205.5.

3.2.3. Synthesis of compound 18. To a solution of hydrazone **1b** (295 mg, 1 mmol) and alkene **4** (210 mg, 1.5 mmol) in dry CH_2Cl_2 (1 mL) was added MgI_2 (14 mg, 5 mol%) under an argon atmosphere. The mixture was stirred at 0 °C until TLC indicated total consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (2×5 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (1:5 Et_2O–petroleum ether) gave 212 mg (75%) of **18** as an inseparable mixture of major isomer (1*R*/2*S*)-*trans* **18** and minor isomer (1*S*,2*R*)-*trans* **18** (d.r. 3:1). IR (film, cm^{-1}): 2951, 2880, 1757, 1734, 1458, 1447, 1321, 1275, 1208, 1123; mass spectrum (CI) *m*/*z* (rel intensity): 283 (100%, M^++1), 282 (11, M^+), 251 (59, M^+-OCH_3), 237 (21), 143 (30); *m*/*z* calcd for $C_{14}H_{22}N_2O_4$ 282.1580, found 282.1581. NMR data for (1*R*,2*S*)-*trans* **18**: ^{1}H NMR (300 MHz, C_6D_6) δ 1.22–1.40 (m, 3H), 1.41–1.55 (m, 1H), 1.62–2.00 (m, 4H), 2.39–2.47 (m, 1H), 2.87–2.94 (m, 1H), 3.15 (s, 3H), 3.35–3.43 (m, 4H), 3.42 (s, 3H), 3.61 (dd,

1H, $J=8.9$, 3.3 Hz), 6.23 (d br, 1H, $J=3.0$ Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 21.9, 26.1, 26.8, 37.2, 43.7, 48.7, 51.5, 58.5, 59.2, 63.0, 74.7, 132.7, 169.2, 209.1. NMR data for (1*S*,2*R*)-*trans* **4**: ^{1}H NMR (300 MHz, C_6D_6) δ 1.22–1.40 (m, 3H), 1.41–1.55 (m, 1H), 1.62–2.00 (m, 4H), 2.48–2.55 (m, 1H), 2.87–3.00 (m, 1H), 3.16 (s, 3H), 3.35–3.43 (m, 4H), 3.43 (s, 3H), 3.61 (dd, 1H, $J=8.9$, 3.3 Hz), 6.21 (d br, 1H, $J=3.6$ Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 21.9, 26.1, 29.8, 37.3, 43.9, 48.7, 51.5, 58.5, 59.3, 63.0, 74.8, 132.6, 169.2, 209.1.

3.2.4. Synthesis of compound 20. To a solution of alkene **5** (209 mg, 1.5 mmol) and MgI_2 (55.6 mg, 20 mol%) in dry CH_2Cl_2 (1 mL) was added **1c** (295 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2×5 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (1:5 Et_2O–petroleum ether) gave 307 mg (71%) of **20** as an inseparable mixture of major isomer (1*R*)-**20** (keto/enol ratio 1:5) and minor isomer (1*S*)-**20** (keto/enol ratio 1:5) (d.r. 2:1). Dimer **A** was isolated as by-product in 9% yield (50 mg). Data for **20**: IR (film, cm^{-1}): 3057, 3000, 2826, 1603, 1491, 1447, 1414, 1350, 1074, 890, 800; mass spectrum (FAB) *m*/*z* (rel intensity): 455 (4%, $M^+ + 23$), 431 (10), 235 (100), 197 (74), 139 (63); *m*/*z* calcd for $C_{27}H_{32}N_2O_3Na$ 455.2311, found 455.2320. NMR data for (1*R*)-enol **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07–0.17 (m, 1H), 1.35–1.42 (m, 1H), 1.60–1.90 (m, 6H), 2.13 (s, 3H), 2.31–2.35 (m, 2H), 2.50–2.58 (m, 1H), 2.83–2.86 (m, 1H), 2.96 (s, 3H), 3.31–3.34 (m, 1H), 4.70–4.74 (m, 1H), 6.28 (d, 1H, $J=6.1$ Hz), 7.22–7.47 (m, 10H), 16.31 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 22.2, 25.1, 25.9, 28.7, 31.0, 37.6, 50.8, 51.3, 67.5, 85.8, 108.7, 126.9, 127.0, 127.2, 129.6, 129.8, 130.1, 135.4, 141.5, 142.2, 182.5, 200.7. Separate ^{1}H NMR signals for (1*R*,2*R*)-*trans*-keto **20**: (500 MHz, $CDCl_3$) δ 2.17 (s, 3H), 4.59–4.61 (m, 1H). NMR data for (1*S*)-enol **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07–0.17 (m, 1H), 1.35–1.42 (m, 1H), 1.60–1.90 (m, 6H), 2.00 (s, 3H), 2.31–2.35 (m, 2H), 2.50–2.58 (m, 1H), 2.83–2.86 (m, 1H), 2.98 (s, 3H), 3.37–3.41 (m, 1H), 4.70–4.74 (m, 1H), 6.36 (d, 1H, $J=4.3$ Hz), 7.22–7.47 (m, 10H), 16.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2, 22.2, 24.9, 26.2, 27.9, 31.0, 37.0, 50.8, 51.2, 66.8, 85.8, 108.8, 126.9, 127.0, 127.2, 129.6, 129.8, 130.1, 135.7, 140.6, 141.3, 182.8, 199.9. Separate ^{1}H NMR signals for (1*S*,2*S*)-*trans*-keto **20**: (500 MHz, $CDCl_3$) δ 2.11 (s, 3H), 4.66–4.69 (m, 1H). Data for dimer **A**: IR (film, cm^{-1}): 2926, 2855, 1536, 1409, 1139, 1000, 988, 869, 750, 718; mass spectrum (IE) *m*/*z* (rel intensity): 587 (6%, $M^+ + 1$), 555 (7), 389 (100); *m*/*z* calcd for $C_{38}H_{42}N_4O_2$ 586.3308, found 586.3307; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10–0.25 (m, 2H), 1.22–1.44 (m, 2H), 1.82–2.01 (m, 4H), 2.68–2.81 (m, 2H), 2.92–3.05 (m, 2H), 3.07 (s, 6H), 4.78–4.84 (m, 2H), 6.99 (s, 2H), 7.10–7.62 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 25.9, 50.5, 51.2, 67.4, 85.7, 126.6, 126,8, 126.9, 127.0, 127.1, 127.3, 127.7, 127.8, 128.1, 129.1, 129.4, 129.5, 129.9, 130.0, 132.3, 133.9, 141.0, 141.8.

3.2.5. Synthesis of compound 22. To a solution of alkene **6** (186 mg, 1.5 mmol) and MgI_2 (14 mg, 5 mol%) in dry MeOH (1 mL) was added **1c** (295 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was concentrated and the residue was diluted with CH_2Cl_2 (10 mL) and washed with water (2×5 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (1:5 Et_2O–petroleum ether) gave 334 mg (80%) of **22** as an inseparable mixture of major isomer (1*R*)-**22** (keto/enol ratio 1:2) and minor isomer (1*S*)-**22** (keto/enol ratio 1:2) (d.e. 52%). IR (film, cm^{-1}): 3057, 2957, 2826, 1742, 1707, 1651, 1616, 1449, 1356, 1227, 1092, 901, 876, 762, 704; mass spectrum (FAB) *m*/*z* (rel intensity): 441 (47%, $M^+ + 23$), 419 (10, $M^+ + 1$), 387 (58), 221 (100), 197 (52); *m*/*z* calcd for $C_{26}H_{31}N_2O_3$ 419.2335, found 419.2331. NMR data for (1*R*)-enol **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02–0.19 (m, 1H), 1.32–1.43 (m, 1H), 1.81 (s, 3H), 1.87–1.95 (m, 2H), 2.12–2.23 (m, 2H), 2.35–2.59 (m, 3H), 2.78–2.88 (m, 1H), 2.99 (s, 3H), 3.51–3.58 (m, 1H), 4.74 (dd, 1H, $J=9.2$, 1.6 Hz), 6.23 (d, 1H, $J=7.1$ Hz), 7.21–7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 22.2, 26.3, 35.3, 38.4, 42.5, 50.7, 51.5, 67.8, 85.9, 111.8, 126.9, 127.0, 127.2, 129.6, 130.2, 130.3, 135.1, 140.4, 141.4, 203.4. NMR data for (1*R*,2*R*)-*trans*-keto **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02–0.19 (m, 1H), 1.32–1.43 (m, 1H), 1.53–1.68 (m, 2H), 1.87–1.95 (m, 2H), 2.34 (s, 3H), 2.35–2.59 (m, 3H), 2.78–2.88 (m, 1H), 2.98 (s, 3H), 3.40–3.45 (m, 1H), 3.51–3.58 (m, 1H), 4.65 (dd, 1H, $J=8.7$, 2.1 Hz), 6.40 (d, 1H, $J=3.6$ Hz), 7.21–7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 26.0, 26.1, 30.8, 35.3, 41.2, 50.1, 51.5, 66.2, 68.1, 85.9, 126.9, 127.0, 127.2, 129.6, 130.2, 130.3, 131.3, 140.1, 141.6, 180.4, 203.4. NMR data for (1*S*)-enol **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07–0.20 (m, 1H), 1.36–1.42 (m, 1H), 1.72–2.08 (m, 2H), 1.99 (s, 3H), 2.12–2.40 (m, 2H), 2.52–2.59 (m, 1H), 2.78–2.86 (m, 1H), 2.96 (s, 3H), 3.53–3.59 (m, 1H), 4.66–4.70 (m, 1H), 6.33 (d, 1H, $J=3.0$ Hz), 7.24–7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 21.8, 25.8, 25.9, 35.2, 40.4, 49.9, 51.4, 67.6, 85.6, 112.0, 112.0, 126.7, 126.8, 126.9, 127.0, 127.1, 129.4, 129.5, 129.9, 130.1, 134.0, 139.9, 141.3, 212.0. NMR data for (1*S*,2*S*)-*trans*-keto **22**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07–0.20 (m, 1H), 1.36–1.42 (m, 1H), 1.72–2.08 (m, 2H), 2.12–2.40 (m, 2H), 2.26 (s, 3H), 2.52–2.59 (m, 1H), 2.78–2.86 (m, 1H), 3.00 (s, 3H), 3.41–3.46 (m, 1H), 3.53–3.59 (m, 1H), 4.66–4.70 (m, 1H), 6.42 (d, 1H, $J=1.9$ Hz), 7.24–7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 25.7, 26.1, 30.3, 37.7, 41.6, 50.5, 51.3, 66.6, 67.3, 85.7, 112.0, 126.7, 126.8, 126.9, 127.0, 127.1, 129.4, 129.5, 129.9, 130.1, 131.6, 139.9, 140.6, 202.0, 204.8.

3.2.6. Synthesis of compound 24. To a solution of alkene **7** (376 mg, 2 mmol) in dry CH_2Cl_2 (2 mL) was added **1b** (142 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was concentrated. Purification by flash chromatography (1:4:1 Et_2O–petroleum ether–CH_2Cl_2) gave 157 mg (48%) of major isomer (1*S*)-**24** (keto/enol ratio 1:1) and 121 mg (37%) of minor isomer (1*R*)-**24** (keto/enol ratio 1:1). Data for (1*S*)-**24**: $[\alpha]_D$ −69.3 (*c* 0.7, CH_2Cl_2); IR (film, cm^{-1}): 3055, 2928, 2880, 2834, 1703, 1605, 1481, 1468, 1263, 1096, 737, 706; mass spectrum (CI) *m*/*z* (rel intensity): 331

(100%, $M^+ + 1$), 285 (36), 189 (20), 116 (30); *m/z* calcd for $C_{18}H_{23}N_2O_4$ 331.1658, found 331.1652. NMR data for (1*S*,2*R*)-*trans*-keto **24**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77–1.96 (m, 4H), 2.32 (s, 3H, $COCH_3$), 2.72–2.81 (m, 1H), 3.18–3.24 (m, 1H), 3.35 (s, 3H, OCH_3), 3.42–3.53 (m, 3H), 4.23 (d, 1H, J=4.8 Hz), 4.29 (dd, 1H, J=4.8, 4.0 Hz), 6.52 (d, 1H, J=4.0 Hz), 7.02–7.27 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 26.5, 29.1, 40.5, 49.0, 56.6, 59.2, 63.1, 74.1, 117.1, 122.3, 124.9, 127.8, 128.7, 130.2, 149.6, 168.9, 200.6. NMR data for (1*S*)-enol **24**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77–1.96 (m, 4H), 2.22 (s, 3H), 2.63–2.68 (m, 1H), 3.18–3.24 (m, 1H), 3.36 (s, 3H), 3.42–3.53 (m, 3H), 4.52 (d, 1H, J=7.2 Hz), 6.31 (d, 1H, J=7.2 Hz), 7.02–7.27 (m, 4H), 13.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.6, 22.0, 26.6, 41.4, 49.4, 59.2, 63.1, 74.6, 97.1, 117.0, 122.3, 124.9, 128.5, 128.8, 136.1, 150.5, 165.4, 180.7. Data for (1*R*)-**24**: $[\alpha]_D$ −23.0 (*c* 0.8, CH_2Cl_2); IR (film, cm^{-1}): 3055, 2928, 2880, 2834, 1703, 1605, 1481, 1468, 1263, 1096, 737, 706; mass spectrum (CI) *m/z* (rel intensity): 331 (100%, $M^+ + 1$), 330 (4, M^+), 329 (8), 285 (16), 116 (12); *m/z* calcd for $C_{18}H_{23}N_2O_4$ 331.1658, found 331.1655. NMR data for (1*R*,2*S*)-*trans*-keto **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–2.00 (m, 4H), 2.30 (s, 3H), 2.60–2.72 (m, 1H), 3.12–3.27 (m, 2H), 3.36 (s, 3H), 3.39–3.58 (m, 2H), 4.19–4.21 (m, 1H), 4.23–4.27 (m, 1H), 6.53 (s br, 1H), 7.01–7.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 26.3, 29.0, 40.2, 49.3, 56.5, 58.9, 62.9, 73.9, 117.0, 122.8, 124.9, 127.2, 128.4, 130.1, 149.5, 168.9, 200.5. NMR data for (1*R*)-enol **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–2.00 (m, 4H), 2.16 (s, 3H), 2.60–2.72 (m, 1H), 3.12–3.27 (m, 2H), 3.36 (s, 3H), 3.39–3.58 (m, 2H), 4.51 (d, 1H, J=6.6 Hz), 6.31 (d, 1H, J=6.6 Hz), 7.01–7.27 (m, 4H), 13.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 21.9, 26.4, 41.1, 49.5, 58.9, 63.3, 74.4, 93.2, 116.8, 120.3, 124.8, 127.7, 128.7, 135.9, 150.3, 165.4, 180.3.

3.2.7. Synthesis of compound 25. To a solution of alkene **8** (436 mg, 2 mmol) and MgI_2 (55.6 mg, 20 mol%) in dry CH_2Cl_2 (2 mL) was added **1b** (142 mg, 1 mmol) under an argon atmosphere. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with water (2×5 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (1:4:1 Et_2O–petroleum ether–CH_2Cl_2) gave 143 mg (40%) of major isomer (1*S*,2*R*)-*trans* **25** and 126 mg (35%) of minor isomer (1*R*,2*S*)-*trans* **25**. Dimer **B** was isolated as by-product in 12% yield (35 mg). Data for (1*S*,2*R*)-*trans* **25**: $[\alpha]_D$ −102.5 (*c* 1.2, CH_2Cl_2); IR (film, cm^{-1}): 2976, 2926, 2880, 1775, 1738, 1613, 1456, 1258, 1221, 1094, 1028, 872, 801, 760, 735, 704; mass spectrum (FAB) *m/z* (rel intensity): 383 (60%, $M^+ + 23$), 361 (43, $M^+ + 1$), 360 (23, M^+), 315 (87), 241 (100), 219 (20); *m/z* calcd for $C_{19}H_{25}N_2O_5$ 361.1763, found 361.1763; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, 3H, J=7.1 Hz), 1.75–1.95 (m, 4H), 2.69–2.75 (m, 1H), 3.15–3.22 (m, 1H), 3.33 (s, 3H), 3.36–3.52 (m, 3H), 4.01–4.15 (m, 2H), 4.18–4.22 (m, 2H), 6.44 (d, 1H, J=3.5 Hz), 7.03–7.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.0, 26.4, 42.5, 48.8, 49.6, 59.2, 62.0, 63.1, 73.9, 117.2, 122.1, 124.7, 128.0, 128.9, 129.8, 151.0, 164.2, 167.5. Data for (1*R*,2*S*)-*trans* **25**: $[\alpha]_D$ −48.91 (*c* 0.9, CH_2Cl_2); IR (film, cm^{-1}): 2976, 2926, 2880, 1775, 1738, 1613, 1456, 1258, 1221, 1094, 1028, 872, 801, 760, 735, 704; mass spectrum (CI) *m/z* (rel intensity): 361 (100%, $M^+ + 1$), 360 (15, M^+), 315 (62), 247 (28), 143 (33); *m/z* calcd for $C_{19}H_{25}N_2O_5$ 361.1763, found 361.1765; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (t, 3H, J=7.1 Hz), 1.75–1.98 (m, 4H), 2.64–2.70 (m, 1H), 3.20–3.26 (m, 1H), 3.38 (s, 3H), 3.39–3.40 (m, 1H), 3.51–3.52 (m, 2H), 4.07–4.18 (m, 2H), 4.21 (d, 1H, J=4.2 Hz), 4.24 (dd, J=4.2, 4.0 Hz), 6.47 (d, 1H, J=4.0 Hz), 7.06–7.29 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 21.9, 26.2, 42.2, 49.0, 49.8, 59.1, 61.9, 62.9, 73.7, 117.1, 122.4, 124.7, 127.9, 128.9, 129.8, 150.9, 164.1, 167.3. Data for dimer **B**: $[\alpha]_D$ −166.4 (*c* 1.2, CH_2Cl_2); IR (film, cm^{-1}): 2923, 2849, 1738, 1664, 1547, 1460, 1386, 1343, 1201, 1121, 979, 911; mass spectrum (IE) *m/z* (rel intensity): 283 (8%, $M^+ + 1$), 282 (45, M^+), 237 (100), 207 (15), 129 (28), 124 (19), 70 (23); *m/z* calcd for $C_{14}H_{26}N_4O_2$ 282.2056, found 282.2048; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78–2.27 (m, 8H), 2.82–2.91 (m, 2H), 3.30–3.39 (m, 4H), 3.30 (s, 6H), 3.44–3.55 (m, 4H), 7.03 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 26.6, 49.3, 59.1, 62.9, 74.4, 134.8.

3.3. Synthesis of α,β-unsaturated compounds 15, 17 and 19 (general procedure)

$NaBH_4$ (38 mg, 1 mmol) was added to a solution of compounds **14**, **16** or **18** (1 mmol) in absolute EtOH (2.5 mL) at 0 °C. The reaction was stirred at 0 °C until TLC indicated total consumption of the starting material. The mixture was concentrated and the residue solved in CH_2Cl_2 (15 mL) and washed with brine (3×5 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was solved in dry CH_2Cl_2 (10 mL) under an argon atmosphere, then mesyl chloride (155 μL, 2 mmol) and Et_3N (558 μL, 4 mmol) were added. The mixture was stirred at room temperature until TLC indicated total consumption of the starting material and then washed with water (3×5 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was solved in absolute EtOH (10 mL) and EtONa (136 mg, 2 mmol) was added. The reaction was stirred at room temperature until TLC indicated total consumption of the starting material. The crude reaction was filtered through a pad of silica using CH_2Cl_2 as eluant, concentrated and the residue was purified by flash chromatography. Eluants, yields and spectral and analytical data for compounds **15**, **17** and **19** are as follows:

3.3.1. Synthesis of compound 15. From compound **14** (415 mg, 1 mmol, mixture (1*R*,2*R*)-*trans*/(1*R*,2*S*)-*cis*/(1*S*,2*S*)-*trans*/(1*S*,2*R*)-*cis* 1:0.3:0.5:0.15), flash chromatography (1:4 Et_2O–petroleum ether) gave 251 mg (63%) of **15** as an inseparable mixture of major isomer (1*R*)-**15** and minor isomer (1*S*)-**15** (2:1 ratio). IR (film, cm^{-1}): 3100, 2934, 2270, 1537, 1449, 1346, 1092, 990, 810, 768; mass spectrum (EI) *m/z* (rel intensity): 399 (10%, M^+), 368 (25), 234 (100); *m/z* calcd for $C_{26}H_{29}N_3O$ 399.2311, found 399.2315. NMR data for (1*R*)-**15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12–0.26 (m, 1H), 1.31–1.42 (m, 1H), 1.50–1.60 (m, 2H), 1.67–1.72 (m, 2H), 1.80–1.88 (m, 1H), 1.91–2.02 (m, 1H), 2.08–2.12 (m, 2H), 2.55–2.68 (m, 1H), 2.78–2.84 (m, 1H), 2.99 (s, 3H), 3.05–3.07 (m, 1H), 4.74–4.80 (m, 1H), 6.28 (d, 1H, J=4.3 Hz), 6.59–6.65 (m, 1H), 7.20–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 21.8, 25.8, 25.9, 26.3, 38.8, 49.7, 51.2, 66.6, 85.7, 114.5, 119.5, 126.7,

126.7, 127.1, 129.5, 129.9, 130.5, 140.8, 141.8, 145.4. NMR data for (1*S*)-**15**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12–0.26 (m, 1H), 1.31–1.42 (m, 1H), 1.50–1.60 (m, 2H), 1.67–1.72 (m, 2H), 1.80–1.88 (m, 1H), 1.91–2.02 (m, 1H), 2.08–2.12 (m, 2H), 2.55–2.68 (m, 1H), 2.78–2.84 (m, 1H), 3.02 (s, 3H), 3.05–3.07 (m, 1H), 4.74–4.80 (m, 1H), 6.31 (d, 1H, J= 5.4 Hz), 6.59–6.65 (m, 1H), 7.20–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 21.9, 25.7, 26.0, 26.4, 39.2, 50.3, 51.2, 67.0, 85.7, 115.0, 119.0, 126.7, 126.9, 127.1, 129.5, 130.0, 131.1, 140.9, 142.0, 145.7.

3.3.2. Synthesis of compound 17. From compound **16** (429 mg, 1 mmol, mixture (1*S*,2*R*)-*trans*/(1*R*,2*S*)-*trans* 1:1), flash chromatography (1:4 Et_2O–petroleum ether) gave 302 mg (73%) of **17** as an inseparable mixture of (1*R*)-**17** and (1*S*)-**17** (1:1 ratio). IR (film, cm^{-1}): 3057, 2959, 2928, 2218, 1732, 1591, 1452, 1350, 1267, 1171, 1092, 916, 737, 704, 610; mass spectrum (EI) *m*/*z* (rel intensity): 413 (5%, M^+), 382 (26), 234 (100); *m*/*z* calcd for $C_{27}H_{31}N_3O$ 413.2467, found 413.2454. NMR data for (1*R*)-**17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01–0.11 (m, 1H), 0.77 (s, 3H), 1.02 (s, 3H), 1.22–1.34 (m, 1H), 1.70–1.97 (m, 2H), 2.09–2.11 (m, 2H), 2.45–2.54 (m, 1H), 2.61–2.70 (m, 1H), 2.87 (s, 3H), 3.07–3.09 (m, 1H), 4.69 (dd, 1H, J=9.3, 1.7 Hz), 6.09 (d, 1H, J=5.2 Hz), 6.42–6.44 (m, 1H), 7.06–7.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 24.9, 26.0, 29.4, 43.1, 47.7, 49.8, 51.3, 59.2, 66.7, 85.9, 116.8, 117.1, 126.8, 126.9, 127.0, 127.0, 127.1, 127.2, 127.3, 127.4, 129.6, 130.0, 130.1, 140.9, 141.9, 147.6. NMR data for (1*S*)-**17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01–0.11 (m, 1H), 0.78 (s, 3H), 1.06 (s, 3H), 1.22–1.34 (m, 1H), 1.70–1.97 (m, 2H), 2.17–2.21 (m, 2H), 2.45–2.54 (m, 1H), 2.61–2.70 (m, 1H), 2.91 (s, 3H), 3.07–3.09 (m, 1H), 4.67–4.71 (m, 1H), 6.00 (d, 1H, J= 7.6 Hz), 6.50–6.52 (m, 1H), 7.06–7.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 24.5, 26.3, 28.8, 43.7, 47.9, 50.3, 52.4, 60.1, 67.1, 85.9, 116.8, 117.1, 126.8, 126.9, 127.0, 127.0, 127.1, 127.2, 127.3, 127.4, 129.6, 130.0, 130.1, 141.0, 142.0, 148.4.

3.3.3. Synthesis of compound 19. From compound **18** (282 mg, 1 mmol, mixture (1*R*,2*S*)-*trans*/(1*S*,2*R*)-*trans* 1:1), flash chromatography (1:4 Et_2O–petroleum ether) gave 66.5 mg (25%) of **18** as an inseparable mixture of (1*R*)-**18** and (1*S*)-**18** (1:1 ratio). IR (film, cm^{-1}): 2954, 2880, 1757, 1736, 1450, 1435, 1300, 1237, 1000; mass spectrum (FAB) *m*/*z* (rel intensity): 267 (5%, $M^+ + 1$), 235 (100). NMR data for (1*R*)-**18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09–1.28 (m, 2H), 1.73–1.95 (m, 2H), 2.02–2.27 (m, 2H), 2.42–2.62 (m, 2H), 2.65–2.79 (m, 1H), 3.29–3.58 (m, 2H), 3.36 (s, 3H), 4.09–4.19 (m, 3H), 6.55 (d, 1H, J=3.0 Hz), 6.65–6.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 15.3, 21.9, 26.4, 28.7, 31.8, 47.3, 59.0, 64.4, 83.4, 138.6, 139.0, 164.8, 174.5. NMR data for (1*S*)-**18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09–1.28 (m, 2H), 1.73–1.95 (m, 2H), 2.02–2.27 (m, 2H), 2.42–2.62 (m, 2H), 2.65–2.79 (m, 1H), 3.29–3.58 (m, 2H), 3.35 (s, 3H), 4.09–4.19 (m, 3H), 6.41–6.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 15.1, 21.8, 26.3, 28.6, 31.8, 47.4, 60.0, 64.7, 83.3, 139.0, 139.1, 172.0, 173.1.

3.4. Synthesis of pyrazol derivatives 21 and 23 (general procedure)

To a solution of hydrazone **20** or **22** (1 mmol) in absolute EtOH (1 mL) was added $NH_2NH_2 \cdot H_2O$ (99 μL, 2 mmol) at 0 °C. The reaction was stirred at room temperature until TLC indicated total consumption of the starting material. The mixture was concentrated and the residue solved in CH_2Cl_2 (10 mL) and washed with water (3×3 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue purified by flash chromatography.

3.4.1. Synthesis of compound 21. From compound **20** [432 mg, 1 mmol, mixture (1*R*)/(1*S*) 1:1], flash chromatography (3:1 Et_2O–petroleum ether) gave 387 mg (97%) of **21** as an inseparable mixture of (1*R*)-**21** and (1*S*)-**21** (1:1 ratio). IR (film, cm^{-1}): 3204, 3140, 3065, 2939, 1734, 1601, 1494, 1450, 1349, 1279, 1191, 1141, 1065, 970, 901, 850; mass spectrum (FAB) *m*/*z* (rel intensity): 451 (18%, $M^+ + 23$), 427 (11), 397 (48), 231 (92), 197 (83), 135 (100); *m*/*z* calcd for $C_{27}H_{32}N_4ONa$ 451.2474, found 451.2461. NMR data for (1*R*)-**21**: ^{1}H NMR (500 MHz, C_6D_6) δ 0.27–0.41 (m, 1H), 1.19–1.24 (m, 1H), 1.52–1.95 (m, 6H), 2.36 (s, 3H), 2.49–2.55 (m, 1H), 2.58–2.62 (m, 1H), 2.64–2.67 (m, 1H), 2.83–2.86 (m, 1H), 3.14 (s, 3H), 3.65–3.69 (m, 1H), 4.91–4.94 (m, 1H), 6.50 (d, 1H, J=5.9 Hz), 7.05–7.25 (m, 6H), 7.56–7.58 (m, 2H), 7.75–7.76 (m, 2H), 10.8 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 11.9, 21.2, 22.8, 22.8, 26.5, 29.6, 36.0, 51.4, 51.6, 68.0, 86.0, 114.0, 127.2, 127.5, 130.1, 130.7, 137.3, 142.5, 143.2, 144.0. NMR data for (1*S*)-**21**: ^{1}H NMR (500 MHz, C_6D_6) δ 0.27–0.41 (m, 1H), 1.19–1.24 (m, 1H), 1.52–1.95 (m, 6H), 2.26 (s, 3H), 2.42–2.48 (m, 1H), 2.58–2.62 (m, 1H), 2.64–2.67 (m, 1H), 2.83–2.86 (m, 1H), 3.13 (s, 3H), 3.65–3.69 (m, 1H), 4.91–4.94 (m, 1H), 6.34 (d, 1H, J=6.9 Hz), 7.05–7.25 (m, 6H), 7.56–7.58 (m, 2H), 7.75–7.76 (m, 2H), 10.8 (s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 11.5, 21.6, 22.8, 22.9, 26.3, 29.8, 36.6, 51.3, 51.6, 68.0, 86.0, 113.8, 127.3, 127.5, 128.3, 130.9, 137.1, 142.1, 142.8, 144.2.

3.4.2. Synthesis of compound 23. From compound **22** [418 mg, 1 mmol, mixture (1*R*)/(1*S*) 2:1], flash chromatography (3:1 Et_2O–petroleum ether) gave 373 mg (90%) of **23** as an inseparable mixture of major isomer (1*R*)-**23** and minor isomer (1*S*)-**23** (2:1 ratio). IR (film, cm^{-1}): 3057, 2926, 1603, 1447, 1262, 1092, 872, 801, 760, 704, 610; mass spectrum (CI) *m*/*z* (rel intensity): 415 (23%, $M^+ + 1$), 383 (100), 217 (90), 121 (43); *m*/*z* calcd for $C_{26}H_{31}N_4O$ 415.2498, found 415.2484. NMR data for (1*R*)-**23**: ^{1}H NMR (500 MHz, C_6D_6) δ 0.30–0.41 (m, 1H), 1.15–1.20 (m, 1H), 1.77–1.81 (m, 1H), 1.90–1.96 (m, 1H), 1.94 (s, 3H), 2.40–2.44 (m, 1H), 2.49–2.52 (m, 2H), 2.57–2.73 (m, 2H), 2.81–2.86 (m, 1H), 2.91 (s, 3H), 3.60 (s br, 1H), 3.87–3.92 (m, 1H), 4.90 (t, 1H, J=8.7 Hz), 6.34 (d, 1H, J=6.5 Hz), 7.15–7.75 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 10.1, 22.7, 24.3, 26.3, 36.7, 40.6, 51.2, 51.3, 67.8, 86.0, 124.3, 127.1, 127.2, 127.3, 127.4, 127.4, 127.5, 130.3, 130.6, 130.8, 136.1, 142.3, 143.1, 159.4. NMR data for (1*S*)-**23**: ^{1}H NMR (500 MHz, C_6D_6) δ 0.70–0.80 (m, 1H), 1.15–1.20 (m, 1H), 1.68–1.81 (m, 2H), 2.06 (s, 3H), 2.22–2.35 (m, 3H), 2.57–2.73 (m, 2H), 2.81–2.86 (m, 1H), 3.15 (s, 3H), 3.46 (dd, 1H, J=9.8, 5.0 Hz), 3.60 (s br, 1H), 3.87–3.92 (m, 1H), 6.47 (d, 1H, J=6.0 Hz), 7.15–7.75 (m, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 10.4, 22.8, 24.2, 26.5, 37.1, 40.5, 51.4, 60.0, 74.9, 87.4, 124.3, 127.1, 127.2, 127.3, 127.4, 127.5, 130.0, 130.1, 130.3, 130.6, 136.8, 141.2, 141.9, 159.4.

3.5. Deprotection of compound 14. Synthesis of acetal 26

Dry ozone was bubbled through a cooled (−78 °C) solution of hydrazone **14** (415 mg, 1 mmol, mixture (1*R*,2*R*)-*trans*/(1*R*,2*S*)-*cis*:(1*S*,2*S*)-*trans*/(1*S*,2*R*)-*cis* 1:0.3:0.4:0.1) in dry CH_2Cl_2 (20 mL) until appearance of a permanent blue colour. The solution was then treated with dimethyl sulfide (1 mL, 13.6 mmol) and the reaction mixture was allowed to warm up to room temperature and concentrated. The resulting residue was solved in dry toluene (8 mL) and 1,2-etanediol (67 μL, 1.2 mmol), *p*-TsOH (cat.) and 4 Å molecular sieves were added. The mixture was stirred at 60 °C until TLC indicated total consumption of the aldehyde. The reaction was diluted with CH_2Cl_2 and washed with water (2×10 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (1:2 ethyl acetate–petroleum ether) gave compound **26** (101 mg, 52%) (3:1 *trans*/*cis* ratio). IR (film, cm^{-1}): 2942, 2890, 2251, 2205, 1730, 1666, 1619, 1449, 1391, 1303, 1256, 1209, 1151, 1045, 952, mass spectrum (CI) *m*/*z* (rel intensity): 195 (3%, M^+), 167 (6), 149 (15), 73 (100); *m*/*z* calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0891; NMR data for **26**-*trans*: ^{1}H NMR (500 MHz, C_6D_6) δ 0.80–1.03 (m, 2H), 1.19–1.50 (m, 3H), 1.87 (tdd, 1H, J=11.0, 4.4, 2.1 Hz), 2.03 (dtd, 1H, J=14.3, 4.3, 1.4 Hz), 3.02 (d, 1H, J=11.0 Hz), 3.16–3.22 (m, 2H), 3.37–3.46 (m, 2H), 4.70 (d, 1H, J=2.1 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 23.4, 23.6, 39.9, 43.6, 44.9, 64.9, 65.4, 103.8, 115.8, 198.5; NMR data for **26**-*cis*: ^{1}H NMR (500 MHz, C_6D_6) δ 0.80–1.03 (m, 4H), 1.70–1.81 (m, 2H), 2.26 (ddd, 1H, J=14.5, 9.5, 5.8 Hz), 3.16–3.22 (m, 3H), 3.37–3.46 (m, 2H), 4.62 (d, 1H, J=4.4 Hz); ^{13}C NMR (125 MHz, C_6D_6) δ 23.9, 24.0, 38.7, 43.0, 44.6, 64.9, 65.0, 104.3, 115.5, 198.6.

3.6. Deprotection of compound 25. Synthesis of dithioacetal 27

To a cooled solution (0 °C) of hydrazone (1*S*,2*R*)-*trans* **25** (360 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) was added 1,2-ethanedithiol (126 μL, 1.5 mmol) and then $BF_3\cdot OEt_2$ (256 mL, 2 mmol) under an argon atmosphere. The mixture was allowed to warm to room temperature and stirred until TLC indicated total consumption of the starting material. The mixture was then washed with saturated $NaHCO_3$ solution (2×10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:8 ethyl acetate–petroleum ether) to yield 214 mg (66%) of dithioacetal (1*S*,2*R*)-*trans* **27**. $[\alpha]_D$ +27.3 (*c* 0.78, $CHCl_3$); IR (film, cm^{-1}): 3289, 2932, 1775, 1736, 1492, 1219, 1161, 1022, 908, 856, 761; mass spectrum (EI) *m*/*z* (rel intensity): 347 (95%, $M^+ + Na^+$), 325 (12, $M^+ + 1$), 279 (60), 241 (19), 219 (50), 147 (100); *m*/*z* calcd for $C_{15}H_{17}O_4S_2$ 325.0568, found 325.0556; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, 3H, J=7.1 Hz), 3.17–3.25 (m, 4H), 3.61 (dd, 1H, J=5.9, 1.3 Hz), 4.05–4.11 (m, 2H), 4.28 (d, 1H, J=1.3 Hz), 4.76 (d, 1H, J=5.9 Hz), 7.09–7.15 (m, 2H), 7.26–7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 38.7, 39.5, 47.0, 49.0, 57.3, 62.4, 117.1, 121.0, 124.6, 129.6, 129.7, 151.1, 163.9, 166.8.

3.7. Deprotection of compound 18. Synthesis of nitrile 28

To a cooled solution (0 °C) of hydrazone **18** (282 mg, 1 mmol, mixture (1*R*:2*S*)-*trans*/(1*S*,2*R*)-*trans* 3:1) in dry MeOH (2 mL) was added a solution of $MMPP\cdot 6H_2O$ (741 mg, 1.5 mmol) in MeOH (4 mL) and the mixture stirred at 0 °C until TLC showed total consumption of starting material (30 min). The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was washed with saturated NaCl solution (10 mL) and H_2O (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (1:1 ether–petroleum ether) to yield 90 mg (54%) of nitrile **28**. **S**pectral and analytical data are in good agreement with those reported in literature.[24]

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Stereoselective preparation of spirane bridged, sandwiched bisarenes

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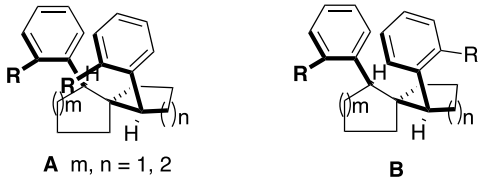
Abstract—Preparation of α-oxo derivatives of spiro[4.4]nonane, spiro[4.5]decane and spiro[5.5]undecane derivatives is described. An efficient method for spiroannulation by Rh(I)-catalysed intramolecular hydroacylation provides α,α′-difunctionalised spiro[4.5]decanes. The α,α′-dioxo groups have been converted into vinyl triflates for arylation by Pd-catalysed cross-coupling reactions under Stille, Negishi or Suzuki conditions depending on relative reactivities. Stereoselective saturation of the conjugated aryl olefinic bonds by catalytic hydrogenation over Pd–carbon provides methodology for stereoselective preparation of α-aryl- and α,α′-*cis*,*cis*-diaryl spiranes, the latter with a sandwich like structure. Single crystal X-ray analyses have been used in the structural assignments.

1. Introduction

The rigid framework in small-ring spiranes constitutes a potentially useful scaffold for attachment of configurationally highly oriented coordinating functions as ligands for metal complexation, or for stereochemically controlled attachment of pharmacophoric groups useful in medicinal chemistry. A spirane bridged sandwich like the bisarene **A** and its conformer **B** in Scheme 1 are reminiscent of certain ligands for metallocenes. In these spiranes the functional substituents R are situated in the α,α′-positions to be close to the spirocenter. Alternative sites are the β- or γ-positions or combinations thereof.



Scheme 1.

The two rings in the spirane are interconnected through a common ring atom. The two rings have an orthogonal relationship. Conformational freedom is highly restricted, and this restriction is transferred to the substituents. The rigidity in the spirane is controlled by the size of the two rings forming the spirane. Small-ring spiranes are very stiff. The larger ring systems are more flexible.

We have initiated studies with the ultimate aim of constructing spirobridges between functional units. Essential intermediates are oxospiranes. A rhodium(II)-carbenoid C–H insertion reaction has been used for spiroannulation to provide β,β′- and α,α′-dioxospiranes. The ring size of the carbocyclic substrate could be varied, but spiroannulation was limited to the addition of five-membered carbocycles.[1] In a method with a potentially wider application, functionalised spiranes were constructed using ruthenium(II)-catalysed ring-closing metathesis. The products were α,α′-dioxospiranes or derivatives thereof. The substrates were appropriately substituted five-, six- and seven-membered cycloalkanes which were spiroannulated by five-, six and seven-membered rings, respectively.[2]

Nucleophilic substitutions in spiranes in the most desirable α-position are complicated by the *neo*-effect from the spirocenter, and reactions involving carbonium intermediates at the α-carbon are likely to result in skeletal rearrangements. Addition of metal hydrides or organometallics to an α,α′-dioxospirane gives diols which are sensitive to ring-opening reactions, especially when the carbon substituent is an arene.[3,4]

A method for carbylation in the α-oxo position has been found by initial formation of enol triflate and a subsequent

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Pd-mediated cross-coupling reaction.[5] Full stereoselectivity in the generation of *cis*,*cis*-α,α′-diarylspiranes has been achieved by way of catalytic hydrogenation of the corresponding α,α′-dienospiranes as shown in Schemes 7 and 8.

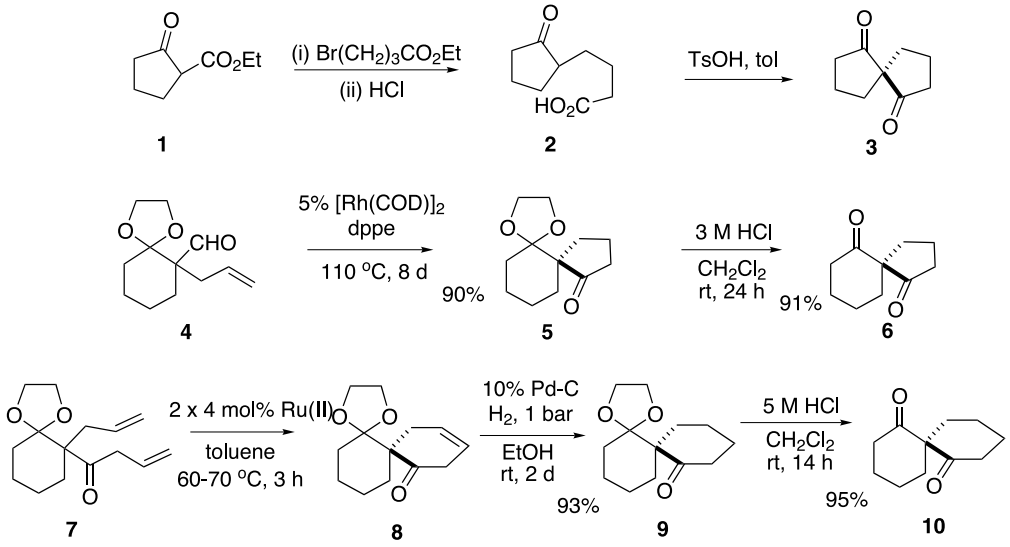
2. Results and discussion

Scheme 2 outlines the preparation of α,α′-dioxospirane intermediates. The smallest member of the dioxospirane family in this work was spiro[4.4]nonane-1,6-dione (**3**), which was available by a simple alkylation of ethyl 2-oxocyclopentanecarboxylate, and provided a subsequent acid hydrolysis product **2** which was cyclised under acid catalysis (Scheme 1).[6] For the higher homologue **6**, a new synthetic route was developed. From the literature, it is known that rhodium-catalysed intramolecular hydroacylation of 4-alkenyls constitutes a useful method for the preparation of cyclopentanones.[7] The main steps in the catalytic hydroacylation reaction are thought to be oxidative insertion into the aldehyde C–H bond, a subsequent olefin insertion to furnish a rhodacycle intermediate which on reductive elimination regenerates the catalyst and produces a cyclopentanone.[8] The synthesis of ketones from aldehydes, however, is complicated by decarbonylation in the acylmetal intermediate by a rearrangement whereby the carbonyl group becomes coordinated to the metal as carbon monoxide leading to a less reactive catalyst complex as well as to decarbonylation.[9] In the synthesis of spiro[4.5]decane-1,6-dione derivatives by hydroacylation of 4-pentenals, product analysis showed extensive decarbonylation. The reactions were run in benzonitrile.[10] In our initial work we also used benzonitrile as solvent at 110 °C with an acetal of 2-allylcyclohexanone-2-carbaldehyde **4** (Scheme 2) as substrate. A satisfactory catalyst system was 10% Rh(COD)(dppe)Cl. Decarbonylation, however, was significant. The desired product was obtained together with 25% of decarbonylated material. With nitromethane as an alternative solvent, there was an increase in the decarbonylation, up to 33%. We then discovered that the decarbonylation could largely be avoided when the hydroacylations were run in the absence of a solvent. In this procedure, the aldehyde and 5% $[Rh(COD)Cl]_2$ were heated together with dppe at 110 °C for 8 d. The yield of decarbonylated material was reduced to barely 2% whereas the spiroannulated cyclopentanone **5** was obtained in a very high yield, 90%. The spiranedione **6** was readily available by acid hydrolysis of the acetal **5**. The spirane **6** could also be prepared from 2-allyl-2-formylcyclohexanone by the rhodium(I)-catalysed hydridoacylation. The relatively high volatility of the aldehyde substrate, however, made this reaction less attractive.

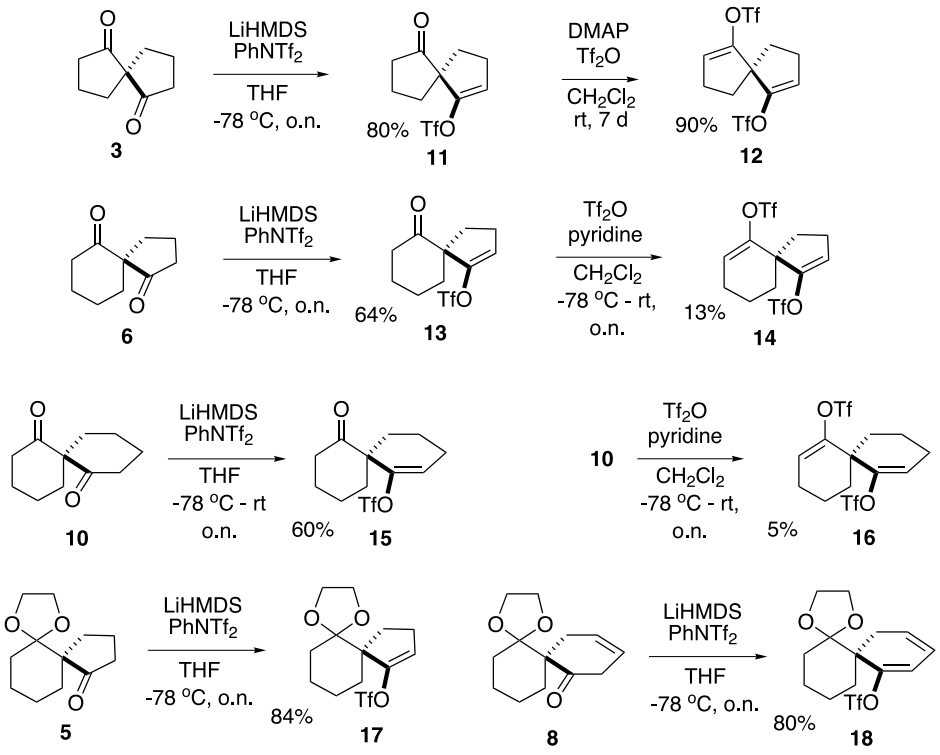
The spiro[5.5]undecan-1,7-dione series was available by an initial Ru(II)-catalysed RCM reaction of the diene **7**.[2] The product was the unsaturated spiranone **8**. Saturation of the carbon–carbon double bond over 10% Pd–C, and a subsequent acid catalysed hydrolysis of the acetal function, furnished the 1,7-dioxospirane **10**.

Scheme 3 shows the preparation of triflate reactants for the cross-coupling carbylation reactions. For triflation at the α-carbon, either $PhNTf_2$ or Tf_2O was used. The milder reagent $PhNTf_2$ was generally the better.

With LiHMDS as base and $PhNTf_2$ for triflation, the monotriflate **11** was isolated in 80% yield, and the ditriflate **12** in 5% yield. A second triflation to form the corresponding α,α′-ditriflate in the spirane series in general has been difficult to effect. In the case of the spiro[4.4]nonane series, however, the ditriflate **12** was finally obtained in excellent yield (90%) when the triflation was run with Tf_2O in DMAP using the monotriflate **11** as substrate. The reaction was slow. Monotriflation in the spiro[4.5]decane-1,6-dione series proceeded well with LiHMDS as base. Only one monotriflated product was seen. The product was the five-membered ring triflate **13**, yield 64%. The α-protons in the five-membered ring ketone are more acidic than in the six-membered ring ketone. Direct ditriflation from the α,α′-diketone **6**, however, gave only the ditriflate **14** in a very low yield. As experienced in the spiro[4.4]nonane series, ditriflation could be effected in a two-step operation albeit



Scheme 2.

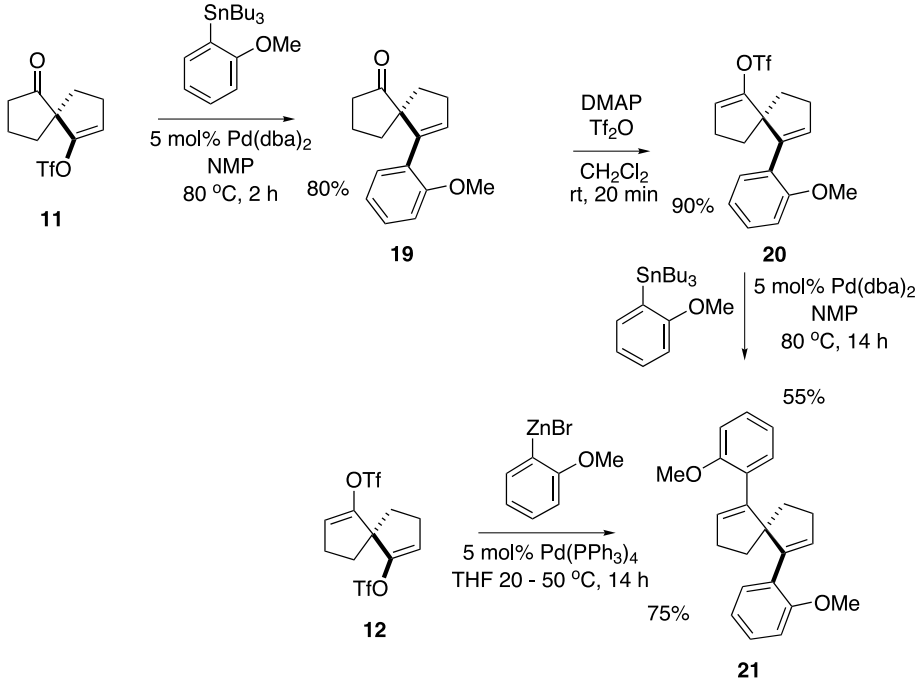


Scheme 3.

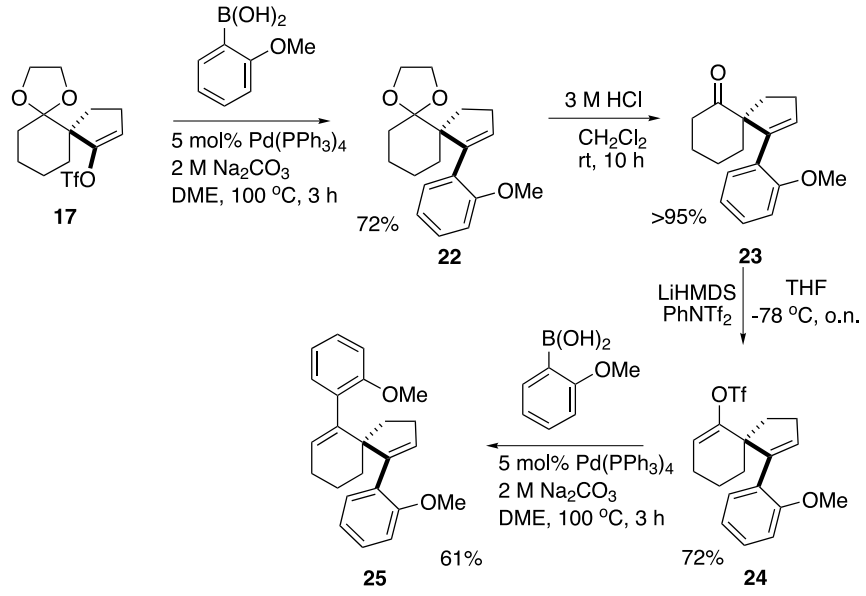
in a low 13% yield of the ditriflate **14** using triflic anhydride in pyridine. Apparently, a H-3 proton in the five-membered ring is abstracted preferentially rather than an α-oxo proton in the six-membered ring.

In the spiro[5.5]undecan-1,7-dione series, the monotriflated product **15** was isolated. Further triflation was difficult to effect. Monotriflation of the acetals **5** and **8** proceeded readily to provide the triflates **17** and **18** in ca. 80% yield.

Carbon–carbon bond forming reactions by Pd-catalysis are shown in Scheme 4. A preliminary study of *ortho*-substituted organometallic reactants showed that the cross-coupling into the shielded α-position in spiranes was sensitive to steric interactions from the *o*-substituent. A



Scheme 4.

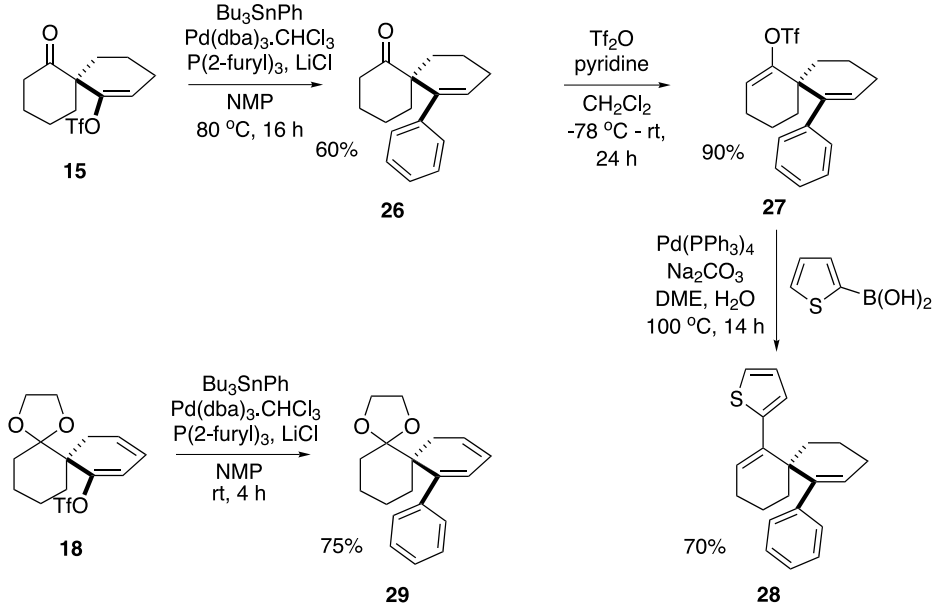


Scheme 5.

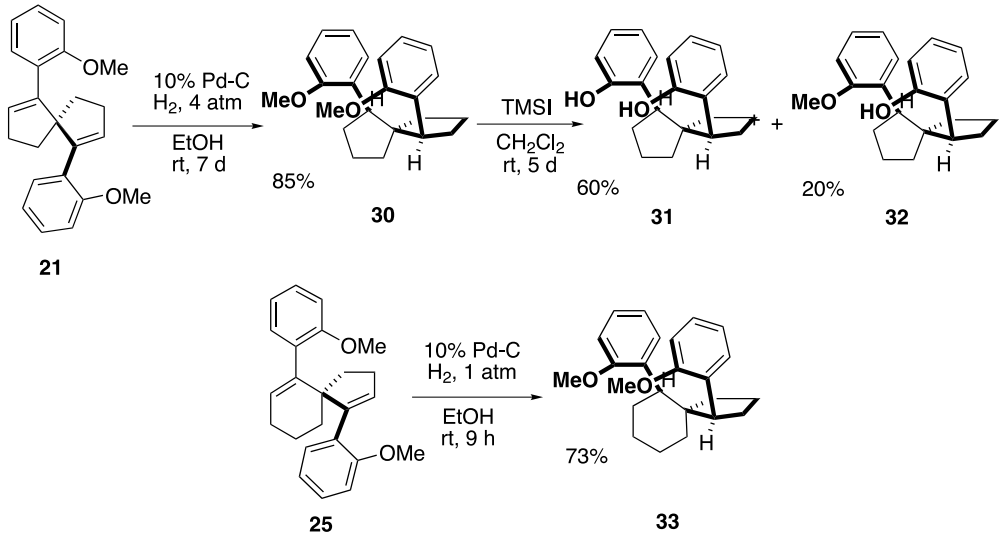
2-methoxy group in the organometallic reactant provided a reasonably good yield in the cross-coupling reaction. Hence organometallic anisole derivatives were used for the subsequent cross-coupling reactions. Thus, the Stille coupling between 2-(tri-*n*-butylstannyl)anisole and the monotriflate **11** proceeded readily to furnish the mono-arylated product **19** in high yield. For a further carbylation reaction, product **19** was triflated using Tf_2O in DMAP. Stille reaction conditions provided the product **21**. This approach allows for differential carbylation in the two α,α′-positions in spiranes. In this case the same stannyl coupling reagent was used, thereby providing the C_2-symmetric diarylated product **21**. The successful preparation of the bistriflate **12**, allowed direct Pd-catalysed dicoupling. In this case, however, Negishi coupling conditions with an organozinc reactant gave a better yield, 75% (Scheme 5).

The cross-coupling under Stille conditions of the acetalised triflate of spiro[4.5]undecane **17** was not satisfactory. We therefore effected the coupling with the appropriate benzeneboronic acid under Suzuki conditions with sodium carbonate as base in aqueous DME. The cross-coupled product **22** was isolated in high yield and was subsequently hydrolysed to ketone **23** under acidic conditions. Triflation of the ketone **23** was effected with lithiation at low temperature and treatment with $PhNTf_2$ to furnish the triflate **24**. Suzuki coupling conditions as above provided the diarylated spirane **25**. Dicoupling with the ditriflate **14** (Scheme 3) as substrate had previously failed to provide the dianisole product **25**.

In the spiro[5,5]undecane series, a two-step process was used for introduction of the two arene groups (Scheme 6).



Scheme 6.

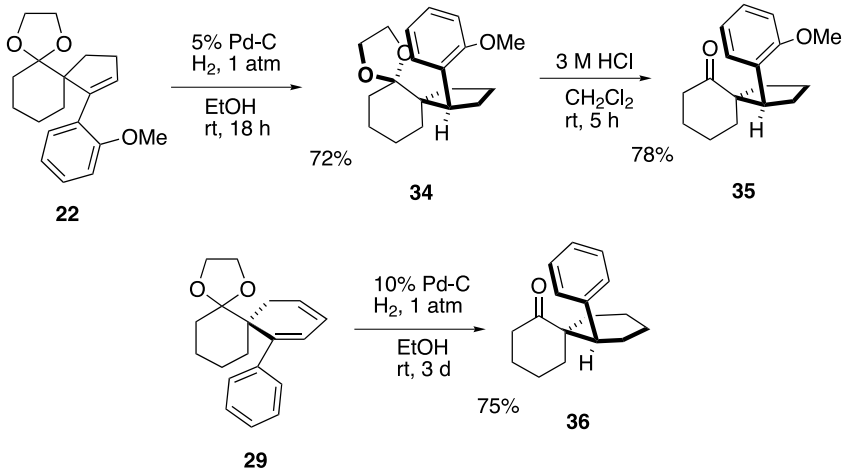


Scheme 7.

With the phospine P(2-furyl)$_3$ for ligation of palladium, the Stille conditions in NMP as solvent provided the arylated spirane **26** from the keto triflate **15**. Triflation in the monoaryl spirane **26** was effected with triflic anhydride in pyridine and furnished the triflate **27** in high yield. As stated above, this two-step process allows for differential carbylation in the two spirane rings. In this case, a 2-thienyl group was introduced under Suzuki conditions to provide the mixed diarylated product **28** in good yield. The coupling of the diene acetal **18** under Stille conditions proceeded more readily than for the ene triflate **15**.

In the target spirane structure **A** in Scheme 1, the functionalized aryl rings have a *cis*,*cis*-relationship. In the substrates from the cross-coupling reactions, the aryl groups are hinged to an sp^2-hybridised carbon and are thus coplanar with the orthogonal spirane rings, respectively. In a saturated spirane, the α,α'-substituents at sp^3-hybridised carbons can have a *cis*,*cis*-, a *cis*,*trans*-, or *trans*,*trans*-relationship. A stereoselective reduction of the double bonds for formation of the *cis*- or the *cis*,*cis*-isomer is required. The *cis*,*cis*-configuration, however, leads to a significant repulsive interaction, and is thermodynamically the least favourable structure of the three geometrical isomers. For steric reasons, on heterogenous hydrogenation the less sterically shielded face of a spirane ring becomes associated with the metal catalyst. A subsequent transfer of hydrogen from the metal to the double bond forces the substituent into a *cis*-position. Thus both the styrene double bonds in structures **21** and **25** were saturated over 10% Pd–charcoal (Scheme 7). The long reaction times may reflect steric crowding, but the reaction was fully stereoselective in that only one product was seen, viz. the *cis*,*cis*-isomers **30** and **33**. The relative configuration assigned for the latter has been ascertained by a single crystal X-ray analysis (vide infra). The assignment of the relative configuration of the former is based on the established configuration of its lower phenyl analogue.[5]

The monoarylated substrates **22** and **29** in Scheme 8 reacted under similar conditions to provide a single reduction product. The spiro[5.5]undecane substrate **29** is a 1,3-diene. Stereoselectivity in the reduction furnished a single product which was found by a single crystal X-ray analysis to be the *cis*-isomer **36**. The double bond in the spiro[4.5]decane substrate **22** was saturated under similar conditions. The



Scheme 8.

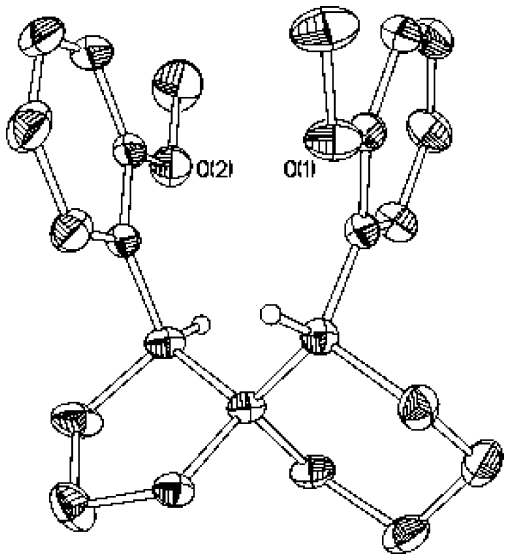


Figure 1. The ORTEP plot of compound **33**. Ellipsoids are shown at 50% probability. For clarity only the hydrogen at stereogenic centers and at double bonds are shown.

product has tentatively been assigned the *cis*-structure **34** by analogy to the formation of the *cis*-isomer **36** and the *cis*,*cis*-isomers **30** and **33**. The ketone **35** was available after acid hydrolysis of the acetal **34**.

In spiro-bridged sandwich-like bisarene structures with ligand properties towards a metal in the center, the aryl group would carry substituents with coordinating properties. The model substituent in the present work was the *o*-methoxy group (Scheme 7). The methoxy group can also be regarded as a methyl *O*-protected phenolic group. Trimethylsilyl iodide was used to cleave the methyl aryl ether **30** to furnish the diphenol sandwich structure **31** (Scheme 7). Slow cleavage required the use of a large excess of the silyl iodide reagent. The diol **31** and the semihydrolysed product **32** were isolated in 76 and 20% respectively, after 5 d at ambient temperature.

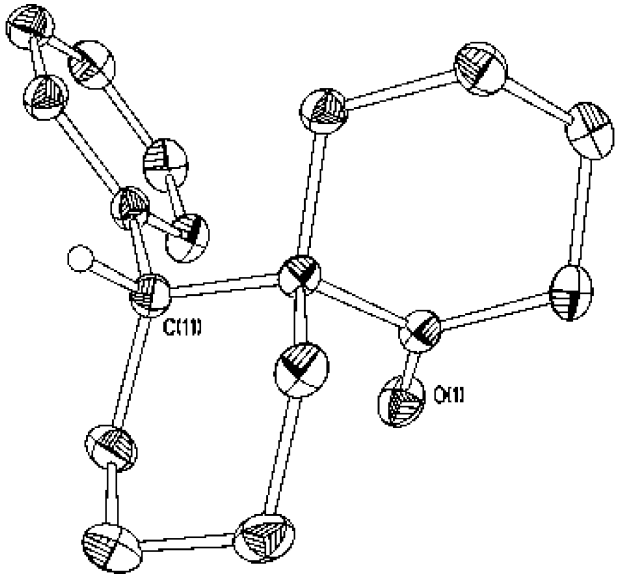


Figure 2. The ORTEP plot of compound **36**. Ellipsoids are shown at 50% probability. For clarity only the hydrogen at stereogenic centers and at double bonds are shown.

The relative stereochemistry of compounds **33** and **36** was determined by single crystal X-ray analyses. The ORTEP plots of the crystal structures are shown in Figures 1 and 2. In the crystal structure the anisole units in structure **33** have an antiparallel arrangement corresponding to conformer **B** in Scheme 1.

3. Conclusion

In conclusion, we have described a method for the preparation of spiro[4.4]nonane, spiro[4.5]decane and spiro[5.5]undecane α-oxo derivatives. In particular, an efficient method for Rh-catalysed intramolecular hydroacylation was developed for the preparation of α,α-difunctionalised spiro[4.5]decanes. Substitutions in the α-positions in the spiranes has been effected from the corresponding ketones by way of vinyl triflates and palladium catalysed cross-coupling reactions. In most cases, ditriflation was best effected in a step-wise manner. To cope with different reactivities of the vinyl triflate substituents in the spiranes, Stille, Negishi and Suzuki conditions were all employed. Catalytic hydrogenation over Pd–carbon provides methodology for stereoselective preparation of α-*cis*-aryl- and α,α′-*cis*,*cis*-diaryl spiranes, the latter with a sandwich like structure.

4. Experimental

The ^{1}H NMR spectra were recorded at 300 or 500 MHz and the ^{13}C NMR spectra at 75 or 125 MHz. Chemical shifts are given in ppm relative to the solvent $CDCl_3$. Coupling constants *J* are given in Hz. Interpretation of the NMR spectra was helped by COSY, DEPT HETCOR and COLOC techniques. The mass spectra were recorded at 70 eV under electron impact conditions (EI) and are presented as *m*/*z* (rel. int.). IR spectra were measured on a Nicolet Magna 550 spectrometer using ATR (attenuated total reflectance).

THF, toluene and diethyl ether were dried over sodium. Dichloromethane was distilled over calcium hydride. Solvents were degassed by bubbling argon through. Reactions under dry conditions were run under an argon atmosphere.

4.1. X-ray crystallographic analysis for compounds 33 and 36

X-ray data were collected on a Siemens SMART CCD diffractometer[11] using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[11] Absorption corrections were applied by the use of the SADABS program.[12] The structures were determined and refined using the SHELXTL program package.[13] The non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were

located from difference Fourier maps and refined with isotropic thermal parameters.

Structural data have been deposited at the Cambridge Crystallographic Data Centre deposition number CCDC 250768 for compound **33**, and CCDC 250769 for compound **36**.

4.1.1. Crystal data for $C_{24}H_{30}O_2$ (33). $M=350.48$, monoclinic, $P2_1/n$, $a=8.133(1)$ Å, $b=25.511(1)$ Å, $c=9.848(1)$ Å, $\beta=107.84(1)°$, $V=1925.3(1)$ Å^3, $Z=4$, $D_x=1.209$ Mg m^{-3}, $\mu=0.075$ mm^{-1}, $T=105(2)$ K, measured 27,375 reflections in 2θ range 5.4–61.0°, $R_{int}=0.032$. 355 parameters refined against 5859 F^2, $R=0.050$ for $I_o>2\sigma(I_o)$ and 0.063 for all data.

4.1.2. Crystal data for $C_{17}H_{22}O$ (36). $M=242.35$, monoclinic, $Pca2_1$, $a=14.367(1)$ Å, $b=12.610(1)$ Å, $c=7.490(1)$ Å, $V=1356.9(1)$ Å^3, $Z=4$, $D_x=1.186$ Mg m^{-3}, $\mu=0.071$ mm^{-1}, $T=105(2)$ K, measured 28,782 reflections in 2θ range 3.2–72.8°, $R_{int}=0.026$. 251 parameters refined against 6380 F^2, $R=0.033$ for $I_o>2\theta(I_o)$ and 0.039 for all data.

4.1.3. 1,4-Dioxadispiro[4.0.4.4]tetradecan-7-one (5). 6-Allyl-1,4-dioxaspiro[4.5]decane-6-carbaldehyde[2] (**4**) (4.929 g, 23.5 mmol), $(Rh(COD)Cl)_2$ (0.261 g, 0.59 mmol) and dppe (0.468 g, 1.18 mmol) were heated together at 110 °C for 8 d when GLC showed the reaction to be complete. Excess hexane was added to the reaction mixture to precipitate the catalyst which was removed by filtration and the filtrate evaporated. The residual material was subjected to flash chromatography using 30% diethyl ether in hexane. The product was a yellow oil; yield 3.641 g (64%). (Found: C 68.51, H 8.67. Calcd for $C_{12}H_{18}O_3$: C 68.54, H 8.63%); HRMS(EI): *M* 210.1260. Calcd for $C_{12}H_{18}O_3$: 210.1256. IR (film) ν cm^{-1} 2935 (m), 2884 (m), 1732 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26–1.95 (11H, m, CH_2), 2.14–2.24 (3H, m, CH_2), 3.79–3.89 (4H, m, H2 and H3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4 (CH_2), 20.3 (CH_2), 23.0 (CH_2), 31.1 (CH_2), 32.1 (CH_2), 32.5 (CH_2), 39.7 (C8), 55.2 (C5), 64.3 (C2 or C3), 65.0 (C3 or C2), 110.7 (C5), 218.9 (C7); *m/z* (EI): 210 (M, 32%), 165 (22), 99 (100), 86 (45).

4.1.4. Spiro[4,5]decane-1,6 dione (6).[14] 1,4-Dioxadispiro-[4.0.4.4]tetradecan-7-one (**5**) (1.242 g, 5.91 was added to 3 M HCl (10 mL) in CH_2Cl_2 (15 mL)and conc. HCl (3 mL) added. The mixture was stirred at room temperature overnight before addition of aqueous saturated $NaHCO_3$ (20 mL). Dichloromethane (5×20 mL) extraction furnished the diketone; yield 1.130 g (91%).

4.1.5. 1,4-Dioxadispiro[4.0.5.4]pentadecan-7-one (9). 1,4-Dioxadispiro[4.0.5.4]pentadec-9 en-7-one (**8**)[2] (500 mg, 2.25 mmol) in ethanol (30 mL) was hydrogenated over 10% palladium on charcoal (500 mg) at 1 atm and ambient temperature for 2 d. The catalyst was filtered off and the solvent evaporated. The crude product was purified by flash chromatography using hexane/EtOAc 20:1.The product appeared as a yellow oil; yield 0.47 g, (93%). HRMS. Found *M* 224.1409. Calcd for $C_{13}H_{20}O_3$: 224.1412. IR (film) ν cm^{-1} 2938 (C–H), 1702 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.74 (12H, m, CH_2), 2.15–2.47 (4H, m, CH_2), 3.79–3.96 (4H, m, H2, H3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (CH_2) 21.1 (CH_2), 23.2 (CH_2), 27.2 (CH_2), 31.8 (CH_2), 32.7 (CH_2), 33.3 (CH_2), 40.4 (CH_2), 56.0 (C6), 64.1 (C2) 64.0 (C3), 110.9 (C5), 213.2 (C7); MS(EI): 224 (M, 26%), 179 (52), 99 (100), 86 (38).

4.1.6. Spiro[5.5]undecane-1,7-dione (10). A solution of the 1,4-dioxadispiro[4.0.5.4]pentadecan-7-one (**9**) (500 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) and 5 M HCl (8 mL) was stirred overnight at ambient temperature. The mixture was extracted with diethyl ether (2×15 mL), washed with water, with saturated $NaHCO_3$ solution and brine. The solvent was evaporated and the crude product purified by flash chromatography using hexane/EtOAc 6:1; yield 0.38 g (95%) of a white crystalline solid, mp 49–50 °C. (Found: C, 73.30; H 8.95. Calcd for $C_{11}H_{16}O_2$: C, 73.09; H, 9.04%). HRMS: *M* 180.1146. Calcd for $C_{11}H_{16}O_2$: 180.1150. IR (film) ν cm^{-1} 2900 (C–H), 1686 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.75 (3H, m, CH_2), 2.45–3.38 (1H, m, H2, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_2), 21.6 (CH_2), 27.7 (CH_2), 36.2 (CH_2), 40.8 (C2, C8), 64.5 (C6), 210.9 (C1, C7). MS (EI): 180 (M, 41%), 152 (57), 124 (70), 111 (61), 67 (63), 55 (95), 41 (100).

4.1.7. Trifluoromethanesulfonic acid 6-trifluoromethanesulfonyloxyspiro[4.4]nona-1,6-diene-1-yl ester (12).[5] A solution of trifluoromethanesulfonic acid 6-oxospiro[4.4]non-1-en-1-yl ester (**11**) (1.5 g, 5.2 mmol) and DMAP (708 mg, 5.8 mmol) in dry dichloromethane (100 mL) was stirred at room temperature for 24 h before triflic anhydride (1.12 mL, 6.76 mmol) was added and the mixture stirred at room temperature for 6 d to complete the reaction (TLC). The solvent was evaporated and the product purified by flash chromatography using hexane/EtOAc 5:1; yield 90% of a colourless oil.[5]

4.1.8. Trifluoromethanesulfonic acid 6-oxospiro[4.5]dec-1-en-1-yl ester (13). A solution of HMDS (0.778 g, 4.82 mmol) and *n*BuLi (1.85 mL, 2.77 mmol) in THF (5 mL) was added dropwise over 20 min to a solution of spiro[4.5]decane-1,6-dione (**6**) (0.401 g, 2.40 mmol) and $PhNTf_2$ (0.987 g, 2.77 mmol) in THF (15 mL). at −78 °C. The mixture was allowed to reach room temperature overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL) and the mixture extracted with diethyl ether (3×20 mL). The ether extracts were dried ($MgSO_4$), evaporated and the residual material subjected to flash chromatography on slica gel using 20% EtOAc in hexane. The product was a yellow oil; yield 0.460 g (64%). (Found: C, 44.14; H, 4.74. Calcd for $C_{11}H_{12}O_4F_3S_1$: C, 44.29; H, 4.39%). HRMS: *M* 299.0570. Calcd for $C_{11}H_{12}O_4F_3S_1$: 299.0565. IR (film) ν cm^{-1} 2944 (m), 2867 (w), 1710 (s), 1425 (s), 1209 (s), 1148 (s), 1017 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66–1.74 (2H, m, CH_2), 1.83–1.88 (2H, m, CH_2), 1.95–2.07 (3H, m, CH_2), 2.13–2.18 (1H, m, H4), 2.32–2.38 (2H, m, H7) 2.39–2.45 (2H, m, H3), 5.78 (1H, t, $J=2.1$ Hz, H2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5 (C4), 24.7 (C3), 25.2 (C10), 32.2 (C11), 34.4 (C12), 38.2 (C7), 60.2 (C5), 115.9 (C2), 117.4 (q, $J=319$ Hz, CF_3), 148.1 (C1), 209.2 (C6); *m/z* (CI): *M* 299 (100%), 281 (85), 254 (62), 165 (89), 149 (73), 121 (46).

4.1.9. Trifluoromethylsulfonic acid 6-trifluoromethylsulfonyloxyspiro[4.5]deca-1,6-dien-1-yl ester (14). Triflic acid anhydride (0.083 mL, 0.50 mmol) was added dropwise over 5 min to a solution of trifluoromethanesulfonic acid 6-oxospiro[4.5]dec-1-en-1-yl ester (**13**) (0.100 g, 0.34 mmol) and pyridine (0.040 g, 0.50 mmol) in dichloromethane (8 mL) at −78 °C. The temperature was allowed to reach room temperature overnight. The reaction mixture was stirred for 3 d at room temperature before the solvents were distilled off and the residual material subjected to flash chromatography on silica gel using 10% EtOAc in hexane. The product was an oily material; yield 0.019 g, 13%. HRMS: *M* 297.0413. Calcd for $C_{11}H_{12}O_4F_3S_1$: 297.0408; IR (film) ν cm^{-1} 2927 (s), 2861 (m), 2358 (w), 1419 (m), 1207 (s), 1140 (m); ^1H NMR (500 MHz, $CDCl_3$) δ 1.56–1.63 (1H, m, H9), 1.75–1.80 (1H, m, H10), 1.80–1.84 (1H, m, H9), 1.91–1.94 (1H, m, H10), 1.95–1.99 (1H, m, H4), 2.20–2.25 (2H, m, H8), 2.25–2.31 (1H, m, H4), 2.35–2.41 (1H, m, H3), 2.44–2.51 (1H, m, H3), 5.81 (1H, dd, J=2.6, 2.5 Hz, H2), 5.91 (1H, dd, J=4.3, 4.0 Hz, H7); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7 (C9), 24.2 (C8), 25.7 (C3), 33.4 (C4), 34.0 (C10), 51.0 (C5), 117.2 (C2), 118.7 (q, J=319 Hz, CF_3), 118.8 (q, J=319 Hz, CF_3), 120.1 (C7), 148.5 (C1), 148.5 (C6); *m/z* (CI, NH_3): 448 ($M+NH_4^+$, 100%), 391 (9), 281 (12), 213 (16), 147 (38).

4.1.10. Trifluoromethanesulfonic acid 7-oxospiro[5.5]-undec-1-en-1-yl ester (15). LiHMDS (2.4 mmol) in THF (10 mL) was added dropwise to a solution of spiro[5.5]-undecane-1,7-dione (**10**) (370 mg, 2.05 mmol) and $PhNTf_2$ (900 mg, 2.46 mmol) in THF (15 mL) under argon at −78 °C. The mixture was allowed to reach ambient temperature overnight. When GLC showed the reaction to be complete, diethyl ether and water were added to the cold reaction mixture, the layers separated and the aqueous layer extracted with diethyl ether (2×). The combined ether extract was shaken with aqueous Na_2CO_3, dried ($MgSO_4$), and the solution evaporated to dryness. The product was isolated from the residual material after flash chromatography using hexane/EtOAc 10:1.The product was a yellow oil; yield 222 mg (60%). HRMS: *M* 313.0713. Calcd for $C_{12}H_{15}O_4SF_3$: 313.0721; IR (film) ν cm^{-1} 2926, 2855 (C–H), 1710 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36–2.31 (12H, CH_2), 2.30–2.60 (2H, m, H8), 5.90 (1H, t, J=4.2 Hz, H2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (CH_2), 20.6 (CH_2), 24.4 (CH_2), 26.5 (CH_2), 33.4 (CH_2), 34.8 (CH_2), 38.5 (C8), 54.5 (C6), 86.7 (CF_3), 120.7 (C2), 149.8 (C1), 209.6 (C7); MS (EI): 313 (M, 55%), 268 (31), 179 (138), 163 (100), 135 (62), 179 (38).

4.1.11. Trifluoromethanesulfonic acid 7-trifluoromethanesulfonyloxyspiro[5.5]undeca-1,7-dien-1-yl (16). Neat triflic anhydride (0.9 mL, 5.6 mmol) was added with a syringe to a solution of spiro[5.5]undecane-1,7-dione (**10**) (0.5 mg, 2.8 mmol) and pyridine (442 mg, 5.6 mmol) in dry dichloromethane (40 mL) at −78 °C under argon. The reaction mixture was allowed to reach room temperature and stirred at room temperature for 7 d. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel using hexane/EtOAc 5:1; yield 0.025 mg, 5%) of a colourless oil. IR (film) ν cm^{-1} 1634 (C=C), 2880 (C–H). ^1H NMR (300 MHz, $CDCl_3$) δ 1.56–1.91 (4H, m, CH_2), 2.17–2.22 (2H, m, H3, H9), 5.95–5.97 (1H, t, J=3.0 Hz, H2, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7 (CH_2), 24.0 (CH_2), 31.7 (CH_2), 43.6 (C6), 116.2 (q, CF_3), 120.3 (C2, C8), 148.6 (C1, C7); MS (CI): 444 (M, 100%), 445 (24), 446 (16), 311 (9), 143 (20).

4.1.12. Trifluoromethanesulfonic acid 1,4-dioxadispiro[4.0.4.4]tetradec-7-en-7-yl ester (17). A solution of HMDS (5.129 g, 31.8 mmol) and *n*BuLi (12.5 mL, 19.1 mmol) in THF (20 mL) was added dropwise over 20 min to a solution of 1,4-dioxadispiro[4.0.4.4]tetradecan-7-one (**5**) (3.337 g, 15.9 mmol) and $PhNTf_2$ (6.812 g, 19.1 mmol) in THF (50 mL) at −78 °C. The temperature was allowed to reach room temperature overnight and saturated aqueous sodium hydrogen carbonate (70 mL) added. The mixture was extracted with diethyl ether (3× 70 mL), the solution dried ($MgSO_4$), filtered, the filtrate evaporated and the residual material subjected to flash chromatograpy on silica gel using 20% Et_2O in hexane. The product was a yellow oil; yield 4.673 g (84%). HRMS (EI): *M* 342.0742. Calcd for $C_{13}H_{17}O_5F_3S_1$: 342.0749. IR (film) ν cm^{-1} 2939 (s), 2895 (s), 2865 (s), 1655 (m), 1421 (s), 1250 (s), 1211 (s); ^1H NMR (500 MHz, $CDCl_3$) δ 1.23–1.32 (1H, m, CH_2), 1.45–1.49 (1H, m, CH_2), 1.52–1.66 (5H, m, CH_2), 1.74–1.77 (1H, m, H10), 1.99 (1H, dt, J=13.3, 3.7 Hz, CH_2) 2.19–2.24 (2H, m, H9, H10) 2.42–2.45 (1H, m, H9), 3.82–3.87 (2H, m, H2, H3), 3.90–3.94 (1H, m, H2 or H3), 3.96–3.98 (1H, m, H3 or H2), 5.70 (1H, t, J=2.6 Hz, H8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2 (CH_2), 23.2 (CH_2), 26.1 (C9), 32.3 (CH_2), 32, 5 (C10), 33.6 (CH_2), 54.5 (C6), 64.4 (C3 or C2), 65.1 (C2 or C3), 112.0 (C8), 118.1 (C5), 118.4 (q, J=318 Hz, CF_3), 150.9 (C7); *m/z* (EI): 342 (M, 1.0%), 279 (16), 209 (41), 167 (33), 149 (100), 99 (43).

4.1.13. Trifluoromethanesulfonic acid 1,4-dioxadispiro-[4.0.5.4]pentadeca-7,9-dien-7-yl ester (18). 1 M LiHMDS (600 mg, 3.76 mmol) in THF (15 mL) was added dropwise to a solution of 1,4-dioxadispiro[4.0.5.4]pentadec-9-en-7-one (**8**) and $PhNTf_2$ (1.36 g, 3.8 mmol) in THF (10 mL) under argon at −78 °C. The mixture was allowed to reach ambient temperature overnight when GLC showed the reaction to be complete. Diethyl ether and water were added to the cold reaction mixture, the layers separated, the aqueous layer extracted with diethyl ether (2×), the combined ether solutions shaken with aqueous Na_2CO_3, dried over $MgSO_4$ and the solution evaporated to dryness. The product was isolated from the residual material after flash chromatography using hexane/EtOAc 10:1. The product was a yellow oil; yield 1.10 g (80%). HRMS: *M* 354.0731. Calcd for $C_{14}H_{17}O_5F_3S$: 354.0749; IR (film) ν cm^{-1} 2950 (C–H), 1664 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.51–1.71 (6H, m, CH_2), 2.15 (2H, m, H15), 2.36 (2H, m, H11), 3.79–4.04 (4H, m, H2, H3), 5.7 (1H, t, J=3.0 Hz, H9) 5.77 (1H, q, J=3.0 Hz, H10), 5.95 (1H, d, J=6.0 Hz, H8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 (CH_2), 23.5 (CH_2), 30.5 (CH_2), 34.0 (CH_2), 35.2 (CH_2), 45.0 (C6), 64.7 (C2 or C3), 65.9 (C3 or C2), 117.0 (q, CF_3), 118.5 (C5), 120.5 (C8), 127.8 (C9), 130.2 (C10), 151.7 (C7). MS (EI): 354 (M, 32), 353 (100), 220 (28), 99 (46).

4.1.14. 6-(2-Methoxyphenyl)spiro[4.4]non-6-en-1-one (19). Trifluoromethanesulfonic acid 6-oxospiro[4.4]non-1-en-1-yl) (**11**) (284 mg, 1 mmol) and $Pd(dba)_2$ (28.8 mg, 0.05 mmol) were dissolved in dry NMP (10 mL) and

2-methoxyphenyltributyltin (436 mg, 1.1 mmol) added with a syringe after 10 min. The solution was stirred at 80 °C until the reaction was completed after 2 h (GLC). 1 M aqueous KF solution (1 mL) was added and the mixture stirred for 30 min, diluted with ethyl acetate and filtered. The filtrate was washed with water (3×), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using hexane/EtOAc 4:1; yield 194 mg (80%) of a pale yellow oil. (Found: C, 79.55; H, 7.62. Calcd for $C_{16}H_{18}O_2$: C, 79.33; H, 7.43%). HRMS: *M* 242.1306. Calcd for $C_{16}H_{18}O_2$: 242.1306. IR (film) ν cm^{-1} 2910, 2220, 1710, 1450, 1250, 820, 720; ^1H NMR (300 MHz): δ 1.8 (4H, m, CH_2), 2.0–2.2 (1H, m, CH_2), 2.2–2.5 (4H, m, CH_2), 2.5–2.8 (1H, m, CH_2), 3.75 (3H, s, CH_3), 6.13 (1H, t, J=2.5 Hz, H7), 6.8–6.95 (2H, m, H-Ar), 7.15–7.35 (2H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8 (CH_2), 30.0 (CH_2), 34.5 (CH_2), 35.6 (CH_2), 37.7 (CH_2), 54.0 (CH_3), 63.7 (C5), 110, 120 (C7), 126, 128, 130, 133, 143, 156, 219 (C1); MS(EI) *m/z* 242 (M, 100), 224 (33), 186 (99), 185 (34), 171 (50), 158 (15), 128 (14), 115 (13).

4.1.15. Trifluoromethanesulfonic acid 6-(2-methoxyphenyl)spiro[4.4]nona-1,6-dien-1-yl ester (20). DMAP (346 mg, 2.48 mmol) was added to a solution of 6-(2-methoxyphenyl)spiro[4.4]non-6-en-1-one (**19**) (345 mg, 1.42 mmol) in dry CH_2Cl_2 (15 mL) at room temperature and the mixture stirred for 20 min. A solution of triflic anhydride (600 mg, 2.13 mmol) in CH_2Cl_2 (1 mL) was added dropwise and the mixture stirred at ambient temperature for another 20 min to complete the reaction (TLC). The solvent was evaporated and the product isolated after flash chromatography of the residual material using 10% EtOAc in hexane; yield 480 mg (90%) of a pale yellow oil. (Found: C, 54.73; H, 4.80. Calcd for $C_{17}F_3H_{17}O_4S$: C, 54.54; H, 4.54%). HRMS: *M* 374.0786. Calcd for $C_{17}F_3H_{17}O_4S$: 374.0799. IR (film) ν cm^{-1} 3000, 2949, 2860, 1600, 1425, 1213; ^1H NMR (300 MHz, $CDCl_3$) δ 1.9–2.6 (8H, m, CH_2), 3.8 (3H, s, CH_3), 5.5 (1H, t, J=2.1 Hz, H2), 5.95 (1H, t, J=2.4 Hz, H7), 6.9–7.25 (4H, m, H-Ar), 7.25 (1H, d, H-Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0 (CH_2), 29.6 (CH_2), 33.9 (CH_2), 37.0 (CH_2), 55.0 (CH_3), 63.0 (C5), 112 (C2), 114 (C7), 120, 126, 128, 130, 133, 142, 154, 158; MS (EI): *m/z* 374 (M, 100%), 241 (34), 213 (46), 171 (41), 133 (46), 131 (45), 121 (72), 115 (50), 69 (94), 55 (80).

4.1.16. 1,6-Bis(2-methoxyphenyl)spiro[4.4]nona-1,6-diene (21).

4.1.16.1. Procedure (i). Trifluoromethanesulfonic acid 6-(2-methoxyphenyl)spiro[4.4]nona-1,6-dien-1-yl ester (**20**) (374 mg, 1 mmol) and $Pd(dba)_2$ (28.8 mg, 0.05 mmol) were dissolved in dry NMP (15 mL). 2-Methoxyphenyltributyltin (436 mg, 1.1 mmol) was added with a syringe after 10 min. The solution was stirred at 80 °C overnight. A solution of aqueous KF (1 M, 1.5 mL) was added and the mixture stirred for 30 min. Dilution with ethyl acetate, filtration, shaking the filtrate with water (3×), drying ($MgSO_4$) and distilling off the solvents left an oily residue. Pure product was isolated after flash chromatography on silica gel using hexane/EtOAc 10:1; yield 55% of a pale yellow oil. (Found: C, 83.32; H, 7.20. Calcd for $C_{23}H_{24}O_2$: C, 83.13; H, 7.22%). HRMS: *M* 332.1766. Calcd for $C_{23}H_{24}O_2$: 332.1776. IR (film) ν cm^{-1} 3050, 3030, 2950, 2843, 2450, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 1.9–2.4 (4H, m, CH_2), 3.8 (3H, s, CH_3), 6.15 (1H, t, J=2.6 Hz, H2, H7), 6.7–7.4 (4H, m, H-Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1 (CH_2), 36.7 (CH_2), 60.0 (CH_3), 63.0 (C5), 111, 120 (C2, C7), 126, 127, 129, 132, 143 (C1, C6), 158 (Ph); MS(EI): *m/z* 332 (M, 100%), 211 (34), 185 (15), 149 (7), 147 (11), 121 (9), 91 (28), 84 (14).

4.1.16.2. Procedure (ii). *n*BuLi (1.6 M in 3.75 mL of THF) was added dropwise to a solution of 2-bromoanisole (1 mL, 5.7 mmol) in dry THF (40 mL) under argon at −78 °C, and the mixture was stirred at room temperature for 2 h. A solution of dried $ZnBr_2$ (1.35 g, 6 mmol) in dry THF (5 mL) was added. The mixture was stirred at −78 °C for 1 h, and the temperature allowed slowly to reach room temperature. Another solution of 1,6-bis(trifluoromethanesulfonyloxy)spiro[4.4]nona-1,6-diene (1.0 g, 2.4 mmol) (**12**) in dry THF (10 mL) and $Pd(PPh_3)_4$ (138.6 mg, 0.12 mmol, 5 mol%) was prepared and stirred at room temperature for 10 min before the solution was added to the solution containing the organozinc reagent. The resultant mixture was stirred at room temperature for 30 min, and at 50 °C for 90 min when GLC showed the reaction to be complete. The reaction mixture was worked up as above; yield 75%.

4.1.17. 7-(2-Methoxyphenyl)-1,4-dioxadispiro[4.0.4.4]-tetradec-7-ene (22). $Pd(PPh_3)_4$ (0.243 g, 2.15 mmol) was added to a mixture of trifluoromethanesulfonic acid 1,4-dioxadispiro[4.0.4.4]tetradec-7-en-7-yl ester (**17**) (1.469 g, 4.30 mmol), 2-anisoleboronic acid (0.950 g, 6.45 mmol), aqueous 2 M Na_2CO_3 (10 mL) and DME (30 mL), and the mixture heated at 100 °C for 3 h. Saturated sodium hydrogen carbonate (30 mL) was added to the cold reaction mixture, the mixture extracted with hexane (3×30 mL), and the dried ($MgSO_4$) hexane solution evaporated. The residual material was subjected to flash chromatography on silica gel using hexane; yield 0.928 g (72%) of a white crystalline material; mp 65–66 °C. (Found C, 75.47; H, 7.85. Calcd for $C_{19}H_{24}O_3$: C, 75.97H, 8.00%). IR (film) ν cm^{-1} 3036 (w), 2928 (s), 2966 (w), 1495 (w); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35–1.54 (6H, m, CH_2), 1.66–1.75 (1H, m, CH_2), 1.85–1.94 (1H, m, H10), 2.01–2.10 (1H, m, CH_2), 2.23–2.51 (3H, m, H9 and H10), 3.41 (1H, m, H2 or H3), 3.68 (1H, q, J= 7.3 Hz, H2 or H3), 3.92 (2H, m, H3 or H2), 3.74 (3H, s, CH_3), 5.68 (1H, t, J=2.4 Hz, H8), 6.84 (2H, m, H-Ar), 7.04 (1H, dd, J=7.3, 1.6 Hz, H-Ar), 7.16 (1H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (CH_2), 23.4 (CH_2), 30.5 (C9), 31.48 (CH_2), 34.3 (C10), 35.5 (CH_2), 55.2 (CH_3), 59.9 (C6), 63.5 (C2 or C3), 64.1 (C3 or C2), 110.4 (C-Ar), 113.2 (C5), 119.3 (C-Ar), 127.3 (C-Ar), 130.3 (C-Ar), 131.4 (C-Ar), 133.22 (C8), 144.4 (C7), 156.9 (C-Ar); *m/z* (EI): 300 (M, 100%), 238 (29), 212 (95), 185 (42), 99 (37).

4.1.18. 1-(2-Methoxyphenyl)spiro[4.5]dec-1-en-6-one (23). A solution of 7-(2-methoxyphenyl)-1,4-dioxadispiro-[4.0.4.4]tetradec-7-ene (**22**) (0.687 g, 2.29 mmol, 1 equiv), 3 M HCl (6 mL) in CH_2Cl_2 (7 mL) was stirred at room temperature for 4 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture extracted with dichloromethane (4×10 mL). Evaporation of the dried ($MgSO_4$) extracts provided a white crystalline material; yield 0.551 g (94%), mp 60–62 °C. HRMS(EI): *M* 256.1462. Calcd for $C_{17}H_{20}O_2$: 256.1463; IR (film) ν cm^{-1} 2937 (s),

2862 (s), 1741 (s), 1698 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.67 (4H, m, CH_2), 1.81–1.95 (3H, m, CH_2), 2.18–2.23 (1H, m, CH_2), 2.31–2.37 (2H, m, H3), 2.39–2.46 (2H, m, CH_2), 3.62 (3H, s, CH_3), 6.10 (1H, dd, J=2.8, 2.3 Hz, H2), 6.75–6.84 (2H, m, H-Ar), 7.10–7.23 (2H, m, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0 (CH_2), 25.2 (CH_2), 30.2 (C3), 36.7 (CH_2), 39.0 (CH_2), 39.2 (CH_2), 54.8 (CH_3), 64.3 (C-Ar), 111.0 (C-Ar), 120.5 (C-Ar), 125.8 (C-Ar), 128.3 (C-Ar), 130.7 C-Ar), 133.1 (C2), 143.7 (C1), 156.3 (C-Ar), 211.0 (C6); *m/z* (EI): 256 (M, 100%), 238 (48), 228 (77), 199 (86), 186 (58), 185 (95).

4.1.19. Trifluoromethanesulfonic acid 1-(2-methoxyphenyl)spiro[4.5]deca-1,6-dien-6-yl ester (24). A solution of HMDS (1.009 g, 6.25 mmol) and *n*BuLi (1.45 mL, 2.03 mmol) in THF (2.0 mL) was added dropwise over 5 min to a solution of 1-(2-methoxyphenyl)spiro[4.5]dec-1-en-6-one (**23**) (0.400 g, 1.56 mmol) and $PhNTf_2$ (0.726 g, 2.03 mmol) in THF (20 mL) at −78 °C. The reaction mixture was allowed to reach room temperature overnight. Saturated aqueous $NaHCO_3$ solution (30 mL) was added and the mixture extracted with diethyl ether (3×30 mL). The dried extracts were evaporated and the residual material subjected to flash chromatography on silica gel using 10% EtOAc in hexane. The product was a colourless oil; yield 0.438 g (72%). HRMS (EI): *M* 388.0948. Calcd for $C_{18}H_{19}F_3O_4S_1$: 388.0947; IR (film) ν cm^{-1} 2936 (m), 2867 (w), 1402 (m), 1248 (m), 1209 (s), 1140 (m), 1032 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40–1.53 (2H, m, H9), 1.67–1.71 (1H, m, H10), 1.88–1.93 (1H, m, H10), 1.96–2.06 (2H, m, H4 and H8), 2.10–2.17 (1H, m, H8), 2.33–2.38 (1H, m, H4), 2.41–2.47 (1H, m, H3), 2.53–2.60 (1H, m, H3), 3.74 (3H, s, CH_3), 5.71 (1H, dd, J=4.9, 3.5 Hz, H7), 6.00 (1H, dd, J=2.5, 2.4 Hz, H2), 6.87 (2H, m, H-Ar), 7.13 (1H, dd, J=7.5, 1.6 Hz, H-Ar), 7.21 (1H, m, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3 (CH_2), 24.5 (CH_2), 30.8 (C3), 35.9 (C8), 37.6 (C4), 55.1 (CH_3), 55.3 (C5), 110.8 (C-Ar), 115.4 (C7), 118.7 (q, J=318 Hz, CF_3), 119.9 (C-Ar), 126.0 (C-Ar), 128.3 (C-Ar), 123.0 (C-Ar), 134.4 (C2), 140.8 (C1), 153.7 (C6), 157.5 (C-Ar); *m/z* (EI): 388 (M, 100%), 238 (25), 207 (100), 111 (16), 121 (41).

4.1.20. 1,6-Bis-(2-methoxyphenyl)spiro[4.5]deca-1,6-diene (25). $Pd(PPh_3)_4$ (0.072 g, 2.15 mmol) was added to a solution of trifluoromethanesulfonic acid 1-(2-methoxyphenyl)spiro[4.5]deca-1,6-dien-6-yl ester (**24**) (0.372 g, 0.95 mmol), 2-anisoleboronic acid (0.216 g, 1.43 mmol) and 2 M Na_2CO_3 (3 mL) in DME (9 mL) and the reaction mixture heated at 100 °C for 4 h. Saturated aqueous $NaHCO_3$ (15 mL) was added to the cold reaction mixture which was extracted with hexane (3×15 mL). The dried ($MgSO_4$) hexane extracts were evaporated and the residual material subjected to flash chromatography on silica gel using 30% CH_2Cl_2 in hexane. The product was a white crystalline material; yield 0.201 g (61%), mp 86–89 °C. HRMS (EI): *M* 346.1929. Calcd for $C_{24}H_{26}O_2$ 346.1933; IR (film) ν cm^{-1} 2994 (w), 2930 (s), 2832 (s), 1595 (m), 1490 (s), 1462 (s), 1433 (s), 1244 (s), 1028 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45–1.51 (1H, m, CH_2), 1.53–1.64 (3H, m, CH_2), 1.73–1.79 (1H, m, CH_2), 2.06–2.20 (4H, m, CH_2), 2.30–2.35 (1H, m, CH_2), 3.69 (3H, s, CH_3), 3.76 (3H, s, CH_3), 5.58 (1H, dd, J=3.1, 3.0 Hz, H7), 6.11 (1H, dd, J=2.6, 2.5 Hz, H2), 6.7 (1H, dd, J=7.6, 7.1 Hz, H-Ar), 6.81 (1H, d, J=8.1 Hz, H-Ar), 6.89–6.93 (2H, m, H-Ar), 7.06 (1H, dd, J=7.6, 1.5 Hz, H-Ar), 7.05–7.15 (1H, m, H-Ar), 7.14–7.22 (1H, m, H-Ar), 7.71 (1H, dd, J=7.7, 1.6 Hz, H-Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2 (CH_2), 25.8 (C7), 31.3 (C2), 36.6 (CH_2), 39.8 (CH_2), 55.3 (CH_3), 55.4 (C5 and CH_3), 110.6 (C-Ar), 111.1 (CH), 119.2 (C-Ar), 119.9 (CH), 127.1 (CH), 127.3 (C1 or C6), 127.3 (CH), 127.7 (CH), 129.8 (C-Ar), 130.8 (C-Ar), 131.9 (C6 or C1), 134.0 (C-Ar), 139.4 (C-Ar), 142.3 (C-Ar), 157.5 (C-Ar), 157.8 (C-Ar); *m/z* (EI): 346 (M, 100%), 318 (12), 225 (18), 199 (34), 160 (14), 91 (9).

4.1.21. 7-Phenylspiro[5,5]undec-7-en-1-one (26). $Pd(dba)_3\cdot CHCl_3$ (13 mg, 0.03 mmol) was added to a solution of trifluoromethanesulfonic acid 7-oxospiro[5.5]-undec-1-yl ester (**15**) (130 mg, 0.42 mmol), tri(2-furyl)phosphine (12 mg, 0.05 mmol) and LiCl (35.2 mg, 0.83 mmol) in dry NMP (7 mL). The mixture was stirred for 10 min at room temperature before phenyltributylstannane (1.6 mL, 0.5 mmol) was added with a syringe. The solution was stirred at 80 °C for 16 h. 1 M aqueous KF (7 mL) was added over 30 min to the cold reaction mixture which was diluted with ethyl acetate and filtered. The filtrate was washed with water (10 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 10:1. The product was a colorless oil; yield 0.08 g (60%). HRMS: *M* 240.1510. Calcd for $C_{17}H_{20}O$: 240.1514; IR (film) ν cm^{-1} 2938, 2862 (C–H), 3028 (C–H, Ar), 1700 (C=O), 1600 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.66 (10H, m, CH_2), 1.80–1.87 (2H, m, CH_2), 2.20–2.61 (2H, m, CH_2), 5.94 (1H, t, J=6.0 Hz, H8), 7.08–7.22 (5H, m, H-Ar); ^{13}CNMR (75 MHz, $CDCl_3$) δ 18.1 (CH_2), 20.5 (CH_2). 25.6 (CH_2), 26.1 (CH_2), 34.4 (CH_2), 37.6 (CH_2), 38.5 (C7), 54.1 (C6), 126.2, 127.8, 128.5, 130.5, 141.1, 142.7, 208.7 (C1); MS (EI): 240 (M, 100%), 211 (77), 169 (31), 155 (31), 141 (38), 91 (27), 77 (15).

4.1.22. Trifluoromethanesulfonic acid 7-phenylspiro-[5.5]undeca-1,7-dien-1-yl ester (27). Neat triflic anhydride (110 mg, 0.39 mmol) was added with a syringe to a solution of 7-phenylspiro[5,5]undec-7-en-1-one (**26**) (63 mg, 0.262 mmol) and pyridine (30.8 mg, 0.39 mmol) in dry CH_2Cl_2 (6 mL) at −78 °C under argon. The reaction mixture was allowed to reach ambient temperature over 24 h. The product was purified by flash chromatography on silica gel using hexane/EtOAc 10:1. The product was a yellow oil; yield 131 mg (90%). (Found: C 57.74; H, 5.65. Calcd for $C_{18}H_{19}O_3F_3S$: C, 57.36; H, 5.87%). IR (film) ν cm^{-1} 2910 (C–H), 3020 (C–H Ar), 1672 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3–2.2 (12H, m, CH_2), 5.80 (1H, dd, J=3.0, 2.7 Hz, H8), 7.0–7.3 (H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (CH_2), 17.3 (CH_2), 23.4 (CH_2), 24.4 (CH_2), 31.5 (CH_2), 32.8 (CH_2), 42.0 (C6), 117.1 (H2), 116.9 (q, CF_3), 125.7, 126.7, 128.1, 139.7, 130.7, 140.9 (C7), 151.9 (C1); MS (EI): 372 (M, 27%), 222 (29), 130 (100), 117 (39), 91 (9).

4.1.23. 2-(7-Phenylspiro[5.5]undeca-1,7-dien-1-yl)thiophene (28). $Pd(PPh_3)_4$ (94 mg, 0.089 mmol) was added to a solution of trifluoromethanesulfonic acid 7-phenylspiro[5.5]undeca-1,7-dien-1-yl ester (**27**) (300 mg, 0.81 mmol), and 2-thiopheneboronic acid (207 mg,

1.61 mmol) in 1:3 2 M Na_2CO_3/DME (10 mL). The reaction mixture was heated at 100 °C overnight. Ethyl acetate and water were added. The aqueous phase was collected, extracted with EtOAc, the combined organic extracts washed with dilute aqueous sodium bicarbonate, brine, and dried ($MgSO_4$) before the solvent was distilled off. Flash chromatography of the residual material using hexane/EtOAc 20:1 gave the product as a colourless oil; yield 174 mg (70%). HRMS: *M* 306.1430. Calcd for $C_{21}H_{22}S$: 306.1442; IR (film) ν cm^{-1} 1618 (C=C), 2824–2966 (C–H), 3072 (C–H Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 1.27–1.74 (8H, m, CH_2), 2.03–2.3 (4H, m, CH_2), 6.01 (1H, t, $J=4.0$ Hz, H8), 6.28 (1H, t, $J=3.0$ Hz, H2), 6.87–6.90 (1H, m, H-Ar), 7.03 (1H, t, $J=3.0$ Hz, H-Ar), 7.16–7.33 (6H, m, CH-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_2), 18.2 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 34.7 (CH_2), 34.9 (CH_2), 42.7 (CH_2), 123.0, 124.2, 126.3, 126.9, 127.6, 128.8, 129.3, 130.6, 138.3, 143.1, 144.8, 146.3. MS (EI): 306 (M, 24%), 302 (16), 208 (100), 212 (29), 176 (12), 91 (38).

4.1.24. 7-Phenyl-1,4-dioxadispiro[4.0.5.4]pentadeca-7,9-diene (29). $Pd(dba)_2$ (130 mg, 0.12 mmol) was added to a solution of trifluoromethanesulfonic acid 1,4-dioxadispiro-[4.0.5.4]pentadeca-7,9-dien-7-yl ester (**18**) (860 mg, 2.43 mmol) in dry *N*-methylpyrrolidin-2-one (NMP, 20 mL) and the mixture stirred at room temperature for 4 h. 1 M aqueous KF solution (9 mL) was added dropwise over 30 min, the mixture diluted with ethyl acetate and filtered. The filtrate was washed with water (2×), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 10:1; yield 0.64 g (75%) of a colorless oil. HRMS: *M* 282.1623. Calcd for $C_{19}H_{22}O_2$: 282.1620. IR (film) ν cm^{-1} 1653 (C=C), 2950 (C–H), 3451 (C–H, Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 1.19–1.68 (8H, m, CH_2), 2.72–2.73 (2H, m, H12), 3.22–3.83 (4H, m, H2, H3), 5.71–5.78 (2H, m, H9, H10), 5.89–5.92 (1H, m, H8), 7.11–7.25 (5H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7 (CH_2), 22.3 (CH_2), 29.6 (CH_2), 31.1 (CH_2), 33.1 (C11), 44.1 (C6), 62.3 (C2), 63.8 (C3), 112.6 (C5), 123.2 (C8), 124.2, 124.7, 125.5, 126.4, 128.6, 143.1, 143.8 (C7); MS (EI): 282 (M, 45%), 281 (44), 220 (83), 167 (79),165 (55), 128 (37), 99 (56), 73 (100).

4.1.25. *cis*,*cis*-1,6-Bis(2-methoxyphenyl)spiro[4.4]nonane (30). A solution of 1,6-bis-(2-methoxyphenyl)-spiro[4.4]-nona-1,6-diene (**21**) (332 mg, 1 mmol) in ethanol (20 mL) was hydrogenated over 10% palladium on charcoal (100 mg, 0.1 mmol) at 4 atm in a Parr apparatus at room temperature for 3 d. The catalyst was removed by filtration through Celite. The filtrate was evaporated and the residual product purified by flash chromatography on silica gel using hexane/EtOAc, 12:1. Recrystallisation of the product from diethyl ether and ethanol yielded 302 mg (90%) of a white crystalline material, mp 131 °C. (Found: C, 82.66; H, 8.54. Calcd for $C_{23}H_{28}O_2$: C, 82.40; H, 8.33%). HRMS: *M* 336.2083. Calcd for $C_{23}H_{28}O_2$: 336.2089. IR (film) ν cm^{-1} 3000, 2950, 2450, 1600, 1500, 1250; ^1H NMR (200 MHz) δ 1.7–2.2 (6H×2, m, CH_2), 3.40 (3H×2, s, CH_3), 3.55 (1H×2, d, $J=7.2$ Hz, H1, H6), 6.2–7.1 (4H×2, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4 (CH_2), 34.8 (CH_2), 41.6 (CH_2), 43.8 (CH_2), 54.9 (CH_3), 60.7 (C-5), 109 (C-Ar), 119 (C-Ar), 125 (C-Ar), 128 (C-Ar), 136 (C-Ar), 156 (C-Ar); MS(EI): *m*/*z* 336 (M, 100%), 202 (7), 187 (25), 174 (36), 173 (24), 134 (15), 121 (24), 91 (25), 77 (6).

4.1.26. *cis*,*cis*-1,6-Bis(2-hydroxyphenyl)spiro[4.4]nonane (31). A flask containing a solution of *cis*,*cis*-1,6-bis(2-methoxyphenyl)spiro[4.4]nonane (**30**) (336 mg, 1 mmol) in dry dichloromethane (10 mL) under argon was protected from light by covering with aluminium foil. TMSI (2 equiv×5) was added at intervals and the mixture stirred at room temperature. TLC monitoring showed that the starting material was consumed after 5 d when the reaction was stopped. Two new major products had been formed after 5 d. The reaction mixture was evaporated to dryness and the residual material subjected to flash chromatography on silica gel using hexane/EtOAc, 12:1. The major product was the diol **31**; yield 60%. The minor product was the monomethoxy intermediate *cis*/*cis*-1-(2-methoxyphenyl)-6-(2-hydroxyphenyl)spiro[4.4]nonane (**32**); yield: 20%.

Product **31** was a white crystalline material, mp 178–180 °C ($CHCl_3$). HRMS: *M* 308.1768. Calcd for $C_{21}H_{24}O_2$: 308.1776. IR (film) ν cm^{-1} 3480 (br.), 2958, 1470. ^1H NMR (200 MHz, $CDCl_3$) δ 1.70 (1H, m, CH_2), 2.03 (4H, m, CH_2), 2.15 (1H, m, CH_2), 3.11 (1H, d, $J=8$ Hz, H1, H6), 3.28 (1H, s, OH), 6.4–7.2 (4H, m, H-Ar);. ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3 (CH_2), 34.2 (CH_2), 40.4 (CH_2), 43.8 (C1, C6), 61.8 (C5), 117 (C-Ar), 122 (C-Ar), 127 (C-Ar), 128 (C-Ar), 135 (C-Ar), 153 (C-Ar); MS(EI): *m*/*z* 308 (M,100%), 173 (37), 160 (43), 159 (44), 149 (24), 145 (25), 133 (25), 120 (25), 107 (57), 91 (29).

The second product was *cis*,*cis*-1-(2-methoxyphenyl)-6-(2-hydroxyphenyl)spiro[4.4]nonane (**32**).

4.1.27. *cis*,*cis*-1-(2-methoxyphenyl)-6-(2-hydroxyphenyl)spiro[4.4]nonane (32). The title compound was obtained as a pale yellow crystalline material, mp 154 °C ($CHCl_3$). (Found: C, 82.20; H, 8.15. Calcd for $C_{22}H_{26}O_2$: C, 81.98; H, 8.07%). HRMS: *M* 322.1941. Calcd for $C_{22}H_{26}O_2$: 322.1932. IR (film) ν cm^{-1} 3480 (br.), 3050, 2945, 2840, 1470. ^1H NMR (300 MHz) δ 1.5–1.7 (2H, m, CH_2), 1.8–2.1 (8H, m, CH_2), 2.1–2.2 (2H, m, CH_2), 3.1–3.3 (1H, m, H1), 3.30 (3H, s, CH_3), 3.40 (1H, s, OH), 3.54 (1H, d, $J=7.5$ Hz, H6), 6.3–7.2 (8H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0 (CH_2), 34.0 (CH_2), 40.4 (CH_2), 40.7 (CH_2), 43.4 (C1), 44.0 (C6), 54.6 (CH_3), 61.1 (C5), 110 (C-Ar), 116 (C-Ar), 120 (C-Ar), 121 (C-Ar), 126.1 (C-Ar), 126.5 (C-Ar), 127.5 (C-Ar), 128.0 (C-Ar), 134.5 (C-Ar), 136.0 (C-Ar), 152.5 (C-Ar), 156.5 (C-Ar); MS(EI): *m*/*z* 322 (M, 100%), 187 (17), 174 (28), 173 (34), 159 (26), 145 (17), 134 (29), 121 (43), 107 (62), 91 (70).

4.1.28. *cis*,*cis*-1,6-Bis(2-methoxyphenyl)spiro[4.5]decane (33). 10% Pd–C (0.204 g) was added to a solution of 1,6-bis(2-methoxyphenyl)spiro[4.5]deca-1,6-diene (**25**) (0.139 g, 0.40 mmol) in ethanol (25 mL) and the mixture stirred under hydrogen (1 atm) for 9 h. The catalyst was filtered off and the product isolated after flash chromatography on silica gel using 3% Et_2O in hexane. The product was a white crystalline material; yield 0.100 g (73%), mp 97–100 °C (MeOH). HRMS: *M* 350.2253. Calcd for $C_{24}H_{30}O_2$: 350.2246. IR (film) ν cm^{-1} 3060 (w), 2928

(s), 2859 (s), 2836 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32–1.36 (1H, m, CH_2), 1.41–1.48 (2H, m, CH_2), 1.53–1.56 (1H, m, CH_2), 1.63–1.71 (3H, m, CH_2), 1.74–1.77 (1H, m, CH_2), 1.84–1.89 (2H, m, CH_2), 1.94–1.97 (1H, m, CH_2), 2.01–2.09 (1H, m, CH_2), 2.22–2.29 (2H, m, CH_2), 3.30 (1H, dd, J= 4.3, 4.0 Hz, H6 or H1), 3.36 (3H, s, C17 CH_3), 3.38 (3H, s, CH_3), 3.56 (1H, s, H1 or H6), 6.29 (1H, d, J=8.1 Hz, CH), 6.37 (1H, d, J=8.11 Hz, CH), 6.62–6.66 (2H, m, CH), 6.85–6.92 (2H, m, CH), 6.99 (1H, s, CH), 7.35 (1H, s, CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_2), 22.7 (CH_2), 22.9 (CH_2), 29.8 (CH_2), 33.4 (CH_2), 35.4 (CH_2), 38.5 (CH_2), 38.6 (C6 or C1), 51.4 (C5), 54.6, 55.0, 108.8 (CH), 109.0 (CH), 118.6 (CH), 119.5 (CH), 125.1 (CH), 125.4 (CH), 128.8 (CH), 123.0 (CH), 134.0 (C), 134.6 (C), 156.0 (C), 156.5 (C); *m/z* (EI): 350 (M, 87%), 188 (28), 147 (40), 121 (100), 91 (67).

4.1.29. 7-(2-Methoxyphenyl)-1,4-dioxadispiro[4.0.4.4]-tetradecane (34). 5% Pd–C (0.212 g) was added to a solution of 7-(2-methoxyphenyl)-1,4-dioxadispiro[4.0.4.4]-tetradec-7-ene (**22**) (0.104 g, 0.35 mmol) in EtOH (20 mL) and the mixture stirred under hydrogen (1 atm) at room temperature for 18 h. The catalyst was filtered off through Celite, the filtrate evaporated and the residual product purified by flash chromatography on silica gel using 5% EtOAc in hexane. The product was a white solid; yield 0.074 g (72%), mp 93–95 °C (MeOH). (Found: C, 75.25; H, 8.95. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H 8.67%). HRMS (EI): M 302.1881. Calcd for $C_{19}H_{26}O_3$: 302.1882. IR (film) ν cm^{-1} 2941 (s), 2884 (s), 1603 (w), 1492 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.62 (8H, m, CH_2), 1.79–1.90 (3H, m, CH_2), 1.95–2.12 (3H, m, CH_2), 2.61 (1H, q, J= 7.2 Hz, H2 or H3), 3.03–3.31 (2H, m, H7 and H2 or H3), 3.46 (1H, dq, J=6.9, 1.3 Hz, H2 or H3), 3.62 (1H, dq, J= 7.3, 1.2 Hz, H3 or H2), 3.81 (3H, s, CH_3), 6.80–6.84 (2H, m, H-Ar), 7.02-7.06 (1H, m, H-Ar), 7.31 (1H, dd, J=7.6, 1.7 Hz, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5 (CH_2), 22.9 (CH_2), 24.0 (CH_2), 31.2 (CH_2), 33.9 (CH_2), 34.2 (CH_2), 37.4 (CH_2), 47.1 (C7), 53.8 (C6), 55.6 (CH_3), 62.7 (C2 or C3), 63.1 (C3 or C2), 110.1 (C-Ar), 113.5 (C5), 119.3 (C-Ar), 125.6 (C-Ar), 130.2 (C-Ar), 134.1 (C-Ar), 157.7 (C-Ar); *m/z* (EI): 302 (M, 40%), 240 (48), 174 (73), 99 (100).

4.1.30. 1-(2-Methoxyphenyl)spiro[4.5]decan-6-one (35). A solution of 7-(2-methoxyphenyl)-1,4-dioxadispiro-[4.0.4.4]tetradecane (**34**). (0.069 g, 0.23 mmol) in 3 M HCl (3 mL) and CH_2Cl_2 (4 mL) was stirred at room temperature for. 5 h. Additional dichloromethane was added, the two phases separated, the organic solution dried ($MgSO_4$) and evaporated. The residual material was subjected to flash chromatography on silica gel using 10% EtOAc in hexane. The product was a yellowish oil; yield 0.049 g (82%). (Found: C, 78.78; H 8.61. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H 8.58%). HRMS(EI): M 258.1623. Calcd for $C_{17}H_{22}O_2$: 258.1620. IR (film) ν cm^{-1}: 2938 (s), 2866 (m), 1699 (s), 1492 (m); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34–1.70 (6H, m, CH_2), 1.72–1.99 (5H, m, CH_2), 2.08–2.17 (2H, m, CH_2), 2.58–2.68 (1H, m, CH_2), 3.79 (1H, dd, J=7.9, 6.9 Hz, H1), 3.81 (3H, s, CH_3), 6.81–6.85 (2H, m, H-Ar), 7.01 (1H, dd, J=7.7, 1.7 Hz, H-Ar), 7.10-7.15 (1H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9 (CH_2), 23.4 (CH_2), 27.3 (CH_2), 35.2 (CH_2), 36.4 (CH_2), 41.2 (CH_2), 41.5 (CH_2), 45.2 (C1), 55.3 (CH_3), 62.1 (C5), 110.3 (C-Ar), 120.8 (C-Ar), 127.2 (C-Ar), 129.3 (C-Ar), 132.1 (C-Ar), 156.5 (C-Ar), 214.5 (C6); *m/z* (EI): 258 (M, 40%), 240 (22), 148 (100), 111 (48), 91 (16).

4.1.31. *cis*-7-Phenylspiro[5,5]undecan-1-one (36). A solution of 7-phenyl-1,4-dioxadispiro[4.0.5.4]pentadeca-7,9-diene (**29**) (220 mg, 0.78 mmol) in ethanol (30 mL) was hydrogenated over 10% palladium on charcoal (440 mg) at 1 atm and ambient temperature for 3 d. The catalyst was filtered off through Celite and the solvent evaporated. The crude product was purified by flash chromatography using hexane/EtOAc 20:1. The product was a white solid with mp 88 °C; yield 160 mg, (75%). HRMS: M 242.1664. Calcd for $C_{17}H_{22}O$: 242.1670. IR (film) ν cm^{-1}: 1702 (C=O), 2900 (C–H), 3030 (C–H Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31–1.80 (12H, m, CH_2), 2.00–2.40 (4H, m, CH_2), 2.60–2.70 (1H, m, H7), 7.1–7.3 (5H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0 (CH_2), 21.1 (CH_2), 25.9 (CH_2), 26.4 (CH_2), 29.6 (CH_2), 36.8 (CH_2), 38.8 (CH_2), 40.1 (CH_2), 52.4 (C6), 53.9 (C7), 127.6 (C-Ar), 130.4 (C-Ar), 143.6 (C-Ar), 162.3 (C-Ar), 214.5 (c1); MS (EI): 242 (M, 100%), 129 (51), 111 (65), 98 (50), 91 (60).

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The synthesis and applications of asymmetric phase-transfer catalysts derived from isomannide and isosorbide

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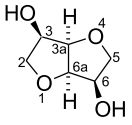
Abstract—We report herein the synthesis of various derivatives of isomannide and isosorbide. Alkylation on *N*-(diphenylmethylene)glycine *tert*-butyl ester show the new catalysts to be effective phase-transfer catalysts with moderately good enantioselectivity. The effect of *exo* and *endo* substituents on the enantioselectivity of alkylation reaction have also been studied.

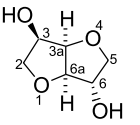
1. Introduction

Catalytic asymmetric phase-transfer reactions constitute an important methodology in synthetic chemistry. Since the pioneering work by O'Donnell et al., the enantioselective alkylation of protected glycine derivative using chiral quaternary ammonium salts has become a very attractive method for the preparation of both natural and unnatural α-amino acids.[1] The phase-transfer catalysts (PTCs) that are used effectively are mainly the derivatives of cinchona alkaloids.[2] Among the non-cinchona based PTCs, chiral spiro ammonium salts derived from binapthol are very promising.[3]

We focused our attention on designing new PTCs based on structurally rigid bicyclic systems. Isomannide (**1**) and isosorbide (**2**) also known as (3*R*,3a*R*,6*R*,6a*R*)-hexahydrofuro[3,2-*b*]furan-3,6-diol and (6*S*,3*R*,3a*R*,6a*R*)-hexahydrofuro[3,2-*b*]furan-3,6-diol, respectively, were selected as the chiral templates for investigating the effect of substituents at the *exo* and *endo* positions on asymmetric alkylation reactions. In these dioxabicyclo systems, hydroxy group at C_3 and C_6 are *endo* in case of isomannide, whereas C_6 is *exo* and C_3 is *endo* in isosorbide. Isomannide and isosorbide are important by-products of the starch industry, arising from dehydration of D-sorbitol and D-mannitol that are produced worldwide at a rate of 650,000 tons per annum.[4] They are widely used in the form of their nitrate esters in the pharmaceutical industry.[5] These commercial starting materials provide an easy and inexpensive access to optically pure functionalized compounds. These have been used as chiral auxiliaries and as chiral ligands in a number of reactions like alkylations,[6] Diels–Alder reaction[7] and asymmetric hydrogenation etc.[8]



(**1**)



(**2**)

2. Results and discussion

In the present study, we discuss the synthesis of various derivatives of isomannide, isosorbide and their use as chiral phase-transfer catalysts. In general, the strategy involves the protection of one of the free hydroxy groups as ether while the other is transformed to the amine function. This amine is then quaternized with different aromatic and aliphatic moieties. D-Mannitol was dehydrated to isomannide (**1**)[9] and converted to its monotosyl derivative (**3**) using tosyl chloride in pyridine. The crude product; which consisted mainly of the mono-tosylate was purified by successive recrystallizations from isopropanol and ethyl acetate. Isomannide mono-tosylate (**3**) was then *O*-alkylated under phase-transfer conditions in good yields with different groups via Scheme 1. The resulting ethers (**4a–c**) were reacted with excess of benzylamine in refluxing condition, to give amino ethers (**5a–c**) in good yields (77–83%). As expected, amination of tosylates occurs via the S_N2

Keywords: Asymmetric alkylations; Chiral phase-transfer catalysts; Isomannide; Isosorbide.
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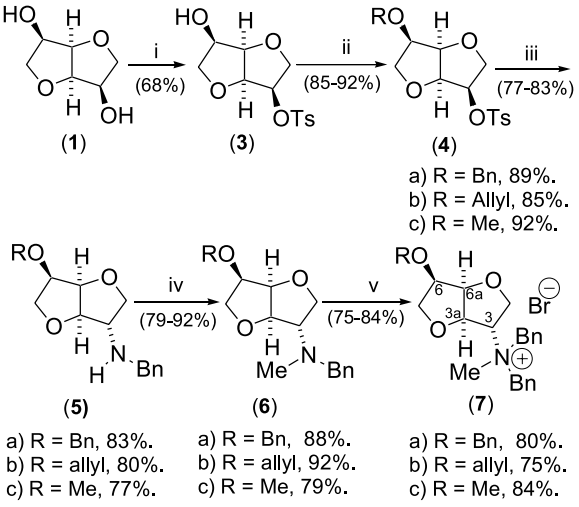
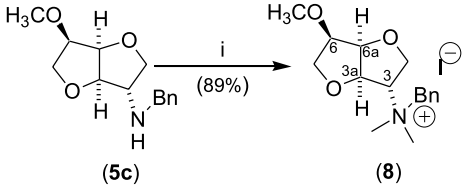


Scheme 1. Reagents and conditions: (i) TsCl, pyridine, CH_2Cl_2, 10 h. (ii) RX, TBAB, 50% aqueous KOH, CH_2Cl_2. (iii) $BnNH_2$, 170 °C, 6 h. (iv) Me_2SO_4, 50% aqueous KOH, TBAB, CH_2Cl_2. (v) BnBr, CH_3CN, 15 h.



Scheme 2. Reagents and conditions: (i) MeI, K_2CO_3, CH_3CN, 25 °C, 9 h.

mechanism resulting in inversion of configuration giving product **5a–c**.[10]

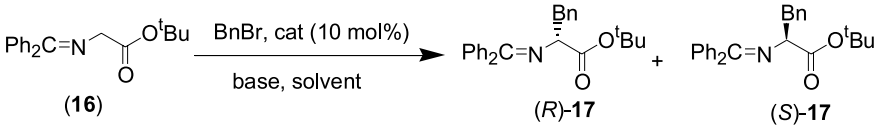
The amino ether **5a–c** were *N*-monomethylated with dimethylsulfate under PTC conditions to give **6a–c**, which were quaternized with benzyl bromide in refluxing acetonitrile to afford the quaternary ammonium salts **7a–c** in 75–84% yield.

Catalysts **7**(**a–c**) were used for the asymmetric alkylation of imine **16** using benzyl bromide as the alkylating agent in a mixture of toluene/dichloromethane (7:3) at −20 °C (Table 1). In all these cases the benzylated product was formed with a preference for the *S*-isomer as detected by chiral HPLC.[3]

Similarly, the amino ether **5c** was treated with an excess of methyl iodide in acetonitrile and K_2CO_3 to afford the quaternary ammonium salt **8** in 89% yield (Scheme 2).

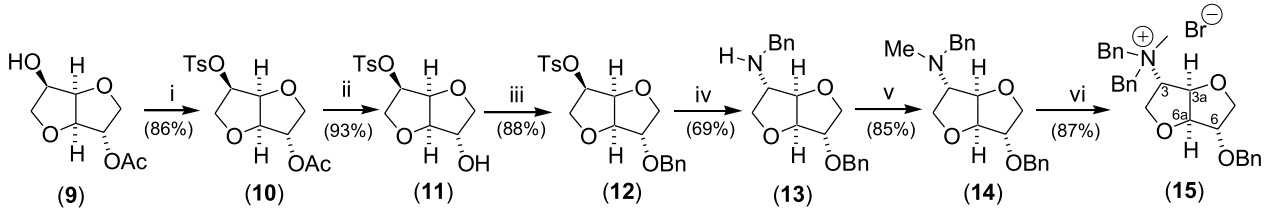
From the table it is evident that when the geometry of these dioxabicyclo systems is 3-*exo*, 6-*endo* and the quaternary nitrogen has aromatic benzyl groups, the enantioselectivity for the benzylation reaction is 70:30 (entry 3, Table 1). The nature of substituent at position C_6 (methyl, allyl, benzyl) has little effect on the enantioselectivity (entries 1–6). However, when the quaternary nitrogen contains the alkyl groups (dimethyl as in catalyst **8**), in place of aromatic moieties (*N*,*N*-dibenzyl as in catalyst **7**), there is drop in enantioselectivity (54:46, entry 7).

Table 1. Benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester



Entry	Catalyst	Base	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)	%Selectivity[b] (*S*:*R*)
1	**7a**	50% aqueous KOH	CH_2Cl_2	0	6	92	64:36
2	**7a**	50% aqueous KOH	$PhCH_3$:CH_2Cl_2 (7:3)	0	9	89	66:34
3	**7a**	50% aqueous KOH	$PhCH_3$:CH_2Cl_2 (7:3)	−20	14	83	70:30
4	**7a**	$CsOH·H_2O$	$PhCH_3$:CH_2Cl_2 (7:3)	−40	29	84	72:28
5	**7b**	50% aqueous KOH	$PhCH_3$:CH_2Cl_2 (7:3)	−20	15	85	70:30
6	**7c**	50% aqueous KOH	$PhCH_3$:CH_2Cl_2 (7:3)	−20	18	78	66:34
7	**8**	50% aqueous KOH	$PhCH_3$:CH_2Cl_2 (7:3)	−20	12	87	54:46
8	**15**	50% aqueous KOH	$PhCH_3$:CH_2Cl_2 (7:3)	−20	6	89	57:43
9	**22**	50% aqueous KOH	$PhCH_3$:CH_2Cl_2 (7:3)	−20	10	90	28:72
10	**22**	$CsOH·H_2O$	$PhCH_3$:CH_2Cl_2 (7:3)	−40	22	88	26:74

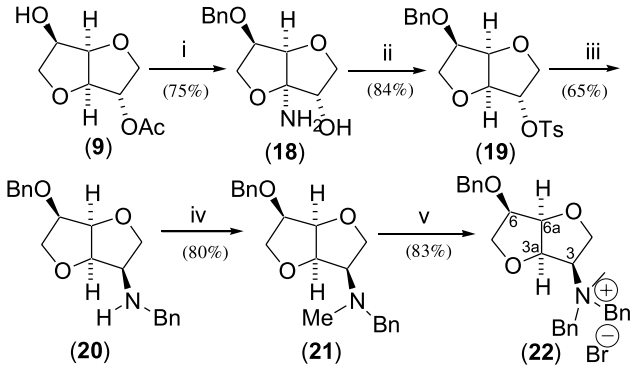
[a] Yield of isolated product.
[b] Based on chiral HPLC using Chiralcel OD-H column using hexane/2-propanol as eluent. Absolute configuration of **17** was determined by comparison of the HPLC retention time with the authentic sample independently synthesized by the reported procedure.[2]



Scheme 3. Reagents and conditions: (i) TsCl, Pyr, CH_2Cl_2, 8 h. (ii) 2 M NaOH, TBAB, CH_2Cl_2, 5 h. (iii) BnBr, TBAB, 50% aqueous KOH. (iv) $BnNH_2$, 170 °C. (v) Me_2SO_4, 50% aq. KOH, TBAB, CH_2Cl_2, 8 h. (vi) BnBr, CH_3CN, 14 h.

To find the effect of substituent if the C_6 is made *exo*, catalyst **15** was synthesized according to Scheme 3, starting from (3*S*,3a*R*,6*R*,6a*R*)-6-hydroxyhexahydrofuro [3,2-*b*]-furan-3-yl acetate (**9**). The free hydroxy group of **9** was activated as its tosylate (**10**) by treatment with *p*-toluene-sulphonyl chloride in pyridine. Deacetylation of **10** was achieved chemoselectively by treatment with 2 N NaOH at 25 °C in the presence of tertrabutylammonium bromide as PTC in dichloromethane to afford the monotosylate **11** in 93% yield. The monotosylate **11** was *O*-benzylated in 88% yield and then converted to amino ether **13** in 69% yield. The amino ether was *N*-methylated and subsequently quaternized with benzyl bromide to afford the quaternary ammonium salt **15** in 87% yield. We found that the 3-*exo*, 6-*exo* combination as in catalyst **15** lowered the enantio-selectivity for the benzylation reaction (57:43, entry 8, Table 1).

To study the effect of 3-*endo*,6-*endo* combination, quaternary ammonium salt **22** was obtained starting from (3*S*,3a*R*,6*R*,6a*R*)-6-hydroxyhexahydrofuro[3,2-*b*]furan-3-yl acetate using different Scheme. This acetate was O-benzylated with benzyl bromide in tetrahydrofuran using sodium hydride and the acetate was hydrolysed in situ with 25% aqueous NaOH to afford the ether **18**. This was converted to the quaternary ammonium salt **22** according to Scheme 4.



Scheme 4. Reagents and conditions: (i) (a) NaH, BnBr, THF, 5 h; (b) 25% aqueous NaOH, TBAB, CH_2Cl_2, 5 h. (ii) TsCl, Pyr, 12 h. (iii) $BnNH_2$, 170 °C. (iv) Me_2SO_4, 50% aqueous KOH, TBAB, CH_2Cl_2, 8 h. (v) BnBr, CH_3CN, 15 h.

When **22** was used as a chiral PTC for the benzylation of **16**, the product was obtained in moderately good enantioselectivity (74%), with preference for the *R*-isomer.

3. Conclusions

In conclusion, we found that rigid 1,4-dioxabicyclic systems such as isomannide and isosorbide, when used as chiral PTCs for the benzylation reaction, the stereochemistry at the C_3 carbon atom adjacent to the ring junction C_{3a}–C_{6a} plays a crucial role in controlling the selectivity (*R*/*S*) of the product. When quaternary nitrogen at C_3 is *exo* (as in **7a**–**c**) it favors the (*S*)-isomer, whereas when it is *endo* (as in **22**) it favours the (*R*)-isomer. The aromatic moieties were found to increase the selectivity as compared to the aliphatic moieties at the quaternary nitrogen atom. Nature of substituent, on the ether functions whether allyl or benzyl does not have much effect on the enantioselectivity. Further, the substituents at the C_6 carbon atom when *exo*, lowers the selectivity as compared to *endo*.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C spectra were recorded at 300 MHz and 75 MHz Bruker Advance Spectrometer respectively, with chemical shifts in ppm and tetramethylsilane as the internal standard. Infra-red absorption spectra were recorded on a Nicolet Impact 410 spectrometer, the frequencies in the IR spectra are indicated in cm^{-1}. Mass spectra data were recorded on a Finnigan-MAT LCMS spectrometer. Elemental analyses were recorded on a Elementa Vario EL. HPLC was performed on a Shimadzu SPD-10A using chiral phase column (DIACEL Chiralcel, OD-H). TLC was performed on plates pre-coated (0.25 mm) with silica gel 60, Merck F-254. The plates were visualized by the use of a combination of UV (254 nm) and iodine. Column chromatography was carried out with silica gel Merck 60 (80–230 mesh).

4.2. General procedure for the benzylation of *tert*-butyl *N*-(diphenylmethylene)glycinate

Benzyl bromide (8.4 mmol) was added to a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester[12] (1.6 mmol) and catalyst (0.16 mmol) in toluene/dichloromethane (7:3) 10 mL. The reaction mixture was cooled to the appropriate temperatures given in Table 1, base (16.94 mmol) was added and the resulting mixture stirred vigorously until the starting material had been consumed (6–18 h). The suspension was diluted with diethyl ether (35 mL), washed with water (2×10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude product. Purification of the residue by silica chromatography afforded the desired product **17** in 78–92% yield as pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): 1.41 (s, 9H), 3.22–3.09 (m, 2H), 4.08 (dd, J=5.0, 9.1 Hz, 1H), 6.53–7.62 (m, 15H); R_t HPLC [99.5:0.5, hexane/*iso*propanol, 18.1 min (*R*-isomer) 26.5 min (*S*-isomer)].

4.2.1. Synthesis of (3*R*,3a*S*,6*R*,6a*R*)-6-hydroxy-3-(4-methylphenyl)sulfonyloxyperhydrofuro[3,2-*b*]furan (3). To a solution of **1** (50 g, 0.342 mol) and pyridine (55.2 mL, 0.682 mmol) in dichloromethane (150 mL) was added *p*-toluenesulphonyl chloride (74.9 g, 0.393 mmol) at 0 °C. After stirring the reaction mixture at rt for 10 h the solution was diluted with dichloromethane (50 mL), washed with 1 N HCl (100 mL), water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by successive recrystallizations (ethyl acetate/isopropanol), to afford **3** as white crystalline solid (69.8 g, 68%). Mp 104–105 °C. $[\alpha]_D^{30}$ = +77.98 (*c*, 0.95, MeOH). IR (KBr): ν 3525, 2929, 2867, 1596, 1359, 1305, 1188, 1173, 1122, 1099, 1050, 1020, 923, 883, 843, 818 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H), 3.55 (dd, J= 7.3, 1.7 Hz, 1H), 3.79 (t, J=7.8 Hz, 1H), 3.93–4.05 (m, 2H), 4.29 (m, 1H), 4.42 (t, J=5.1 Hz, 1H), 4.49 (t, J= 4.8 Hz, 1H), 4.91 (dd, J=6.6, 5.50 Hz, 1H), 7.35 (d, J=

8.0 Hz, 2H), 7.83 (d, $J=8.2$ Hz, 2H). MS (MALDI): m/z 300 (M^+).

4.2.2. Synthesis of (3*R*,3a*S*,6*R*,6a*R*)-6-(benzyloxy)-3-[(4-methylphenyl)sulfonyloxy]hexahydrofuro[3,2-*b*]furan (4a). To a solution of **3** (10 g, 33.3 mmol), 50% aqueous KOH (5.59 mL) and TBAB (0.322 g, 1 mmol) in dichloromethane (80 mL) was added benzyl bromide (6.54 g, 38.2 mmol). After stirring the contents at rt for 5 h, the reaction mixture was diluted with water (10 mL), organic layer separated and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/EtOAc, 85:15) to afford **4a** as oil (11.6 g, 89%). $[\alpha]_D^{30}=+82.35$ (c, 0.79, MeOH). IR (film): ν 3057, 3032, 2976, 2944, 2874, 1599, 1494, 1454, 1361, 1326, 1306, 1191, 1175, 1143, 1097, 1014, 977, 951, 887, 825, 758 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.63 (t, $J=8.6$ Hz, 1H), 3.84 (t, $J=7.6$ Hz, 1H), 3.83–4.06 (m, 3H), 4.74 (t, $J=2.3$ Hz, 2H), 4.52 (d, $J=11.9$ Hz, 1H), 4.69 (d, $J=11.8$ Hz, 1H), 4.86 (dd, $J=4.8$, 6.9 Hz, 1H), 7.26–7.34 (m, 7H), 7.81 (d, $J=8.2$ Hz, 2H). MS (MALDI): m/z 391 ($M^+ +1$), 390. Anal. Calcd for $C_{20}H_{22}O_6S$: C, 61.52; H, 5.68; S, 8.21 Found: C, 61.42; H, 5.74; S, 8.16.

4.2.3. Synthesis of (3*R*,3a*S*,6*R*,6a*R*)-6-(allyloxy)-3-[(4-methylphenyl)sulfonyloxy]hexahydrofuro[3,2-*b*]furan (4b). To a solution of **3** (5.0 g, 16.6 mmol), 50% aqueous KOH (2.79 mL, 24.9 mmol) and TBAB (0.161 g, 0.49 mmol) in dichloromethane (50 mL) was added allyl bromide (2.4 g, 19.8 mmol). After stirring the contents at rt for 6 h, the reaction mixture was diluted with water (10 mL), organic layer separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 85:15) to afford **4b** as oil (4.81 g, 85%). $[\alpha]_D^{30}=+163.65$ (c 0.5, MeOH). IR (film): ν 2979, 2950, 2925, 2879, 1645, 1597, 1365, 1190, 1177, 1141, 1026 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.62 (t, $J=7.5$ Hz, 1H), 3.82 (t, $J=7.5$ Hz, 1H), 3.96–4.0 (m, 6H), 4.14 (dd, $J=5.6$, 5.9 Hz, 1H), 4.46–4.52 (m, 2H), 4.87 (dd, $J=5.4$, 5.3 Hz, 1H), 5.91 (m, 1H), 7.34 (d, $J=8.3$ Hz, 2H), 7.82 (d, $J=8.2$ Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.5, 70.0, 70.7, 71.5, 78.4, 78.9, 80.0, 80.0, 117.7, 127.7, 129.7, 133.0, 134.1, 145.0. MS (APCI): m/z 340 (M^+), 316, 272. Anal. Calcd for $C_{16}H_{20}O_6S$: C, 56.46; H, 5.92; S, 9.42. Found: C, 53.36; H, 5.81; S, 10.14.

4.2.4. Synthesis of (3*R*,3a*S*,6*R*,6a*R*)-6-(methoxy)-3-[(4-methylphenyl)sulfonyloxy]hexahydrofuro[3,2-*b*]furan (4c). The procedure described in Section 4.2.2 was followed; **4c** was obtained as oil (4.81 g, 92%) from **3** (5.0 g, 16.6 mmol). $[\alpha]_D^{30}=+103.14$ (c, 1, MeOH). IR (film): ν 3436, 2948, 2880, 1597, 1456, 1364, 1190, 1174, 1146, 1098, 1084, 1030, 916, 853, 817 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H), 3.58 (s, 3H), 3.61 (t, $J=8.3$ Hz, 1H), 3.79 (t, $J=7.7$ Hz, 1H), 3.93 (d, $J=6.4$ Hz, 1H), 3.99 (dd, $J=7.2$, 7.8 Hz, 2H), 4.50–4.53 (m, 2H), 4.8 (dd, $J=5.0$, 6.3 Hz, 1H), 7.34 (d, $J=8.1$ Hz, 2H), 7.82 (d, $J=7.9$ Hz, 2H). MS (APCI): m/z 314 (M^+), 241. Anal. Calcd for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77; S, 10.20. Found: C, 53.36; H, 5.81; S, 10.14.

4.3. General procedure for the synthesis of 5a–c

A solution of **4a–c** and benzylamine was heated at 170 °C for 8 h under argon atmosphere. The contents were cooled to rt benzylamine was removed under reduced pressure and the residue was purified by chromatography (SiO_2, hexane/ethyl acetate, 50:50) to afford **5a–c** as colourless oil (83–77%).

4.3.1. Synthesis of *N*-benzyl-*N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]amine (5a). The procedure discussed in Section 4.3 was followed; **5a** was obtained as oil (2.76 g, 83%) from **4a** (4.0 g, 10.2 mmol) and benzylamine (20 mL). $[\alpha]_D^{30}=+78.89$ (c 1, MeOH). IR (film): ν 3324, 3025, 2945, 2864, 1532, 1489, 1444, 1332 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.33 (bs, 1H), 3.66 (t, $J=8.1$ Hz, 1H), 3.80 (s, 3H), 3.80–3.85 (m, 2H), 3.97–4.05 (m, 2H), 4.40 (d, $J=4.3$ Hz, 1H), 4.54 (d, $J=11.8$ Hz, 1H), 4.60 (t, $J=4.5$ Hz, 1H), 4.74 (d, $J=11.9$ Hz, 1H) 7.21–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 51.9, 64.8, 72.2, 74.0, 78.9, 80.0, 87.6, 127.0, 127.7, 127.7, 127.9, 128.2, 128.3, 128.7, 137.6, 139.5. MS (APCI): m/z 327 ($M^+ +2$), 326. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.69; H, 7.18; N, 4.25.

4.3.2. Synthesis of *N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-(allyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-*N*-benzylamine (5b). The procedure discussed in Section 4.3 was followed; **5b** was obtained as oil (3.23, 80%) from **4b** (5.0 g, 14.7 mmol) and benzylamine (30 mL). $[\alpha]_D^{30}=+157.70$ (c 1, 0.5 MeOH). IR (film): ν 3027, 2940, 2874, 1645, 1494, 1454, 1360, 1327 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.72 (bs, 1H), 3.32 (bs, 1H), 3.61 (t, $J=8.1$ Hz, 1H), 3.75–3.86 (m, 1H), 3.86 (s, 2H), 3.90 (dd, $J=7.0$, 1.37 Hz, 1H), 3.95–4.05 (m, 3H), 4.10 (dd, $J=7.0$, 5.5 Hz, 1H), 4.42 (d, $J=4.3$ Hz, 1H), 4.57 (t, $J=4.4$ Hz, 1H), 5.18 (d, $J=10.3$ Hz, 1H), 5.31 (dd, $J=1.4$, 15.8 Hz, 1H), 5.91 (m, 1H), 7.20–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 51.8, 61.8, 64.7, 69.6, 70.8, 71.3, 72.4, 73.8, 79.1, 79.8, 80.8, 87.4, 117.3, 126.8, 127.8, 128.2, 134.3, 139.4. MS (MALDI): m/z 276 ($M^+ +1$). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.64; H, 7.75; N, 4.92.

4.3.3. Synthesis of *N*-benzyl-*N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-methoxyhexahydrofuro[3,2-*b*]furan-3-yl]amine (5c). The procedure discussed in Section 4.3 was followed; **5c** was obtained as oil (3.05 g, 77%) from **4c** (5.0 g, 15.9 mmol) and benzyl amine (30 mL). $[\alpha]_D^{30}=+108.48$ (c 1.26, $CHCl_3$). IR (film): ν 3316, 3027, 2927, 1666, 1603, 1537, 1494, 1454, 1380, 1218, 1067, 1019 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.67 (bs, 1H), 3.36 (m, 1H), 3.45 (s, 3H), 3.58–3.64 (m, 1H), 3.84 (s, 2H), 3.80–3.84 (m, 1H), 3.95–3.86 (m, 2H), 3.99 (dd, $J=4.8$, 4.5 Hz, 1H), 4.45 (d, $J=4.2$ Hz, 1H), 4.64 (t, $J=4.2$ Hz, 1H), 7.22–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 51.9, 58.1, 64.8, 69.6, 74.1, 79.7, 81.6, 87.2, 127.1, 127.4, 127.7, 128.0, 128.4, 139.5. MS (APCI): m/z 251 ($M^+ +2$), 249. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.32; H, 7.74; N, 5.52.

4.4. General procedure for the *N*-methylation of 5a–c

To a solution of **5a–c** (9.21 mmol), 50% aqueous KOH (2.0 mL) and TBAB (0.089 g, 0.27 mmol) in CH_2Cl_2 (50 mL), was added dimethyl sulfate (1.27 g, 10.0 mmol). After stirring for 5 h at rt, the reaction mixture was diluted with water (15 mL), organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 80:20) to afford **6a–c** as oil (88–79%).

4.4.1. Synthesis of *N*-benzyl-*N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-*N*-methylamine (6a). The procedure discussed in Section 4.4 was followed; **6a** was obtained as yellowish oil (88%) from **5a**. $[\alpha]_D^{30}=+89.73$, (*c* 1 MeOH). IR (film): *ν* 3316, 3027, 2927, 1666, 1603, 1537, 1494, 1454, 1380, 1218, 1067, 1019 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.14 (s, 3H), 3.11 (td, *J*=2.2, 4.3 Hz, 1H), 3.40 (d, *J*=13.3 Hz, 1H), 3.70 (t, *J*=7.9 Hz, 2H), 3.83 (m, *J*=1.9, 4.6 Hz, 2H), 3.90 (m, 1H), 4.20 (dd, *J*=6.7, 4.2 Hz, 1H), 4.55 (d, *J*=8.7 Hz, 2H), 4.61 (dd, *J*=2.3, 2.9 Hz, 1H), 4.75 (d, *J*=11.8 Hz, 1H), 7.21–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$): *δ* 39.5, 60.0, 68.8, 72.0, 72.3, 78.5, 80.5, 86.4, 126.9, 127.7, 127.8, 128.1, 128.3, 128.7, 137.6, 138.3. MS (APCI): *m*/*z* 341 (M^++2), 340. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.26; H, 7.49; N, 4.04.

4.4.2. *N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-(Allyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-*N*-benzyl-*N*-methylamine (6b). The procedure discussed in Section 4.4 was followed; **6b** was obtained as yellowish oil (92%) from **5b**. $[\alpha]_D^{30}=+93.33$, (*c* 0.5, MeOH). IR (film): *ν* 3459, 3027, 2942, 2853, 1644, 1494, 1454, 1366, 1317, 1139, 1104, 1039 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.14 (s, 3H), 3.12 (dd, *J*=2.5, 4.1 Hz, 1H), 3.41 (d, *J*=13.7 Hz, 1H), 3.64–3.71 (m, 2H), 3.94 (dd, *J*=5.2, 3.7 Hz, 1H), 3.93–3.96 (m, 2H), 4.01 (dd, *J*=5.2, 4.6 Hz, 1H), 4.16–4.21 (m, 2H), 4.52 (d, *J*=4.7 Hz, 1H), 4.65 (dd, *J*=2.4, 2.7 Hz, 1H), 5.20 (d, *J*=10.3 Hz, 1H), 5.32 (dd, *J*=1.4, 15.7 Hz, 1H), 5.93 (m, 1H), 7.23–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): *δ* 39.5, 60.1, 68.6, 71.5, 72.1, 72.3, 78.8, 80.4, 86.5, 117.6, 127.0, 128.1, 134.3, 138.3. MS (APCI): *m*/*z* 291 (M^++2), 290. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.44; H, 4.93; N, 4.73.

4.4.3. Synthesis of *N*-benzyl-*N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-methoxyhexahydrofuro[3,2-*b*]furan-3-yl]-*N*-methylamine (6c). The procedure discussed in Section 4.4 was followed; **6c** was obtained as yellowish oil (79%) from **5c**. $[\alpha]_D^{30}=+118.23$ (*c* 0.5, MeOH). IR (film): *ν* 2975, 2940, 2870, 2796, 1644, 1668, 1602, 1494, 1454, 1139, 1128, 1063, 1084, 1040, 1027 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.15 (s, 3H), 3.11 (td, *J*=2.3, 2.3 Hz, 1H), 3.42 (d, *J*=13.3 Hz, 1H), 3.47 (s, 3H), 3.63 (d, *J*=8.1 Hz, 1H), 3.69 (d, *J*=12.9 Hz, 1H), 3.79–3.85 (m, 2H), 3.93 (dd, *J*=6.3, 1.70 Hz, 1H), 4.17 (dd, *J*=6.6, 2.5 Hz, 1H), 4.56 (t, *J*=5.0 Hz, 1H), 4.67 (dd, *J*=2.4, 2.8 Hz, 1H), 7.22–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): *δ* 39.5, 58.2, 60.1, 72.1, 72.4, 80.2, 81.1, 86.6, 127.0, 128.2, 128.8, 138.3. MS (APCI): *m*/*z* 264 (M^++1), 263. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32 Found: C, 68.34; H, 8.12; N, 5.22.

4.4.3.1. Synthesis of (3*S*,6a*S*,3a*R*,6*R*)-dibenzyl-(6-benzyloxy-hexahydrofuro[3,2-*b*]furan-3-yl)methyl ammonium bromide (7a). A solution of compound **6a** (1.0 g, 2.94 mmol) and benzyl bromide (1.0 g, 5.84 mmol) in acetonitrile (10 mL) was stirred at 80 °C under argon for 15 h. The contents were cooled to rt and evaporated to dryness in vacuo. The residue was diluted with hexane (15 mL), stirred at rt for 15 min and filtered to afford **7a** as white solid (1.20 g, 80%). Analytical sample was prepared by purification with preparative TLC. Mp 94–95 °C. $[\alpha]_D^{30}=+27.86$ (*c* 1.1, MeOH). IR (KBr): *ν* 3034, 2925, 2879, 1630, 1455, 1373, 1214, 1135, 1110, 1080 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 3.08 (s, 3H), 3.75–3.80 (m, 3H), 4.01 (dd, *J*=4.5, 4.4 Hz, 1H), 4.27 (dd, *J*=6.1, 6.2 Hz, 1H), 4.38 (d, *J*=11.6 Hz, 1H), 4.58 (d, *J*=11.6 Hz, 1H), 4.65 (d, *J*=12.1 Hz, 1H), 4.88 (d, *J*=12.8 Hz, 1H), 5.05 (d, *J*=5.2 Hz, 1H), 5.10 (d, *J*=6.2 Hz, 1H), 5.19 (t, *J*=5.1 Hz, 1H), 5.43 (d, *J*=12.9 Hz, 1H), 6.13 (d, *J*=5.4 Hz, 1H), 7.24–7.42 (m, 11H), 7.67 (d, *J*=6.7 Hz, 2H), 7.74 (d, *J*=6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): *δ* 29.6, 46.9, 64.2, 64.7, 68.6, 72.1, 72.7, 78.6, 82.1, 83.1, 126.5, 126.5, 127.7, 128.4, 129.1, 129.3, 130.7, 130.7, 133.8, 137.7. MS (APCI): *m*/*z* 430 (M^+−80), 356. Anal. Calcd for $C_{28}H_{32}BrNO_3$: C, 65.88; H, 6.32; N, 2.74. Found: C, 65.02; H, 6.85; N, 2.54.

4.4.3.2. Synthesis of (3*S*,6a*S*,3a*R*,6*R*)-dibenzyl-(6-allyloxy-hexahydrofuro[3,2-*b*]furan-3-yl)methylammonium bromide (7b). The procedure discussed in Section 4.4.3.1 was followed; **7b** was obtained from **6b** (1.0 g, 3.4 mmol) as white solid (1.19 g, 75%). Analytical sample was prepared by purification with preparative TLC. Mp 147–148 °C. $[\alpha]_D^{25}=+60.68$ (*c* 0.82, MeOH). IR (KBr): *ν* 3420, 2938, 2944, 2856, 1635, 1457, 1421, 1213, 1129, 1113, 1059, 1034, 992, 913, 884, 749 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 3.11 (s, 3H), 3.72–3.83 (m, 3H), 3.91–4.04 (m, 3H), 4.24 (dd, *J*=5.3, 4.4 Hz, 1H), 4.60 (d, *J*=12.8 Hz, 1H), 4.81 (d, *J*=12.8 Hz, 1H), 5.10–5.18 (m, 5H), 5.24 (d, *J*=12.8 Hz, 1H), 5.81 (m, 1H), 6.16 (d, *J*=5.0 Hz, 1H), 7.30–7.41 (m, 6H), 7.70 (d, *J*=6.7 Hz, 2H), 7.76 (d, *J*=6.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): *δ* 47.0, 64.1, 64.4, 68.6, 71.5, 71.9, 78.5, 80.5, 82.0, 82.9, 117.2, 126.4, 126.5, 128.3, 129.1, 129.2, 130.6, 130.7, 133.5, 133.7, 134.1. MS (APCI): *m*/*z* 379 (M^+−81), 306. Anal. Calcd for $C_{24}H_{30}BrNO_3$: C, 62.61; H, 6.57; N, 3.04. Found: C, 63.47; H, 6.89; N, 2.83.

4.4.3.3. Synthesis of (3*S*,6a*S*,3a*R*,6*R*)-dibenzyl-(6-methoxy-hexahydrofuro[3,2-*b*]furan-3-yl)methyl ammonium bromide (7c). The procedure discussed in Section 4.4.3.1 was followed; **7c** was obtained from **6c** (1.0 g, 3.79 mmol) as white solid (1.38 g, 84%). Analytical sample was prepared by purification with preparative TLC. Mp 143–144 °C. $[\alpha]_D^{30}=+56.78$ (*c* 0.98, MeOH). IR (KBr): *ν* 2931, 2894, 1455, 1421, 1376, 1288, 1212, 1137, 1107, 1067, 1037, 999, 883, 757 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.66 (s, 3H), 3.32 (s, 3H), 3.80–3.83 (m, 5H), 4.18 (t, *J*=6.3 Hz, 2H), 4.55 (d, *J*=12.5 Hz, 1H), 4.74 (d, *J*=12.4 Hz, 1H), 5.14 (d, *J*=10.5 Hz, 1H), 5.24 (d, *J*=12.5 Hz, 1H), 5.36 (d, *J*=12.5 Hz, 1H), 7.32–7.40 (m, 6H), 7.75 (t, *J*=7.4 Hz, 4H). ^{13}C NMR ($CDCl_3$): *δ* 45.2, 54.4, 65.6, 66.0, 71.1, 71.4, 84.4, 87.9, 89.3, 89.9, 133.5, 133.7, 136.2, 136.3, 137.8,

138.4, 140.7, 140.9. MS (APCI): *m/z* 353 (M^+-81), 281. Anal. Calcd for $C_{22}H_{28}BrNO_3$: C, 60.83; H, 6.50; N, 3.22. Found: C, 59.94; H, 6.94; N, 2.94.

4.4.4. Synthesis of (3*S*,6a*S*,3a*R*,6*R*)-benzyl-(6-methoxy-hexahydro-furo[3,2-*b*]furan-3-yl)-dimethyl-ammonium iodide (8). To a solution of **5c** (1.0 g, 4.0 mmol), K_2CO_3 (0.554 g, 4.0 mmol) in acetonitrile (10 mL) was added methyl iodide (2.27 g, 15.9 mmol) under argon. After stirring at rt, for 9 h, the solvent was evaporated and the residue was diluted with water (10 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×40 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo, to afford white solid, recrystallization from acetone afforded **8** as crystalline solid (1.44 g, 89%). Mp 165–166 °C. $[\alpha]_D^{30}=+48.62$, (*c* 1.02, MeOH). IR (KBr): *ν* 2969, 2856, 1616, 1465, 1379, 1288, 1215, 1141, 1109, 1031 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 3.11 (s, 3H), 3.16 (s, 3H), 3.45 (s, 3H), 3.79–3.98 (m, 2H), 4.00 (q, *J*=5.2 Hz, 1H), 4.11 (t, *J*=4.0 Hz, 1H), 4.29 (m, 1H), 4.59 (dd, *J*=3.2, 8.6 Hz, 1H), 4.76 (d, *J*=16.2 Hz, 2H), 4.96 (t, *J*=5.6 Hz, 1H), 5.41 (d, *J*=5.7 Hz, 1H), 7.50–7.59 (m, 3H), 7.69 (d, *J*=6.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): *δ* 49.5, 49.7, 58.9, 68.5, 69.1, 72.3, 80.1, 81.9, 83.0, 83.5, 128.2,130.3, 132.1, 134.6. MS (APCI): *m/z* 277 (M^+-128), 207. Anal. Calcd for $C_{16}H_{24}INO_3$: C, 47.42; H, 5.97; N, 3.46. Found: C, 47.20; H, 5.68; N, 3.29.

4.4.5. Synthesis of (3*S*,3a*R*,6*R*,6a*S*)-6-{[(4-methylphenyl) sulfonyl]oxy}hexahydrofuro[3,2-*b*]furan-3-yl-acetate (10). To a solution of (3*S*,3a*R*,6*R*,6a*R*)-6-hydroxyhexahydrofuro[3,2-*b*]furan-3-yl acetate[11] (5.0 g, 26.5 mmol) in pyridine (30 mL) was added *p*-toluenesulphonyl chloride (5.57 g, 29.2 mmol) at 0 °C. After stirring the reaction mixture for 8 h at rt, pyridine was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (60 mL) and washed successively with 1 N HCl, water, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **10** as white solid (7.8 g, 86%). Mp 56–58 °C. $[\alpha]_D^{30}=+72.50$ (*c* 1, ethanol). IR (KBr): *ν* 3052, 2980, 2874, 1740, 1596, 1451, 1379, 1345, 1287, 1242, 1174, 1112, 1081, 1011, 973 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.05 (s, 3H), 2.45 (s, 3H), 3.74 (dd, *J*=6.7, 2.9 Hz, 1H), 3.87 (dd, *J*=6.2, 3.3 Hz, 1H), 3.9 (m, 2H), 4.46 (d, *J*=4.3 Hz, 1H), 4.68 (t, *J*=4.6 Hz, 1H), 4.9 (q, *J*=5.5 Hz, 1H), 5.1 (s, 1H), 7.3 (d, *J*=7.9 Hz, 2H), 7.8 (d, *J*=8.0 Hz, 2H). MS (ESI): *m/z* 342 (M^+).

4.4.6. Synthesis of (3*R*,3a*S*,6*S*,6a*R*)-6-hydroxyhexahydrofuro[3,2-*b*]furan-3-yl-4-methylbenzenesulfonate (11). To a solution of **10** (7.0 g, 20.4 mmol) and TBAB (0.197 g, 0.61 mmol) in CH_2Cl_2 (50 mL) was added 2 M NaOH (12 mL, 24.5 mmol). After stirring for 5 h at rt, the reaction mixture was cooled to 0 °C and neutralized with 1 N HCl. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2×50 mL). The combined organic extract was dried over Na_2SO_4 and concentrated in vacuo to afford **11** as white solid (5.7 g, 93%). Mp 48–49 °C. $[\alpha]_D^{30}=+57.58$ (*c* 1, ethanol). IR (KBr): *ν* 3564, 2929, 2875, 1598, 1455, 1364, 1190, 1170, 1098, 1010, 972 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.41 (s, 1H), 2.45 (s, 3H), 3.70 (t, *J*=9.2 Hz, 1H), 3.83 (d, *J*=6.2 Hz, 1H), 3.88 (s, 2H), 4.29 (s, 1H), 4.38 (d, *J*=4.1 Hz, 1H), 4.65 (t, *J*=4.6 Hz, 1H), 4.86 (t, *J*=5.7 Hz, 1H), 7.35 (d, *J*=7.9 Hz, 1H), 7.83 (d, *J*=7.9 Hz, 2H). MS (ESI) *m/z* (%): 300 (M^+,100), 218 (64).

4.4.7. Synthesis of (3*R*,3a*S*,6*S*,6a*R*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl-4-methylbenzenesulfonate (12). The procedure discussed in Section 4.2.2 was followed; **12** was obtained from **11** (5.0, 16.6 mmol) as white solid (5.72 g, 88%). Mp 52–53 °C. $[\alpha]_D^{30}=+57.914$ (*c* 1.7, $CHCl_3$). IR (KBr): *ν* 3030, 2912, 2873, 1598, 1454, 1360, 1189, 1170, 1103, 1044, 1005, 973 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.42 (s, 3H), 3.71 (t, *J*=7.1 Hz, 1H), 3.82–3.89 (m, 2H), 3.97 (d, *J*=10.2 Hz, 1H), 4.03 (bs, 1H), 4.47 (d, *J*=4.2 Hz, 1H), 4.52 (s, 2H), 4.58 (t, *J*=4.4 Hz, 1H), 4.85 (dd, *J*=5.8, 5.71 Hz, 1H), 7.27–7.34 (m, 7H), 7.82 (d, *J*=7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$): *δ* 21.5, 69.2, 71.3, 73.3, 78.6, 80.1, 83.1, 85.8, 127.6, 127.8 (2C), 128.4, 129.8, 133.1, 137.3. MS (APCI): *m/z* (%) 390 (M^+, 100), 298 (85). Anal. Calcd for $C_{20}H_{22}O_6S$: C, 61.52; H, 5.68; S, 8.21. Found: C, 61.45; H, 5.76; S, 8.16.

4.4.8. Synthesis of *N*-benzyl-*N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]amine (13). The procedure discussed in Section 4.3 was followed; **13** was obtained from **12** (5.0 g, 12.8 mmol) as white solid (2.87 g, 69%). Mp 54–55 °C. $[\alpha]_D^{30}=+24.06$, (*c* 1.25, MeOH). IR (KBr): *ν* 3309, 3029, 2950, 2882, 1493, 1464, 1342, 1216, 1190, 1085 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 3.33 (bs, 1H), 3.68 (d, *J*=9.2 Hz, 1H), 3.76–3.91 (m, 6H), 4.04 (s, 1H), 4.51–4.65 (m, 4H), 7.22–7.31 (m, 10H). ^{13}C NMR: *δ* 51.9, 63.9, 71.4, 72.1, 72.8, 83.0, 85.6, 87.0, 127.1, 127.6, 127.7, 128.0, 128.4, 137.5, 139.6. MS (APCI): *m/z* 326 (M^++1), 325. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.71; H, 7.23; N, 4.19.

4.4.9. Synthesis of *N*-benzyl-*N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-*N*-methylamine (14). The procedure discussed in Section 4.4 was followed; **14** was obtained from **13** (2.0 g, 6.14 mmol) as white solid (1.77 g, 85%). Mp 60–61 °C. $[\alpha]_D^{30}=+23.26$ (*c* 0.85, MeOH). IR (KBr): *ν* 3031, 2989, 2911, 2853, 2796, 1498, 1454, 1362, 1340, 1215, 1106, 1078, 1054, 1032, 970, 920, 885 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 2.12 (s, 3H), 3.07 (t, *J*=13.2 Hz, 1H), 3.41 (d, *J*=12.5 Hz, 1H), 3.72 (d, *J*=12.5 Hz, 1H), 3.75 (d, *J*=6.1 Hz, 1H), 3.86 (dd, *J*=3.7, 6.3 Hz, 1H), 3.88 (t, *J*=9.9 Hz, 1H), 4.01–4.05 (m, 2H), 4.58 (dd, *J*=11.8, 5.0 Hz, 3H), 4.78 (d, *J*=3.2 Hz, 1H), 7.23–7.33 (m, 10H). ^{13}C NMR ($CDCl_3$): *δ* 39.5, 60.0, 71.2, 71.3, 71.7, 83.0, 85.8, 86.6, 127.1, 127.7, 128.2, 128.4, 128.9, 137.5, 138.4. MS (APCI): *m/z* 340 (M^++1), 339. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.19; H, 7.53; N, 4.06.

4.4.9.1. Synthesis of (3*S*,6*S*,6a*S*,3a*R*)-dibenzyl-(6-benzyloxy-hexahydro-furo[3,2-*b*]furan-3-yl)methyl ammonium bromide (15). The procedure discussed in Section 4.4.3.1 was followed; **15** was obtained from **14** (1.0 g, 2.94 mmol) as white solid (1.30 g, 87%). Analytical sample was prepared by purification with preparative TLC. Mp 106–107 °C. $[\alpha]_D^{30}=-2.73$ (c, 0.62, MeOH). IR (KBr): *ν* 3025, 2922, 2863, 1491, 1469, 1454, 1369, 1340, 1211, 1163, 1084, 1023, 912, 875, 755, 703 cm^{-1}. ^1H NMR ($CDCl_3$): *δ* 3.14 (s, 3H), 3.81 (t, *J*=5.2 Hz, 1H), 3.86–3.90 (m, 2H), 4.01 (bs, 1H), 4.09 (dd, *J*=6.5, 5.4 Hz, 1H), 4.45

(d, J=11.7 Hz, 1H), 4.60 (d, J=11.7 Hz, 1H), 4.85–4.92 (m, 3H), 5.03 (dd, J=4.2, 3.9 Hz, 1H), 5.18 (d, J=12.8 Hz, 1H), 5.31 (d, J=12.8 Hz, 1H), 5.63 (d, J=4.5 Hz, 1H), 7.26–7.47 (m, 11H), 7.71 (t, J=7.8 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 47.0, 64.4, 67.1, 71.5, 71.8, 76.6, 81.8, 82.4, 87.2, 126.5, 126.6, 127.8, 128.3, 129.1, 130.7, 133.5, 133.7, 137.2. MS (APCI): m/z 430 (M^+-80), 356. Anal. Calcd for $C_{28}H_{32}BrNO_3$: C, 65.88; H, 6.32; N, 2.74. Found: C, 65.16; H, 6.83; N, 2.58.

4.4.10. Synthesis of (3*S*,3a*R*,6*R*,6a*R*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-ol (18). To an ice cooled (0 °C) suspension of sodium hydride (1.27 g, 52.9 mmol) in dry tetrahydrofuran (50 mL) under argon was added a solution of (3*S*,3a*R*,6*R*,6a*R*)-6-hydroxyhexahydrofuro[3,2-*b*]furan-3-yl acetate (10.0 g, 53.14 mmol) in tetrahydrofuran (40 mL) dropwise via an addition funnel over a period of 0.5 h. The reaction mixture was stirred at 25 °C for 3 h, followed by heating at 60 °C for 2 h. The reaction mixture was cooled to rt and 25% aqueous NaOH (8.5 mL) was added and continued stirring for 4 h. The reaction mixture was cooled externally by ice and the contents neutralized by adding 1 N HCl solution. Tetrahydrofuran was removed under reduced pressure and the residue diluted with water (30 mL) and CH_2Cl_2 (50 mL). The organic layer was separated and aqueous layer extracted with CH_2Cl_2 (3× 30 mL). The combined organic extract was washed with cold water (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel [hexane/ethyl acetate, 60:40 (v:v)] to afford **18** as white solid (9.41 g, 75%). Mp 59–61 °C (lit. mp 60–62 °C).[10] $[\alpha]_D^{25}$ & +97.92 (c 2.7 MeOH) [lit. $[\alpha]_D^{25}$ = +121.2 (c 0.53, $CHCl_3$)].[10] IR (KBr): ν 3447, 2959, 2939, 2892, 2878, 1499, 1371, 1327, 1208, 1134, 1110, 1081, 1065, 1020, 981, 890 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.71 (bs, 1H), 3.58 (t, J= 8.1 Hz, 1H), 3.83 (t, J=7.8 Hz, 1H), 3.89–4.05 (m, 3H), 4.26 (s, 1H), 4.38 (s, 1H), 4.54 (d, J=11.8 Hz, 1H), 4.67 (bs, 1H), 4.74 (d, J=11.8 Hz, 1H), 7.31 (m, 5H). MS (APCI): m/z (%) 236 (M+, 40), 180 (100).

4.4.11. Synthesis of (3*S*,3a*S*,6*R*,6a*R*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl-4-methylbenzenesulfonate (19). The procedure discussed in Section 4.2.1 was followed; **19** was obtained from **18** (8.0 g, 33.8 mmol) as white solid (11.10 g, 84%). Mp 84–85 °C (lit. mp 85 °C). $[\alpha]_D^{25}$ = +89.2 (c 1, EtOH) [lit. $[\alpha]_D^{25}$ = +95.1 (c 0.51, $CHCl_3$)].[10] IR (KBr): ν 3050, 2974, 2872, 1598, 1455, 1362, 1173, 1142, 1094, 980, 951 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H), 3.57 (t, J=7.9 Hz, 1H), 3.81 (dd, J=6.7, 2.1 Hz, 1H), 3.95–4.06 (m, 3H), 4.50–4.53 (m, 2H), 4.66 (t, J= 4.3 Hz, 1H), 4.72 (d, J=11.8 Hz, 1H), 4.87 (bs, 1H), 7.32 (m, 7H), 7.78 (d, J=8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.5, 70.4, 72.4, 73.1, 78.8, 80.4, 83.91 85.7, 127.7, 127.8, 127.8, 128.4, 129.9, 133.1, 137.4, 145.22. MS (APCI) m/z (%): 390 (M^+,100), 298 (90). Anal. Calcd for $C_{20}H_{22}O_6S$: C, 61.52; H, 5.68; S, 8.21 Found: C, 61.44; H, 7.19; S, 8.13.

4.4.12. Synthesis of *N*-benzyl-*N*-[(3*R*,3a*R*,6*R*,6a*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]amine (20). The procedure discussed in Section 4.3 was followed; **20** was obtained from **19** (1.5 g, 3.84 mmol) as white solid (0.812 g, 65%). Mp 59–60 °C. $[\alpha]_D^{30}$ = +128.79 (c 0.95). IR (KBr): ν 3325, 3029, 2941, 2871, 1495, 1454, 1367, 1309, 1136, 1083, 1027 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.09 (bs, 1H), 3.40 (dd, J=4.1, 2.5 Hz, 1H), 3.46 (dd, J=8.2, 2.0 Hz, 1H), 3.66 (t, J=8.4 Hz, 1H), 3.78 (d, J=12.8 Hz, 1H), 3.90 (d, J=7.8 Hz, 1H), 3.92 (d, J=9.6 Hz, 1H), 4.08 (dd, J=2.5, 4.9 Hz, 1H), 4.13 (t, J=7.5 Hz, 1H), 4.45 (t, J=4.1 Hz, 1H), 4.53–4.60 (m, 2H), 4.76 (d, J=11.9 Hz, 1H), 7.26–7.37 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 52.1, 61.8, 70.9, 72.2, 72.4, 79.6, 80.0, 80.9, 126.8, 127.6, 127.7, 127.9, 128.2, 137.6, 139.8. MS (APCI): m/z 327 (M^++2), 326. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.72; H, 7.19; N, 4.23.

4.4.13. Synthesis of *N*-benzyl-*N*-[(3*R*,3a*R*,6*R*,6a*S*)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-*N*-methylamine (21). The procedure discussed in Section 4.4 was followed; **21** was obtained from **20** (0.700 g, 2.15 mmol) as off-white solid (0.584 g, 80%). Mp 55–56 °C. $[\alpha]_D^{30}$ = +135.45 (c 0.44, MeOH). IR (KBr): ν 3065, 3025, 2979, 2948, 2879, 2792, 1497, 1452, 1402, 1342, 1296, 1223, 1132, 1085, 1064, 1022, 889 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.88 (d, J=3.9 Hz, 1H), 3.48 (d, J=13.1 Hz, 1H), 3.71–3.85 (m, 3H), 3.96 (t, J=8.3 Hz, 1H), 4.05 (d, J=2.8 Hz, 1H), 4.13 (t, J=5.9 Hz, 1H), 4.54 (d, J=2.3 Hz, 1H), 4.59 (m, 2H), 4.72 (d, J=11.9 Hz, 1H), 7.29–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 40.7, 60.8, 68.6, 71.1, 72.1, 72.2, 79.3, 81.0, 81.6, 127.0, 127.7, 128.0, 128.2, 129.3, 137.1, 137.6. MS (APCI): m/z (%) 341 (M^++2, 22), 340 (100). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.23; H, 7.36; N, 4.07.

4.4.13.1. Synthesis of (6a*S*,3*R*,3a*R*,6*R*)-dibenzyl-(6-benzyloxy-hexahydrofuro[3,2-*b*]furan-3-yl)methyl ammonium bromide (22). The procedure discussed in Section 4.4.3.1 was followed; **22** was obtained from **21** (0.500 g, 1.47 mmol) as a white solid (0.624 g, 83%). Analytical sample was prepared by purification with preparative TLC. Mp 99–100 °C. $[\alpha]_D^{30}$ = +66.64 (c 0.70, MeOH). IR (KBr): ν 3033, 2952, 2634, 1641, 1456, 1369, 1214, 1137, 1093, 1024, 919, 879 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.95 (t, J=7.8 Hz, 1H), 3.14 (s, 3H), 3.49 (t, J=9.2 Hz, 1H), 3.79–4.01 (m, 3H), 4.16 (d, J=5.2 Hz, 1H), 4.44 (d, J=5.2 Hz, 1H), 4.55–4.76 (m, 2H), 5.02 (d, J=12.2 Hz, 1H), 5.14 (s, 1H), 5.50 (bs, 1H), 5.80 (d, J=12.5 Hz, 1H), 6.14 (d, J=12.2 Hz, 1H), 7.28–7.51 (m, 11H), 7.65 (d, J= 6.8 Hz, 2H), 7.78 (d, J=6.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 44.3, 60.9, 65.2, 67.2, 68.3, 71.2, 72.4, 72.7, 78.5, 80.2, 81.5, 127.4, 127.9, 128.0, 128.1, 128.4, 128.9, 129.3, 129.6, 130.9, 131.1, 132.8, 133.8, 137.1. MS (APCI): m/z 430 (M^+-80), 356. Anal. Calcd for $C_{28}H_{32}BrNO_3$: C, 65.88; H, 6.32; N, 2.74. Found: C, 65.27; H, 6.93; N, 2.36.

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Synthesis of (±)-5′-methoxyhydnocarpin-D, an inhibitor of the *Staphylococcus aureus* multidrug resistance pump

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Abstract—The total synthesis of regioisomerically pure (±)-5′-methoxyhydnocarpin-D (**6**) from commercially available vanillin (**7**), methyl gallate (**9**) and 2′,4′,6′-trihydroxyaceophenone (**10**) is achieved.

1. Introduction

Multidrug resistance (MDR) remains a significant impediment to the successful chemotherapeutic treatment of bacterial infections and cancer.[1] This resistance is mainly attributed to the ubiquitous transmembrane efflux proteins that actively export a wide variety of structurally unrelated therapeutics from the cell, resulting in a low intracellular concentration of the drug. To date, many such efflux pump proteins have been identified and classified.[2] One of these well-characterized membrane proteins is the NorA efflux pump, which is found in bacteria *Staphylococcus aureus*[3] and employs the transmembrane electrochemical gradient of protons to drive the extrusion of drugs from the cell. The NorA pump in *S. aureus* also extrudes a broad spectrum of substrates from amphiphilic ethidium bromide to basic puromycin and neutral fluoroquinolone antibiotics. As MDR has already emerged in some bacteria in clinical settings, the identification and development of effective bacterial efflux pump inhibitors is needed. There are only a few known inhibitors of NorA MDR pump (Fig. 1). The first identified NorA MDR pump inhibitor was the alkaloid reserpine (**1**), which is toxic at high dosages.[4] Other modulators of NorA MDR pump have since been discovered including synthetic amide **2**, amino alcohol **3**, amide **4**, and naturally occurring phenylpiperidine **5**.[5]

Recently, Stermitz reported that a flavonolignan, namely (±)-5′-methoxyhydnocarpin-D (**6**), isolated from the plant *Berberis fremontii*, was a potent NorA MDR pump inhibitor.[6] In 2003, Pettit and Musumeci also reported the isolation of **6** from the plant *Hymeneae palustris* and *Berberis aetnensis*.[7] The naturally occurring **6** was optically inactive and has no antimicrobial activity by itself. It potentiates the growth inhibitory activity of the natural antibacterial alkaloid berberine and the commonly used fluoroquinolone antibiotics norfloxacin. Further structure activity relationships (SARs) studies also provided detailed structural requirements to the success of NorA efflux pump inhibition.[8] Recently, Guz reported a synthesis of regioisomeric mixture of racemic **6** by employing the silver ion

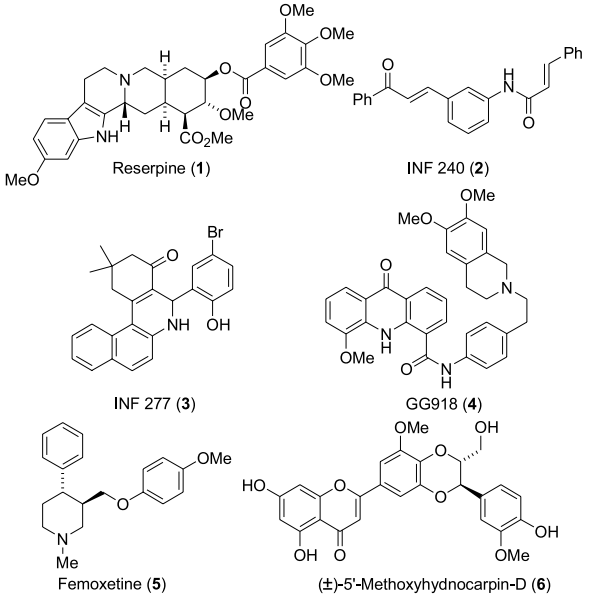

Figure 1.

Keywords: *Staphylococcus aureus*; Multidrug resistance; NorA; 5′-Methoxyhydnocarpin-D; Mitsunobu reaction.
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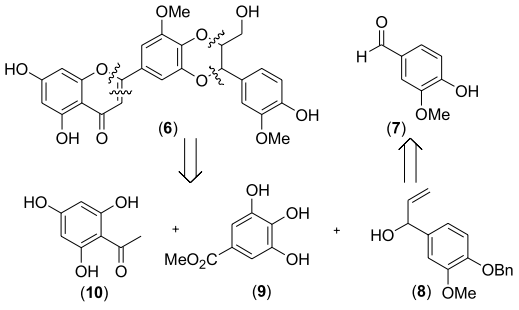
mediated coupling of selgin and coniferyl alcohol.[9] To the best of our knowledge, no report on the synthesis of regioisomerically pure **6** has appeared up to now in the literature. Although the exact binding site of NorA inhibitor remains unclear, it is believed that such inhibitors bind directly to the hydrophobic region of NorA efflux pump thus preventing the drug efflux.[10] Information from the binding studies of synthetic analogs will be useful in delineating the pharmacophore for the inhibition of NorA.[11] Herein we describe the regioselective total synthesis of **6**.

2. Results and discussion

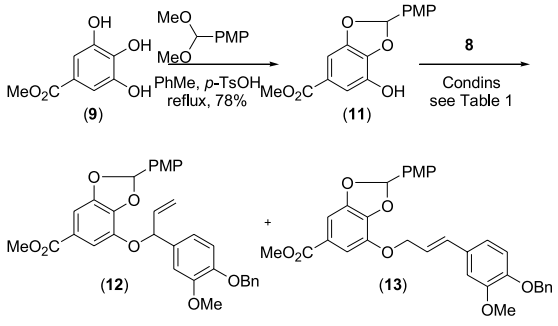
Our retrosynthetic approach to the total synthesis of **6** is to assemble the skeleton with synthons **8**, **9** and **10** as depicted in Scheme 1. The allyl alcohol **8** can in turn be derived from the commercially available vanillin (**7**) according to literature.[12] Then, stepwise assembly of the allyl alcohol **8** with methyl gallate (**9**) at the *meta*-position followed by cyclization at *para*-phenoxy moiety should furnish the 1,4-benzodioxane moiety of **6** with control of regiochemistry. This necessitates the selective protection of the hydroxyl groups in **9**. Final construction of the flavone core with 2′,4′,6′-trihydroxyacetophenone (**10**) should be easily achieved.



Scheme 1.

2.1. Regioselective connection of 8 and 9

With the requisite alcohol **8** in hand,[12] we embarked on the regioselective connection of **8** and **9** as shown in Scheme 2. Selective protection of the 3,4-dihydroxy function of methyl gallate (**9**) with either dichlorotoluene or acetone gave poor yield (<40%).[13] Instead, acid-catalyzed reaction of ester **9** with *p*-ansialdehyde dimethyl acetal (PMP: *p*-methoxyphenyl) in refluxing toluene furnished ester **11** in good yield (78%). The presence of electron-donating *p*-methoxy functionality in the acetal probably activated such transacetalization process.



Scheme 2.

Of the various methods available for the ether formation, the Mitsunobu reaction[14] is undoubtedly the reaction of choice. Initial attempts to synthesize the alkene **12** by reaction of ester **11** and allyl alcohol **8** under the standard protocol of using triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD) in THF were accomplished in low yield and low regioselectivity (Table 1, Entry 1). From proton NMR of the product mixture, the desired branched isomer **12** derived from S_N2 reaction showed a multiplet signal at 6.1 ppm and the linear isomer **13** derived from S_N2' showed a characteristic doublet of triplet at 6.3 ppm. Integrations of both proton signals revealed that the ratio of **12/13** was 3.8:1. Similar results were obtained when using toluene as solvent (Table 1, Entry 3). In both cases, removal of the highly soluble phosphine oxide from the reaction mixture was a tedious process. Improved regioselectivity was obtained by using dioxane as solvent with a ratio of **12/13** at 7.8:1, but the yield was still unacceptable at 38% (Table 1, Entry 2). The success of replacing PPh_3 by 1,2-bis(diphenylphosphino)ethane (dppe) for ease of products separation prompted us to use the diphosphine ligands for the Mitsunobu reaction.[15] Initial attempts to use bis(diphenylphosphino)methane (dppm) as phosphine source failed to improve the amount of alkene **12** (Table 1, Entry 4). Interestingly, high regioselectivity and reasonably good yield were finally achieved by using dppe (Table 1, Entry 5). Increasing the chain length by using 1,3-bis(diphenylphosphino)propane (dppp) had a similar result as dppe (Table 1, Entry 6). We also observed that those diphosphine oxides were insoluble in dioxane, therefore they could be removed by simple filtration through a short pad of silica gel.

Table 1. Mitsunobu reaction of compounds **8** and **11**

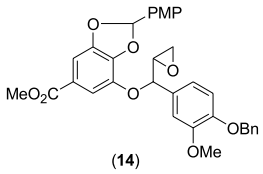
Entry	Conditions	**12**:**13**[a]	Yield (%)
1	DEAD, PPh_3, THF, 0 °C to rt	3.8:1	36
2	DEAD, PPh_3, Dioxane, 0 °C to rt	7.8:1	38
3	DEAD, PPh_3, PhMe, 0 °C to rt	4.3:1	44
4	DEAD, dppm, Dioxane, 0 °C to rt	2.6:1	52
5	DEAD, dppe, Dioxane, 0 °C to rt	17.5:1	48
6	DEAD, dppp, Dioxane, 0 °C to rt	13.7:1	55

[a] Determined from the purified product by NMR spectroscopy.

2.2. Construction of the 1,4-benzodioxane moiety

The construction of 1,4-benzodioxane moiety in a *trans* manner with control of regiochemistry presented a more difficult challenge. An extensive search of chemical literature yielded three examples: the first, described by Pan,[16] reported an intramolecular ring opening of a chiral oxirane. A second route, described by Buchwald,[17] reported a palladium-catalyzed intramolecular etherification of hydroxyl aryl halides. A third route, described by Valoti,[18] reported an intramolecular substitution of ditosylates. Since the Buchwald route requires an aryl halide,[19] we did not attempt that approach. For the Pan approach,[18] suffice it to say that we have prepared the epoxide **14**, but numerous

attempts to selectively remove the PMP protecting group invariably led to the opening of the epoxide first. We therefore turned our attention on the Valoti approach[20] proceeding from synthon **8**.



(**14**)

As outlined in Scheme 3, the successful reaction sequence for the construction of 1,4-benzodioxane moiety consisted in the following steps: (a) dihydroxylation of terminal alkene **12** using catalytic amount of Osmium tetroxide (OsO_4) and 4-methylmorpholine N-oxide (MNO) gave diol **15** in reasonably good yield as a mixture of diastereomers; (b) selective protection of the primary OH of **15** with pivaloyl chloride (PivCl) in pyridine at 0 °C furnished alcohol **16** in good yield; (c) tosylation of the secondary OH in **16** with tosyl chloride in pyridine gave the tosylate **17** in high yield; (d) acid-promoted cleavage of the acetal functionality of **17** without destroying the tosyl and pivaloyl moiety gave isomeric tosylates **18** and **19** in high yield in an isolated ratio of 1:1. The two tosylates were separable by chromatography and they showed the same number of proton and carbon signals in the NMR spectroscopy; (e) intramolecular nucleophilic substitution of tosylate **19** by the *para*-phenoxy moiety under basic conditions gave 1,4-benzodioxane **20**. The *trans* disposition of the two substituents on the dioxane ring in **20** was evident from the coupling constants of the hydrogens on the dioxane ring. Methylation of **20** with dimethyl sulfate under basic conditions followed by sequential deprotection of benzyl group of **21** and pivaloyl group of **22** furnished ester **23** in high yield. Interestingly, successful intramolecular nucleophilic substitution under basic conditions only proceeded with tosylate **19**, but not tosylate **18**. We attributed the difference to the fact that two bulky groups (OPiv and substituted benzene ring) were sufficiently far away from each other in tosylate **19** and the intramolecular substitution was not hindered (Fig. 2). An unidentified alkene byproduct was observed in the tosylate **18** cyclization reaction, presumably due to the tosylate group elimination. Finally, efforts to convert **18** to an iodide with the same stereochemistry as **19** have thus far not been successful.

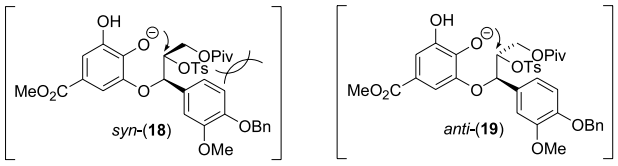
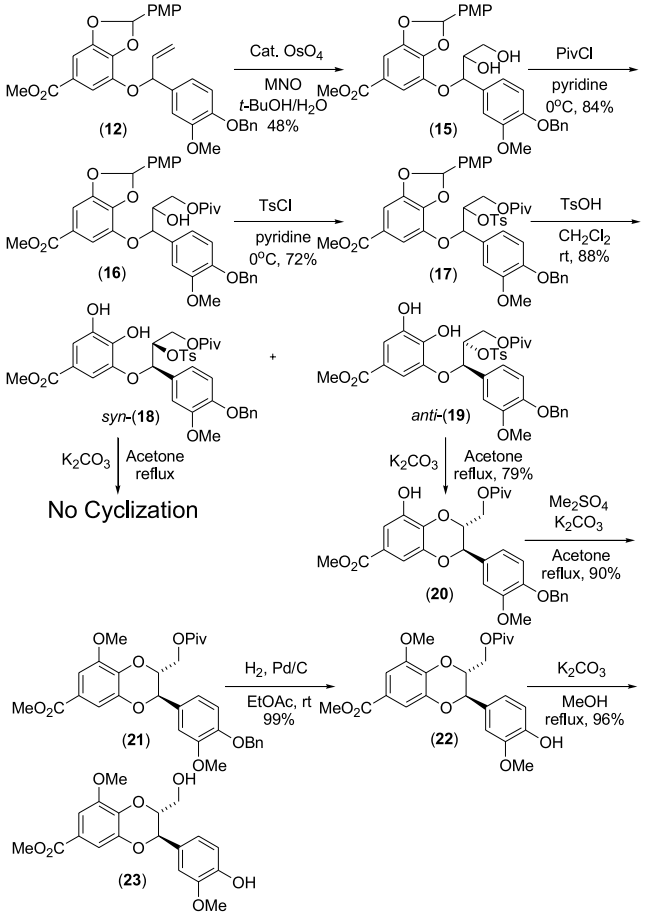


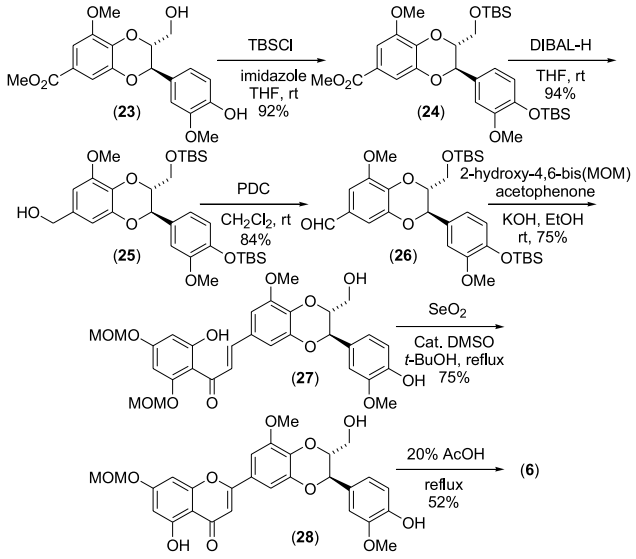
Figure 2.

2.3. Completion of synthesis of 5′-methoxyhydnocarpin-D

A number of synthetic routes are known for the preparation of flavones.[19] The most commonly used precursors were 2′-hydroxychalcones, which could be oxidatively cyclized to give flavones in high yield. As shown in Scheme 4, further protection of ester **23** with *tert*-butyldimethylsilyl chloride (TBSCl) gave disilyl ether **24**. The ester functionality of **24** was successfully converted to the corresponding aldehyde **26** in high yield by sequential diisobutylaluminium hydride (DIBAL-H) reduction in THF followed by pyridinium dichromate (PDC) oxidation. Attempts to synthesize



Scheme 3.



Scheme 4.

Table 2. Antibiotic activities of selected compounds against *Staphylococcus aureus* in the absence and presence of synthetic **6**

Drug	EC_{50} without addition of **6** (μg/mL)	EC_{50} with addition of 10 μg/mL **6** (μg/mL)	Activity potentiated
Norfloxacin	0.32	0.16	2-fold
Ethidium bromide	1.57	0.27	6-fold
Tetraphenyl-phosphonium	4.53	2.14	2-fold
Pentamidine	>64	5.3	>12-fold

aldehyde **26** by one step DIBAL-H reduction of ester **24** at lower temperature were unsuccessful. The dimethoxymethyl-protected acetophenone was prepared from 2′,4′,6′-trihydroxyacetophenone (**10**) according to the literature.[20] Then condensation of aldehyde **32** with acetophenone was accomplished in basic medium to give chalcone **27**, together with the cleavage of both silyl groups. It should be mentioned that cleavage of mono-silyl ether was observed when reaction time was insufficient. Selenium dioxide mediated cyclization of chalcone **27** in the presence of catalytic amount of dimethylsulfoxide (DMSO) followed by acetic acid deprotection of methoxymethyl (MOM) group of **28** furnished **6**. Initial attempts of deprotection of **28** using 6 M HCl resulted in polymerization of **6**. Its spectroscopic data were similar to those reported in the literature for 5′-methoxyhydnocarpin-D.[9]

2.4. Biological assays

We have tested the potencies of **6** in terms of its ability to potentiate a wide range of NorA substrates (norfloxacin, ethidium bromide, tetraphenylphosphonium and pentamidine) against *Staphylococcus aureus* using the Lewis's method.[6a] The results obtained are summarized in Table 2. In all cases, the synthetic **6** showed MDR modulating activity.

3. Conclusion

We have described the first regioselective total synthesis of (±)-5′-methoxyhydnocarpin-D (**6**) from commercially available vanillin (**7**), methyl gallate (**9**) and 2,4,6-trihydroxy-acetophenone (**10**). The key steps included the Mitsunobu reaction of **11** with **8** and the intramolecular substitution of tosylate **19** to give 1,4-benzodioxane moiety. The enantioselective synthesis of **6** is now in process.

4. Experimental

4.1. General

All NMR spectra were recorded on a Bruker MHz DPX400 spectrometer at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C. Low-resolution and high-resolution mass spectra were obtained on a HP 5989B Mass Spectro-meter by electron spray ionization mode at an ionizing voltage of 30 eV. Melting points were measured using Electrothermal IA9100 digital melting point apparatus and were uncorrected.

4.2. Materials

All reagents and solvents were reagent grade. Reagents were purchased from commercial suppliers and were used without further purification unless otherwise stated. Solvents were purified and dried using standard procedures when necessary. All organic solvents were evaporated under reduced pressure with a rotary evaporator. The plates used for thin-layer chromatography (TLC) were E. Merck Silica Gel $60F_{254}$ (0.25-mm thickness) precoated on an aluminum plate and they were visualized under short (254-nm) UV light. Compounds on TLC plate were visualized with a spray of 5% w/v dodecamolybdo-phosphoric acid in ethanol, or with acidified potassium permanganate solution, and with subsequent heating. Chromatographic purifications were carried out using MN silica gel 60 (230–400 mesh).

4.2.1. Methyl 7-hydroxy-2-(4-methoxyphenyl)-1,3-benzo-dioxole-5-carboxylate (11). To a round-bottom flask equipped with a Dean-Stark trap and water condenser was charged with methyl gallate (**9**) (3.7 g, 20 mmol), *p*-ansi-aldehyde dimethyl acetal (4.6 g, 25 mmol), *p*-toluene-sulfonic acid monohydrate (10 mg) and toluene (80 mL). The reaction mixture was then heated to reflux for 2 h. The solvent collected at the side arm of the Dean-Stark trap was continuously removed. When TLC indicated complete consumption of ester **9**, the reaction mixture was then cooled and diluted with CH_2Cl_2 (80 mL). The mixture was poured into a separating funnel containing saturated Na_2CO_3 solution (150 mL) and extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to 30 mL. After addition of *n*-hexane (100 mL), precipitation and filtration, the ester **11** (4.7 g, 78%) was obtained as an off-white solid: mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 3.86 (s, 3H), 6.93 (d, J=8.4 Hz, 2H), 6.96 (s, 1H), 7.13 (s, 1H), 7.38 (s, 1H), 7.47 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.3, 55.4, 102.9, 111.9, 114.1, 114.1, 124.1, 127.3, 128.0, 138.7, 138.9, 148.9, 161.3, 166.9; LRMS *m*/*z* 303 (M^++H, 100); HRMS Calcd for $C_{16}H_{15}O_6$ (M^++H) 303.0869, found 303.0843.

4.2.2. Methyl 7-[3-(3-methoxy-4-benzyloxyphenyl)prop-1-enyloxy]-2-(4-methoxyphenyl)-1,3-benzodioxole-5-carboxylate (12). To a well-stirred solution of ester **11** (0.27 g, 0.89 mmol), allyl alcohol **8** (0.30 g, 1.1 mmol) and 1,2-bis(diphenylphosphino)ethane (0.31 g, 0.78 mmol) in dioxane (10 mL) at 0 °C was added diethyl azodicarboxlate (0.3 mL, 1.9 mmol). The mixture was allowed to stir vigorously and warm slowly to room temperature over 16 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate was then poured into a separating funnel containing 0.5 M HCl (100 mL) and extracted with

CH_2Cl_2 (10 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered and evaporated to afford a brown oil, which was subjected to flash column chromatography (20% EtOAc in *n*-hexane) on silica gel (25 g) to afford a mixture of terminal alkene **12** (0.24 g, 48%) and internal alkene **13**. The pure alkene **12** for characterizations was obtained by further flash column chromatography as white foam: ^{1}H NMR ($CDCl_3$) δ 3.81–3.90 (m, 9H), 5.12 (s, 2H), 5.24 (d, J=10.4 Hz, 1H), 5.33 (dd, J=8.8, 16.8 Hz, 1H), 5.75 (d, J=6.0 Hz, 1H), 6.06–6.10 (m, 1H), 6.82–6.96 (m, 6H), 7.18 (s, 1H), 7.29–7.47 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 52.0, 55.3, 55.9, 55.9, 70.9, 82.3, 82.4, 103.9, 103.9, 110.4, 110.5, 111.7, 113.6, 113.7, 114.0, 115.2, 115.3, 119.4, 119.4, 124.0, 127.2, 127.5, 127.8, 128.1, 128.1, 128.5, 132.4, 137.0, 137.2, 137.3, 140.5, 140.5, 148.0, 149.1, 149.7, 161.3, 166.3; LRMS *m*/*z* 557 (M^++Na, 12); HRMS Calcd for $C_{33}H_{30}O_8Na$ (M^++Na) 577.1838, found 577.1822.

4.2.3. Methyl 7-[3-(3-methoxy-4-benzyloxyphenyl)-1,2-dihydroxypropyloxy]-2-(4-methoxyphenyl)-1,3-benzodioxole-5-carboxylate (15). To a round-bottomed flask was charged with *t*-BuOH (10 mL), water (10 mL) 4-methylmorpholine N-oxide monohydrate (0.54 g, 4 mmol) and alkene **12** (0.54 g, 1 mmol). Then catalytic amount of OsO_4 (0.1 mL, 2.5 wt% solution in *t*-BuOH) was added and the resulting mixture was stirred vigorously for 40 h. The mixture was then cooled to 0 °C and $Na_2S_2O_3$ (3 g) was added. The resulting mixture was allowed to warm to room temperature and was stirred for a further 1 h after which time the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (10 mL×3) and the combined organic layers were washed with water (100 mL). After drying over $MgSO_4$, filtration, and evaporation, a pale yellow oil was obtained, which was subjected to flash column chromatography on silica gel (10 g) with gradient elution (20–60% EtOAc in *n*-hexane) to afford diol **15** (0.28 g, 48%) as white foam: ^{1}H NMR ($CDCl_3$) δ 2.52–2.65 (m, 1H), 3.48–3.56 (m, 1H), 3.72–3.79 (m, 1H), 3.80 (s, 9H), 3.96–3.98 (m, 1H), 5.08 (s, 2H), 5.26–5.32 (m, 1H), 6.80–6.93 (m, 6H), 7.13 (s, 1H), 7.25–7.42 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 52.0, 55.3, 55.8, 55.9, 62.2, 62.8, 70.8, 74.3, 75.4, 76.7, 81.9, 82.2, 104.0, 104.1, 110.6, 111.8, 113.4, 114.0, 114.5, 114.8, 119.8, 119.9, 124.0, 127.2, 127.3, 127.8, 128.0, 128.0, 128.5, 129.6, 129.9, 136.8, 140.2, 140.3, 140.4, 140.4, 140.7, 148.3, 148.9, 148.9, 149.0, 149.6, 149.7, 161.3, 166.1; LRMS *m*/*z* 611 (M^++Na, 37); HRMS Calcd for $C_{33}H_{32}O_{10}Na$ (M^++Na) 611.1893, found 611.1909.

4.2.4. Methyl 7-[3-(3-methoxy-4-benzyloxyphenyl)-1-pivaloyloxy-2-hydroxypropyloxy]-2-(4-methoxyphenyl)-1,3-benzodioxole-5-carboxylate (16). Pivaloyl chloride (0.5 mL, 4.1 mmol) was added slowly to a stirred solution of diol **15** (1.21 g, 2.2 mmol) in anhydrous pyridine (15 mL) at 0 °C under N_2. The mixture was stirred for further 0.5 h. The reaction was quenched by addition of 1 M HCl (100 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL). After drying over $MgSO_4$, filtration and evaporation, a pale yellow oil was obtained, which was subjected to flash column chromatography on silica gel (20 g) with gradient elution (10–30% EtOAc in *n*-hexane) to afford alcohol **16** (1.23 g, 84%) as white foam: ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 2.49 (br, 1H), 3.67–3.85 (m, 10H), 4.16–4.19 (m, 1H), 4.31 (dd, J=4.8, 10.2 Hz, 1H), 5.09 (s, 2H), 5.27–5.32 (m, 1H), 6.90–6.94 (m, 6H), 7.14 (s, 1H), 7.26–7.42 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 26.9, 27.0, 38.7, 52.0, 55.2, 55.7, 55.8, 64.7, 70.8, 72.6, 72.6, 73.3, 81.9, 104.0, 104.1, 111.7, 111.8, 113.4, 113.5, 113.9, 115.1, 120.0, 124.1, 127.2, 127.3, 127.8, 128.0, 128.0, 128.4, 129.3, 129.4, 136.8, 136.8, 140.1, 140.8, 149.0, 149.1, 149.6, 149.7, 161.3, 166.0, 178.6; LRMS *m*/*z* 695 (M^++Na, 20); HRMS Calcd for $C_{38}H_{40}O_{11}Na$ (M^++Na) 695.2468, found 695.2520.

4.2.5. Methyl 7-[3-(3-methoxy-4-benzyloxyphenyl)-1-pivaloyloxy-2-tosyloxypropyloxy]-2-(4-methoxyphenyl)-1,3-benzodioxole-5-carboxylate (17). *p*-Toluenesulfonyl chloride (0.90 g, 4.7 mmol) was added to a stirred solution of alcohol **16** (1.23 g, 1.8 mmol) in anhydrous pyridine (6 mL) at room temperature. The mixture was stirred for further 16 h. The reaction was quenched by addition of 1 M HCl (100 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL). After drying over $MgSO_4$, filtration and evaporation, a pale yellow oil was obtained, which was subjected to flash column chromatography on silica gel (20 g) with gradient elution (10–30% EtOAc in *n*-hexane) to afford tosylate **17** (1.06 g, 72%) as white foam: ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 9H), 2.34 (s, 3H), 3.64–3.85 (m, 9H), 3.69–3.97 (m, 1H), 4.31–4.52 (m, 1H), 5.00–5.08 (m, 3H), 5.41–5.49 (m, 1H), 6.96–7.53 (m, 19H); ^{13}C NMR ($CDCl_3$) δ 21.4, 26.9, 38.6, 38.6, 51.9, 55.2, 55.3, 55.6, 70.6, 70.6, 80.5, 80.6, 95.5, 111.8, 113.9, 113.9, 124.0, 127.0, 127.1, 127.1, 127.5, 127.5, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0, 128.4, 128.4, 129.3, 129.4, 136.6, 136.7, 140.5, 144.5, 149.0, 161.2, 165.8, 165.8; LRMS *m*/*z* 849 (M^++Na, 13); HRMS Calcd for $C_{45}H_{46}O_{13}NaS$ (M^++Na) 849.2557, found 849.2606.

4.2.6. *syn*-methyl 3,4-dihydroxy-5-[3-(3-methoxy-4-benzyloxy-phenyl)-1-pivaloyloxy-2-tosyloxypropyloxy]-benzoate (18) and *anti*-methyl 3,4-dihydroxy-5-[3-(3-methoxy-4-benzyloxyphenyl)-1-pivaloyloxy-2-tosyloxy-propyloxy]-benzoate (19). *p*-Toluenesulfonic acid monohydrate (0.70 g, 3.7 mmol) was added to a stirred solution of tosylate **17** (1.06 g, 1.3 mmol) in CH_2Cl_2 (20 mL) at room temperature. The mixture was stirred for further 1 h. The reaction was quenched by addition of saturated $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to furnish pale brown oil, which was subjected to flash column chromatography on silica gel (25 g) with gradient elution (20–50% EtOAc in *n*-hexane) to afford the diastereomeric tosylates. Less polar tosylate *syn*-**18** (0.38 g, 42%) as white foam: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H), 2.42 (s, 3H), 3.64 (dd, J=3.2, 12.8 Hz, 1H), 3.76 (s, 3H), 3.87 (s, 3H), 4.35 (dd, J=2.0, 12.8 Hz, 1H), 5.12–5.18 (m, 4H), 6.91 (m, 4H), 7.27–7.80 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.6, 27.0, 38.8, 51.9, 56.1, 61.6, 70.9, 80.1, 80.5, 107.6, 109.7, 111.1, 114.0, 119.5, 121.2, 127.3, 127.7, 127.8, 128.0, 128.6, 129.8, 132.8, 136.6, 137.9, 144.2, 144.8, 145.5, 149.2, 150.3, 166.6, 177.7; LRMS *m*/*z* 731 (M^++Na, 9); HRMS Calcd for $C_{37}H_{40}O_{12}NaS$ (M^++Na) 731.2138, found 731.2183. More polar tosylate *anti*-**19**

(0.42 g, 46%) was isolated as white foam: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 9H), 2.41 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.90 (dd, J=7.6, 12.4 Hz, 1H), 4.23 (dd, J=4.0, 12.0 Hz, 1H), 5.07 (s, 2H), 5.31 (d, J=3.6 Hz, 1H), 5.42–5.46 (m, 1H), 6.79–6.96 (m, 4H), 7.26–7.41 (m, 8H), 7.74 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.6, 27.0, 38.7, 51.9, 55.7, 62.1, 70.8, 78.2, 80.2, 107.7, 110.5, 111.2, 113.2, 120.1, 121.1, 126.3, 127.2, 127.4, 127.9, 128.5, 129.8, 133.4, 136.7, 138.3, 143.6, 144.2, 145.3, 148.8, 149.7, 166.6, 178.0; LRMS m/z 731 (M^++Na, 28); HRMS Calcd for $C_{37}H_{40}O_{12}NaS$ (M^++Na) 731.2138, found 731.2114.

4.2.7. *trans*-methyl 2-pivaloyloxymethyl-8-hydroxy-3-(3-methoxy-4-benzyloxyphenyl)-2,3-dihydrobenzo[1,4]-dioxane-6-carboxylate (20). To a round-bottom flask was charged with tosylate **19** (0.42 g, 0.59 mmol), K_2CO_3 (0.16 g, 1.2 mmol) and acetone (50 mL). The reaction mixture was then heated to reflux for 2 h. When TLC indicated complete consumption of tosylate **19**, the reaction mixture was cooled and filtered through a short pad of silica gel. The solvent was evaporated and the resulting residue was subjected to flash column chromatography on silica gel (20 g) with gradient elution (10–30% EtOAc in *n*-hexane) to afford ester **20** (0.25 g, 79%) as white foam: ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9H), 3.84 (s, 3H), 3.87–3.91 (m, 1H), 3.89 (s, 3H), 4.27–4.30 (m, 1H), 4.52 (dd, J=2.4, 12.4 Hz, 1H), 4.91 (d, J=8.4 Hz, 1H), 5.16 (s, 2H), 6.25 (br, 1H), 6.89–6.92 (m, 3H), 7.26–7.30 (m, 3H), 7.34–7.38 (m, 2H), 7.42–7.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.0, 38.8, 52.0, 56.0, 62.0, 70.8, 76.3, 76.6, 109.7, 110.4, 110.6, 113.7, 119.9, 122.9, 127.1, 127.8, 128.5, 135.0, 136.6, 143.5, 144.9, 149.0, 149.9, 166.5; LRMS m/z 559 (M^++Na, 49); HRMS Calcd for $C_{30}H_{32}O_9Na$ (M^++Na) 559.1944, found 559.1970.

4.2.8. *trans*-methyl 2-pivaloyloxymethyl-8-methoxy-3-(3-methoxy-4-benzyloxyphenyl)-2,3-dihydrobenzo[1,4]-dioxane-6-carboxylate (21). To a round-bottom flask was charged with ester **20** (0.25 g, 0.47 mmol), K_2CO_3 (0.12 g, 0.87 mmol), dimethyl sulfate (0.15 g, 5.8 mmol) and acetone (50 mL). The reaction mixture was then heated to reflux for 2 h. When TLC indicated complete consumption of ester **20**, the reaction mixture was cooled and filtered through a short pad of silica gel. The solvent was washed with 0.5 M NaOH solution and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were evaporated and the residue was subjected to flash column chromatography (15 g) with gradient elution (10–20% EtOAc in *n*-hexane) to afford product **21** (0.23 g, 90%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H), 3.86 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 4.01 (dd, J=4.0, 12.0 Hz, 1H), 4.29–4.31 (m, 1H), 4.38 (dd, J=3.2, 12.4 Hz, 1H), 4.90 (d, J=8.0 Hz, 1H), 5.16 (s, 2H), 6.87–6.90 (m, 3H), 7.24–7.44 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 27.0, 38.7, 52.0, 55.9, 56.2, 62.4, 70.7, 75.8, 76.1, 105.7, 110.3, 111.9, 113.6, 119.8, 122.2, 127.1, 127.8, 128.1, 128.4, 136.6, 136.9, 143.6, 148.5, 148.8, 149.8, 166.4, 177.6; LRMS m/z 573 (M^++Na, 54); HRMS Calcd for $C_{31}H_{34}O_9Na$ (M^++Na) 573.2101, found 573.2054.

4.2.9. *trans*-methyl 2-pivaloyloxymethyl-8-methoxy-3-(3-methoxy-4-hydroxyphenyl)-2,3-dihydrobenzo[1,4]-dioxane-6-carboxylate (22). To a round-bottom flask was charged with ester **21** (0.23 g, 0.42 mmol), 5% palladium on activated carbon (15 mg) and EtOAc (20 mL). The reaction mixture was then subjected to a H_2 atmosphere at balloon pressure and stirred for 14 h. When TLC indicated complete consumption of ester **21**, the reaction mixture was filtered through and the solvent was evaporated. The resulted residue was subjected to flash column chromatography (15 g) with gradient elution (10–30% EtOAc in *n*-hexane) to afford ester **22** (0.19 g, 99%) as white foam: ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9H), 3.84 (s, 6H), 3.88 (s, 3H), 3.99 (dd, J=3.6, 12.4 Hz, 1H), 4.28 (dd, J=3.6, 7.0 Hz, 1H), 4.36 (dd, J=2.4, 12.2 Hz, 1H), 4.62 (d, J=8.0 Hz, 1H), 6.03 (s, 1H), 6.83–6.92 (m, 3H), 7.21 (s, 1H), 7.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.0, 38.7, 52.0, 55.8, 56.2, 62.5, 75.9, 76.2, 105.8, 109.4, 111.9, 114.7, 120.6, 122.2, 127.0, 137.0, 143.6, 146.5, 146.9, 148.5, 166.5, 177.7; LRMS m/z 483 (M^++Na, 100); HRMS Calcd for $C_{24}H_{28}O_9Na$ (M^++Na) 483.1631, found 483.1632.

4.2.10. *trans*-methyl 2-hydroxymethyl-8-methoxy-3-(3-methoxy-4-hydroxyphenyl)-2,3-dihydrobenzo[1,4]-dioxane-6-carboxylate (23). To a round-bottom flask was charged with ester **22** (0.14 g, 0.30 mmol), K_2CO_3 (0.12 g, 0.87 mmol) and methanol (20 mL). The reaction mixture was then heated to reflux for 2 h. When TLC indicated complete consumption of ester **22**, the reaction mixture was then cooled and neutralized with 1 M HCl solution and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and evaporate to furnish a colorless oil, which was subjected to flash column chromatography on silica gel (15 g) with gradient elution (20–40% EtOAc in *n*-hexane) to afford ester **23** (0.11 g, 96%) as white solid: mp 138–140 °C; ^{1}H NMR ($CDCl_3$) δ 3.02 (br, 1H), 3.57 (br, 1H), 3.86 (s, 6H), 3.87–3.89 (m, 2H), 3.91 (s, 3H), 4.02–4.05 (m, 1H), 4.94 (d, J=8.0 Hz, 1H), 6.03 (br, 1H), 6.90–6.92 (m, 3H), 7.22 (d, J=1.2 Hz, 1H), 7.35 (d, J=1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 52.1, 55.9, 56.1, 61.2, 75.9, 78.9, 105.3, 109.6, 112.2, 114.7, 120.6, 122.1, 127.5, 137.1, 143.8, 146.3, 146.9, 148.3, 166.6; LRMS m/z 399 (M^++Na, 49); HRMS Calcd for $C_{19}H_{20}O_8Na$ (M^++Na) 399.1056, found 399.1054.

4.2.11. *trans*-methyl 2-*tert*-butyldimethylsilyloxymethyl-8-methoxy-3-(3-methoxy-4-*tert*-butyldimethylsilyloxyphenyl)-2,3-dihydrobenzo[1,4]dioxane-6-carboxylate (24). To a round-bottom flask was charged with ester **23** (0.14 g, 0.37 mmol), imidazole (76 mg, 1.12 mmol) and anhydrous THF (20 mL). *tert*-butyldimethylsilyl chloride (TBSCl) (0.11 g, 0.73 mmol) was added in one portion and the reaction mixture immediately became milky. When TLC indicated complete consumption of ester **23** (typically 2 h), the reaction mixture was quenched by washing with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over $MgSO_4$, evaporated. The resulting residue was subjected to flash column chromatography on silica gel (15 g) with elution (5% EtOAc in *n*-hexane) to afford ester **24** (0.21 g, 93%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.15 (s, 6H), 0.88 (s, 9H), 0.99 (s, 9H), 3.58 (dd, J=2.4, 11.8 Hz, 1H), 3.80 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 3.94 (dd, J=2.4, 12.0 Hz, 1H), 4.03–4.05 (m, 1H), 4.99 (d, J=8.0 Hz, 1H), 6.85–6.93 (m, 3H), 7.23 (d, J=1.6 Hz, 1H), 7.36 (d, J=1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.7, −5.4,

−4.7, −4.7, 18.2, 18.3, 25.6, 25.6, 25.7, 51.9, 55.3, 56.2, 62.0, 75.7, 78.8, 105.7, 111.1, 112.1, 119.9, 120.9, 121.7, 129.5, 137.7, 143.7, 145.4, 148.6, 151.0, 166.7; LRMS *m/z* 627 (M^++Na, 100); HRMS Calcd for $C_{31}H_{48}O_8NaSi_2$ (M^++Na) 627.2785, found 627.2796.

4.2.12. *trans*-2-*tert*-butyldimethylsilyloxymethyl-8-methoxy-3-(3-methoxy-4-*tert*-butyldimethylsilyloxy-phenyl)-2,3-dihydrobenzo[1,4]dioxane-6-methanol (25). To a well-stirred solution of ester **24** (0.20 g, 0.33 mmol) in anhydrous THF (10 mL) at 0 °C under N_2 atmosphere was added diisobutylaluminum hydride (DIBAL-H) (1 M in hexane, 0.8 mL, 0.8 mmol). The mixture was stirred for further 15 minutes at 0 °C and at room temperature for 2 h. The reaction was quenched by addition of Et_2O (50 mL), H_2O (1 mL) and 2 M NaOH (2 mL) until a heavily white precipitate was formed. The precipitate was removed by filtration and the filtrate was washed with saturated NH_4Cl solution, separated and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave alcohol **25** (0.18 g, 94%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.16 (s, 6H), 0.88 (s, 9H), 0.98 (s, 9H), 2.15 (br, 1H), 3.56 (dd, J=2.8, 11.6 Hz, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 3.92 (dd, J=2.4, 11.8 Hz, 1H), 3.96–3.99 (m, 1H), 4.53 (s, 2H), 4.98 (d, J=7.6 Hz, 1H), 6.56 (s, 1H), 6.60 (s, 1H), 6.85–6.93 (m, 3H); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.3, −4.7, 18.2, 18.4, 25.6, 25.8, 55.3, 56.2, 62.2, 65.2, 75.8, 78.3, 103.6, 108.5, 111.2, 120.0, 120.8, 130.0, 132.8, 132.9, 144.1, 145.3, 148.9, 150.9; LRMS *m/z* 599 (M^++Na, 100); HRMS Calcd for $C_{30}H_{48}O_7NaSi_2$ (M^++Na) 599.2836, found 599.2814.

4.2.13. *trans*-2-*tert*-butyldimethylsilyloxymethyl-8-methoxy-3-(3-methoxy-4-*tert*-butyldimethylsilyloxy-phenyl)-2,3-dihydrobenzo[1,4]dioxane-6-carbaldehyde (26). To a well-stirred mixture of pyridinium dichromate (PDC) (0.16 g, 0.43 mmol) and 4 Å powdered molecular sieves (1 g) in anhydrous CH_2Cl_2 (20 mL) at room temperature, was added alcohol **25** (0.12 g, 0.21 mmol) dissolved in CH_2Cl_2 (10 mL). The resulting mixture darkened immediately and was stirred under N_2 atmosphere for 12 h. The resulting dark brown mixture was filtered through a short pad of silica gel and the filter cake was washed with EtOAc (50 mL). The pale brown filtrate was evaporated and the residue was chromatographed on silica gel (20 g, 15% EtOAc in *n*-hexane) to afford aldehyde **26** (0.1 g, 84%) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.16 (s, 6H), 0.88 (s, 9H), 0.98 (s, 9H), 3.59 (dd, J=2.4, 12.0 Hz, 1H), 3.81 (s, 3H), 3.93 (s, 3H), 3.96 (dd, J=2.4, 12.2 Hz, 1H), 4.06–4.08 (m, 1H), 5.00 (d, J=7.6 Hz, 1H), 6.87–6.93 (m, 3H), 7.10 (d, J=1.6 Hz, 1H), 7.13 (d, J=1.6 Hz, 1H), 9.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.4, −4.7, 18.2, 18.4, 25.6, 25.8, 55.4, 56.2, 61.9, 75.8, 79.0, 103.3, 111.1, 114.5, 120.0, 121.0, 128.9, 129.2, 139.3, 144.3, 145.6, 149.6, 151.1, 190.8; LRMS *m/z* 597 (M^++Na, 100); HRMS Calcd for $C_{30}H_{46}O_7NaSi_2$ (M^++Na) 597.2680, found 597.2674.

4.2.14. *trans*-3-[2-hydroxymethyl-8-methoxy-3-(3-methoxy-4-hydroxyphenyl)-2,3-dihydrobenzo[1,4]-dioxin-6-yl]-1-[2-hydroxy-4,6-bis(methoxymethoxy)phenyl]propenone (27). To a round-bottom flask was charged with aldehyde **26** (0.11 g, 0.19 mmol), 2-hydroxy-4,6-bis-(methoxymethoxy)-acetophenone (86 mg, 0.34 mmol) and ethanol (5 mL). 2 M KOH solution in ethanol (10 mL) was added at once and the reaction mixture turned yellow immediately and was stirred for 24 h at room temperature. When TLC indicated complete consumption of aldehyde **26**, water (100 mL) was added. The resulting mixture was extracted with EtOAc (10 mL×3). The combined organic layers were dried over $MgSO_4$, evaporated and subjected to flash column chromatography on silica gel (15 g) with elution (20% EtOAc in *n*-hexane) to afford chalcone **27** (84 mg, 75%) as yellow foam: ^{1}H NMR ($CDCl_3$) δ 2.77 (br, 1H), 3.47 (s, 3H), 3.51 (s, 3H), 3.52–3.53 (m, 1H), 3.87–3.90 (m, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 4.04–4.08 (m, 1H), 4.96 (d, J=8.4 Hz, 1H), 5.17 (s, 2H), 5.26 (s, 2H), 5.97 (s, 1H), 6.21 (d, J=2.0 Hz, 1H), 6.30 (d, J=2.0 Hz, 1H), 6.78 (d, J=1.6 Hz, 1H), 6.91–6.95 (m, 4H), 7.67 (d, J=15.6 Hz, 1H), 7.79 (d, J=15.2 Hz, 1H), 13.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.4, 56.9, 61.3, 76.1, 78.8, 94.0, 94.7, 95.1, 97.4, 104.4, 107.4, 109.6, 110.4, 114.7, 120.7, 125.8, 127.6, 128.0, 135.1, 142.7, 144.5, 146.4, 146.9, 148.8, 159.7, 163.3, 167.2, 192.6; LRMS *m/z* 585 (M^++H, 35), HRMS Calcd for $C_{30}H_{33}O_{12}$ (M^++H) 585.5093, found 585.5085.

4.2.15. *trans*-5-hydroxy-2-(2-hydroxymethyl-8-methoxy-3-(3-methoxy-4-hydroxyphenyl)-2,3-dihydrobenzo[1,4]-dioxin-6-yl)-7-methoxymethoxychromen-4-one (28). To a round-bottom flask was charged with chalcone **27** (70 mg, 0.12 mmol), selenium dioxide (53 mg, 0.48 mmol), three drops of DMSO and *t*-butanol (10 mL). The reaction mixture was heated to reflux for 48 h until ^{1}H NMR indicated complete consumption of chalcone **27**. If the reaction did not complete, additional portions of selenium dioxide and DMSO were added. The reaction mixture was then quenched by adding water (100 mL) and the aqueous layer was then extracted with EtOAc (10 mL×3). The combined organic layers were dried over $MgSO_4$, evaporated to afford chromenone **28** (46 mg, 75%) as yellow foam; ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 3.56–3.59 (m, 1H), 3.90 (s, 3H), 3.94 (s, 3H), 4.06–4.11 (m, 1H), 4.98 (d, J=8.4 Hz, 1H), 5.22 (s, 2H), 6.54 (s, 1H), 6.60 (s, 1H), 6.63 (s, 1H), 6.87–6.95 (m, 3H), 7.21 (s, 1H), 12.60 (br, 1H); LRMS *m/z* 539 (M^++H, 100); HRMS Calcd for $C_{28}H_{27}O_{11}$ (M^++H) 539.1553, found 539.1547.

4.2.16. (±)-5′-Methoxyhydnocarpin-D (6). To a 50 mL round-bottom flask was charged with chromenone **28** (40 mg, 0.07 mmol) and 20% AcOH in H_2O. The reaction mixture was heated to reflux for 1 h. The reaction mixture was then quenched by neutralizing with saturated $NaHCO_3$ solution and the aqueous layer was then extracted with EtOAc (10 mL×3). The obtained organic layer was dried over $MgSO_4$, evaporated to afford **6** (19 mg, 52%) as yellow solid. The pure sample was obtained by by washing the yellow solid with boiling chloroform: mp 210 °C (decomp.); ^{1}H NMR (d_6-DMSO) δ 3.51–5.44 (m, 1H), 3.82–3.86 (m, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.17–4.19 (m, 1H), 5.04 (d, J=8.0 Hz, 1H), 6.23 (d, J=1.6 Hz, 1H), 6.55 (s, 1H), 6.71 (s, 1H), 6.89 (d, J=8.0 Hz, 1H), 6.98–7.00 (m, 1H), 7.14 (d, J=4.4 Hz, 1H), 7.25 (s, 2H), 9.77 (br, 1H), 12.90 (s, 1H); ^{13}C NMR (d_6-DMSO) δ 56.1, 56.5, 60.3, 76.2, 78.7, 94.6, 99.3, 103.2, 104.2, 104.5, 108.5, 112.2, 115.7, 121.0, 122.7, 127.5, 137.0, 144.6, 147.5, 148.0, 149.5, 157.8, 161.8, 163.4, 164.6, 182.2; LRMS *m/z* 495 (M^++H, 100); HRMS Calcd for $C_{26}H_{23}O_{10}$ (M^++H) 495.1291, found 495.1327.

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Studies on *t*-BuOK-catalyzed Michael addition of 1,2-allenic ketones with 2-substituted diethyl malonates: highly selective synthesis of β,γ-unsaturated enones

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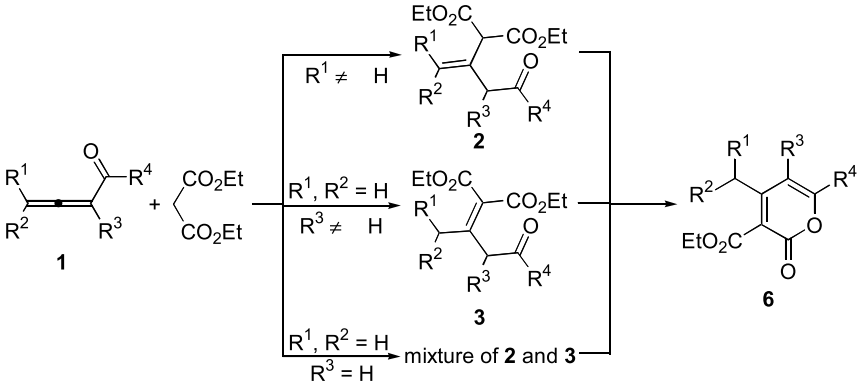
Abstract—In this paper, we have demonstrated a facile nucleophilic addition of 2-substituted diethyl malonate to various substituted 1,2-allenic ketones to afford β,γ-unsaturated enones using a catalytic amount of *t*-BuOK as the base. The reaction usually completes within 10 min in acetone at room temperature. The stereoselectivity of the reaction with γ-substituted allenic ketones is very high affording the β,γ-unsaturated *E*-enones.

1. Introduction

The Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds is an important reaction in organic synthesis,[1] as the product obtained are valuable building blocks in organic chemistry.[2] 1,2-Allenic ketones can be viewed as methylene-substituted α,β-unsaturated carbonyl compounds which constituted of two mutually vertical π-systems (π^2–π^4) rather than a plannar conjugated π-system + (π^6).[3] The attractive feature of these compounds confers on them an otherwise unattainable chemical reactivity and regioselectivity in organic synthesis.[4] β,γ-unsaturated enones can be found in some natural products[5] and are important intermediate in organic synthesis. Instead of β,γ-unsaturated enones, the Michael reaction to 1,2-allenyl ketones usually gives α,β-unsaturated enones.[6] In our previous work, we have demonstrated that diethyl malonate with various substituted 1,2-allenic ketones afforded β,γ-unsaturated enones **2** or **3** or their mixtures depending on where the substituents located (Scheme 1).[7] In our continuous effort for the synthesis of β,γ-unsaturated enones,[8] we propose that we may



Scheme 1.

Keywords: Michael addition; 1,2-Allenic ketones; β,γ-Unsaturated enone; Catalysis.
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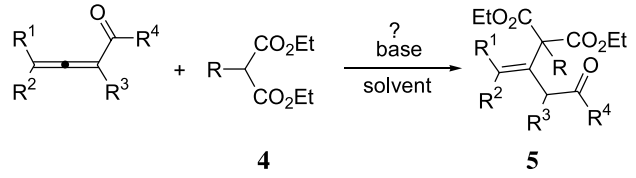
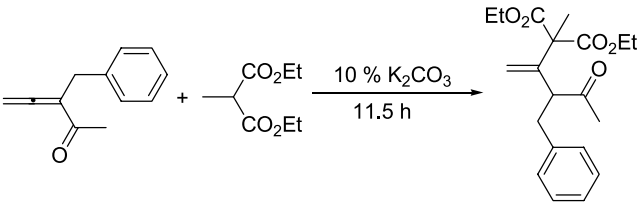
exclusively get the β,γ-unsaturated enones **5** if a substitutent was introduced at the 2-position of diethyl malonate, which blocks the migration of carbon–carbon double bond to form **3**-type product (Scheme 2). However, the reaction of 3-benzyl-3,4-penten-2-one **1a** with 2-methyl malonate under the standard reaction condition we used in Ref. 7 was slow (Scheme 3). In this paper, we would like to disclose a general and highly efficient method for the synthesis of β,γ-unsaturated enones from the reaction of 1,2-allenic ketones and 2-substituted diethyl malonate.



4 **5**

Scheme 2.



1a **4a** **5aa**

solvent	Temp.	yield of **5aa**(%)
acetone	reflux	44[a]
DMF	80°C	27
EtOH	80°C	9

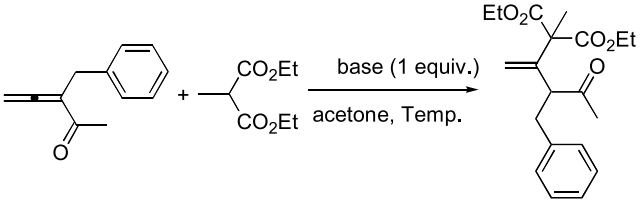
[a] 30% of **1a** was recovered

Scheme 3.

The Michael addition of 2-methyl diethyl malonate **4a** to 1,2-allenic ketone **1a** in different solvent under various base was investigated. The effect of solvents for the reaction was briefly investigated. Among the solvents tested (acetone, DMF, and EtOH), acetone gave the best yield (44%) (Scheme 3). Further studies showed that the yield was improved substantially when the reaction was carried out with 1 equiv of K_2CO_3 affording **5aa** in 75% yield (Table 1, entry 1). The base also affected the reaction greatly. For organic bases, such as NEt_3, pyridine and DABCO, no products were formed (Table 1, entries 2–4); the product **5aa** was obtained in low yields when NaOAc or NaOEt was used as the base (Table 1, entries 5–6); when strong base such as NaOH was used, **5aa** was formed in a moderate yield (Table 1, entry 7); However, the Cs_2CO_3-promoted Michael addition of **4a** to **1a** proceeded to yield **5aa** in 78% yield (Table 1, entry 8); the reaction also proceeded well in the presence of DBU producing **5aa** in the yield of 80% at room temperature in 10 min (Table 1, entry 9); It is interesting to find that with 10 mol% of *t*-BuOK the Michael addition of **1a** and **4a** was complete within 10 min to afford the product **5aa** in 82% yield (Table 1, entry 10). Thus, in following cases the reaction was conducted at room temperature in acetone using 10% *t*-BuOK as the catalyst.

The potential and scope of the *t*-BuOK (10 mol%)-catalyzed Michael addition is demonstrated by the reaction of 1,2-allenic ketones **1a–g** with 2-substituted diethyl malonate **4a–c**. The results are presented in Table 2. In a similar way, 2-allyl diethyl malonate **4b** and 2-benzyl diethyl malonate **4c** reacts with **1a** in the presence of 10% *t*-BuOK to afford the β,γ-unsaturated enones **5ab** and **5ac** in 85 and 81% yield, respectively (Table 2, entries 1 and 2). The Michael addition also proceeded smoothly with α-allyl-1,2-allenic ketone **1b** to give products **5ba**, **5bb** and **5bc** in 83, 78 and 76% yield, respectively (Table 2, entries 3–5). The reaction of **1c** with **4a** in the presence of 100 mol% *t*-BuOK in acetone instead of the standard 10 mol% *t*-BuOK

Table 1. Base-catalyzed michael addition of 2-benzyl-1,2-propadienyl methyl ketone **1a** with **4a**

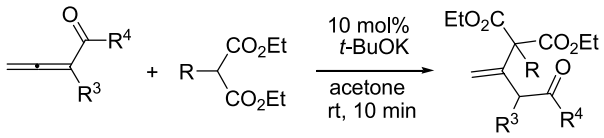


1a **4a** **5aa**

Entry	Base	Time	Temperature	Yield of **5aa** (%)
1	K_2CO_3	11.5 h	Reflux	75
2	NEt_3	12 h	Reflux	NR
3	Pyridine	12 h	Reflux	NR
4	DABCO	12 h	Reflux	NR
5	NaOAc	12.5 h	Reflux	5[a]
6	NaOEt	12.5 h	Reflux	4[b]
7	NaOH	12.5 h	Reflux	52
8	Cs_2CO_3	1 h	Reflux	78
9	DBU	10 min	rt	80
10	10% *t*-BuOK	10 min	rt	82

[a] 53% of **1a** was recovered.
[b] 49% of **1a** was recovered.

Table 2. *t*-BuOK-catalyzed michael addition of 1,2-allenic ketones with 2-substituted diethyl malonates

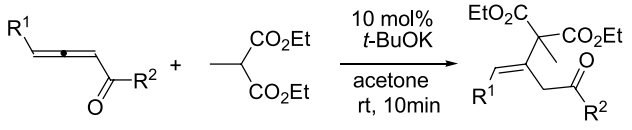


1 **4** **5**

Entry	1		4	Yield of **5** (%)
	R^3	R^4	R	
1	Bn	Me (**1a**)	Allyl(**4b**)	85 (**5ab**)
2	Bn	Me (**1a**)	Bn (**4c**)	81 (**5ac**)
3	allyl	Me (**1b**)	Me (**4a**)	83 (**5ba**)
4	allyl	Me (**1b**)	Allyl (**4b**)	78 (**5bb**)
5	allyl	Me (**1b**)	Bn (**4c**)	76 (**5bc**)
6	*n*-C_4H_9	Me (**1c**)	Me (**4a**)	Trace
7[a]	*n*-C_4H_9	Me (**1c**)	Me (**4a**)	83 (**5ca**)
8	Ph	Bn (**1d**)	Me (**4a**)	64 (**5da**)
9	H	*n*-C_8H_{17} (**1e**)	Me (**4a**)	66 (**5ea**)
10	H	*n*-C_7H_{15} (**1f**)	Me (**4a**)	62 (**5fa**)
11	H	H (**1 g**)	Me (**4a**)	44 (**5ga**)

[a] 100 mol% of *t*-BuOK was used.

afforded **5ca** in 83% yield (Table 2, entries 6–7). Similarly, **1e**–**1f** also reacted with 2-methyl diethyl malonate in the presence of 10 mol% *t*-BuOK to afford **5ea** and **5fa** in moderate yield (Table 2, entries 9–10). The Michael addition can be further applied to γ-substituted allenic ketones. Under similar reaction conditions, the simplest 1,2-allenic ketone **1g** reacted with 2-methyl diethyl malonate **4a** affording **5ga** in a relatively low yield (44%) (Table 2, entry 11). Reaction of **1h**–**1j** with **4a** also afforded β,γ-unsaturated enones *E*-**5ha**, *E*-**5ia**, and *E*-**5ja** as sole product (Scheme 4). The stereochemistry of this product was determined by the ^1H–^1H NOESY spectra (Fig. 1).



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

R^1	R^2	yield of (*E*)-**5** (%)
n-C_4H_9	CH_3 (**1h**)	49 ((*E*)-**5ha**)
n-C_7H_{15}	CH_3 (**1i**)	59 ((*E*)-**5ia**)
n-C_7H_{15}	*n*-C_7H_{15} (**1j**)	53 ((*E*)-**5ja**)

Scheme 4.

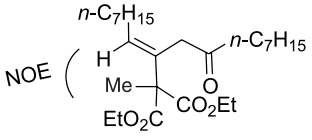
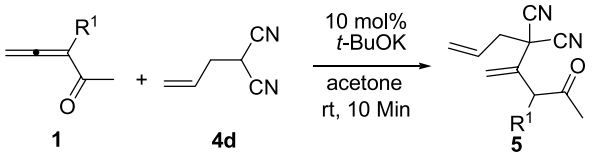


Figure 1. ^1H–^1H NOE effect of product *E*-**5ja**.

In addition, this transformation may be extended to other 2-substituted active methylene compounds. For example, 2-substituted malononitrile is also an effective nucleophile. In this case, α-substituted allenic ketones **1a**, **1b** and **1c** reacted with 2-allyl malononitrile **4d** to afford the corresponding products **5ad**, **5bd** and **5cd** in relative good yields (Scheme 5). However, when 2-allyl substituted



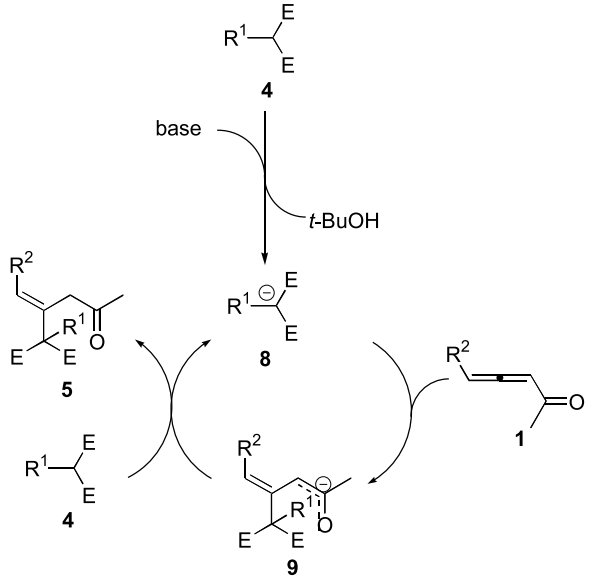
1 **4d** **5**

R^1	yield of **7**(%)
B*n* (**1a**)	65 (**5ad**)
Allyl (**1b**)	63 (**5bd**)
n-C_4H_9 (**1c**)	79 (**5cd**)

Scheme 5.

acetoacetone, nitroacetic acid ethyl ester and benzenesulfonylacetic acid ethyl ester were treated similarly, complicated reactions were observed.

A rationale for the catalytic reaction is shown in Scheme 6.



Scheme 6.

t-BuOK plays a role as an initiator to generate anion **8**, which adds to the conjugated carbon–carbon double bond in 1,2-allenic ketones from the less hindered side to form intermediate **9**. Immediate proton transfer between **9** and **4**, which may prevent the formation of α,β-unsaturated enones, affords products **5** and regenerates malonate anion **8** (Scheme 6).

In summary, we have demonstrated a facile nucleophilic addition of 2-substituted diethyl malonates or malononitriles to various substituted 1,2-allenic ketones to afford β,γ-unsaturated enones using *t*-BuOK as the basic catalyst. The reaction usually completes in 10 min in acetone at room temperature. With the γ-substituted allenic ketones the *E*-isomer was afforded highly stereoselectively.

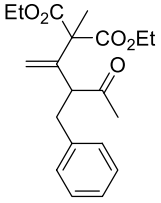
2. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were obtained using HP 5989A spectrometers. IR spectra were measured on Avatar 360 spectrophotometer. High-resolution mass spectra were carried out with Concept 1H spectrometer. TLC was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}).

2.1. General procedure for *t*-BuOK-catalyzed 1,4-addition of diethyl 2-substituted malonate with 1,2-allenic ketones

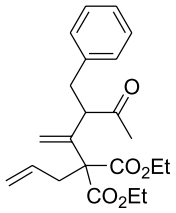
A solution of **1** (1.0 mmol), diethyl 2-substitutedmalonate or malononitrile (1.0–1.2 mmol), and 11 mg (10 mol%) of *t*-BuOK in 2 mL of acetone was stirred at room temperature. The reaction usually completed within 10 min as monitored by TLC. After the reaction was over, the solvent was evaporated and the crude product was purified by chromatography on silical gel (petroleum ether /ethyl acetate 10/1) to afford **5**.

2.1.1. 3-Benzyl-4-(1′,1′-bis(ethoxycarbonyl)ethyl)-4-penten-2-one (5aa).



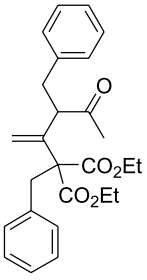
The reaction of **1a** (202 mg, 1.2 mmol), *t*-BuOK (12 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (174 mg, 1.0 mmol) in 2 mL of acetone afforded 282 mg (82%) of **5aa**: yellow liquid; IR (neat) 1731, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.14(m, 5H), 5.51 (s, 1H), 5.34 (s, 1H), 4.21 (q, J=7.2 Hz, 4H), 3.67 (dd, J_1=10.2 Hz, J_2=4.2 Hz, 1H), 3.06 (dd, J_1=13.5 Hz, J_2=10.2 Hz, 1H), 2.88 (dd, J_1=13.5 Hz, J_2=4.2 Hz, 1H), 1.96 (s, 3H), 1.62 (s, 3H), 1.28–1.22 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.3, 170.9, 170.7, 143.5, 139.5, 128.8, 128.4, 126.3 117.0, 61.73, 61.66, 60.3, 57.0, 41.0, 30.6, 20.8, 13.93, 13.90; MS *m*/*z* (%) 43 (100), 346 (M^+, 2.92); HRMS *m*/*z* (MALDI) calcd for $C_{20}H_{26}O_5Na^+$(M^++Na) 369.1678. Found 369.1673.

2.1.2. 3-Benzyl-4-methylene-5,5-bis(ethoxycarbonyl)-7-octen-2-one (5ab).



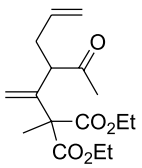
The reaction of **1a** (172 mg, 1.0 mmol), *t*-BuOK (11 mg, 0.1 mmol) and diethyl 2-allylmalonate **4b** (200 mg, 1.0 mmol) in 2 mL of acetone afforded 316 mg (85%) of **5ab**: yellow liquid; IR (neat) 1731, 1638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.09 (m, 5H), 5.84–5.68 (m, 1H), 5.56 (s, 1H), 5.46 (s, 1H), 5.12–4.97 (m, 2H), 4.24–4.03 (m, 4H), 3.69 (dd, J_1=10.2 Hz, J_2=4.5 Hz, 1H), 2.98 (dd, J_1=10.2 Hz, J_2=13.2 Hz, 1H), 2.89 (d, J=4.5 Hz, 1H), 2.85 (d, J=6.6 Hz, 2H), 1.87 (s, 3H), 1.22 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 169.5, 169.3, 141.7, 139.3, 132.9, 128.7, 128.2, 126.2, 118.5, 118.3, 63.7, 61.5, 61.4, 57.0, 41.0, 38.4, 30.5, 13.84, 13.80; MS *m*/*z* (%) 91 (100), 331 ($M^+-C_3H_5$, 9.89); HRMS *m*/*z* (MALDI) calcd for $C_{22}H_{28}O_5Na^+$(M^++Na) 395.1834. Found 395.1829.

2.1.3. 3-Benzyl-4-(1′,1′-bis(ethoxycarbonyl)-2′-phenylethyl)-4-penten-2-one (5ac).



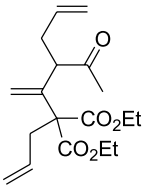
The reaction of **1a** (172 mg, 1.0 mmol), *t*-BuOK (11 mg, 0.1 mmol) and diethyl 2-benzylmalonate **4c** (250 mg, 1.0 mmol) in 2 mL of acetone afforded 342 mg (81%) of **5ac**: yellow liquid; IR (neat) 1721, 1633 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.14 (m, 10H), 5.62 (s, 1H), 5.57 (s, 1H), 4.18–3.90 (m, 4H), 3.77 (dd, J_1=10.2 Hz, J_2=4.2 Hz, 1H), 3.50 (d, J=25.2 Hz, 1H), 3.45 (d, J=25.2 Hz, 1H), 3.03 (dd, J_1=10.2 Hz, J_2=13.2 Hz, 1H), 2.87 (dd, J_1=13.2 Hz, J_2=4.2 Hz, 1H), 1.90 (s, 3H), 1.18 (t, J=7.05 Hz, 3H), 1.10 (t, J=7.05 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 169.4, 169.2, 142.8, 139.3, 136.2, 130.0, 128.8, 128.2, 127.8, 126.7, 126.2, 118.7, 64.9, 61.4, 61.3, 57.2, 40.61, 40.58, 30.3, 13.7, 13.5; MS *m*/*z* (%) 91 (100), 331 ($M^+-C_7H_7$, 48); HRMS *m*/*z* (MALDI) calcd for $C_{26}H_{30}O_5Na^+$(M^++Na) 445.1991. Found 445.1986.

2.1.4. 3-(1′-Methylene-2′,2′-bis(ethoxycarbonyl)propyl)-5-hexen-2-one (5ba).



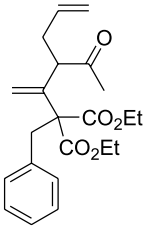
The reaction of **1b** (122 mg, 1.0 mmol), *t*-BuOK (11 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (174 mg, 1.0 mmol) in 2 mL of acetone afforded 309 mg (83%) of **5ba**: yellow liquid; IR (neat) 1733, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.71–5.50 (m, 1H), 5.26 (s, 1H), 5.24 (s, 1H), 5.00–4.79 (m, 2H), 4.21–4.05 (m, 4H), 3.34 (dd, $J_1=9.3$ Hz, $J_2=5.4$ Hz, 1H), 2.57–2.40 (m, 1H), 2.28–2.09 (m, 1H), 1.93 (s, 3H), 1.55 (s, 3H), 1.16–1.26 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 170.8, 170.5, 143.3, 135.5, 116.7, 116.5, 61.54, 61.50, 60.1, 55.2, 38.3, 29.2, 20.7, 13.78, 13.76; MS (CI) *m/z* (%) 181 (100), 297 (M^+ + H, 9); HRMS *m/z* (MALDI) calcd for $C_{16}H_{24}O_5Na^+$(M^+ + Na) 319.1521. Found 319.1516.

2.1.5. 3-Allyl-4-methylene-5-bis(ethoxycarbonyl)-7-octen-2-one (5bb).



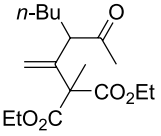
The reaction of **1b** (122 mg, 1.0 mmol), *t*-BuOK (11 mg, 0.1 mmol) and diethyl 2-allylmalonate **4b** (200 mg, 1.0 mmol) in 2 mL of acetone afforded 251 mg (78%) of **5bb**: yellow liquid; IR (neat) 1728, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.82–5.62 (m, 2H), 5.44 (s, 1H), 5.39 (s, 1H), 5.12–4.85 (m, 4H), 4.25–4.08 (m, 4H), 3.41 (dd, $J_1=9.3$ Hz, $J_2=5.1$ Hz, 1H), 2.84 (d, $J=7.2$ Hz, 2H), 2.57–2.43 (m, 1H), 2.34–2.21 (m, 1H), 2.17 (s, 3H), 1.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.4, 169.5, 169.2, 141.7, 135.5, 132.9, 118.5, 118.2, 116.6, 63.7, 61.43, 61.38, 55.4, 38.5, 38.4, 29.3, 13.8; MS (CI) *m/z* (%) 235 (100), 323 (M^++H, 19); HRMS *m/z* (MALDI) calcd for $C_{18}H_{26}O_5Na^+$(M^++Na) 345.1678. Found 345.1673.

2.1.6. 3-(1′-Methylene-2′,2′-bis(ethoxycarbonyl)-3′-phenylpropyl)-5-hexen-2-one (5bc).



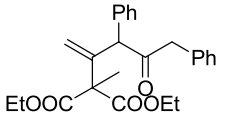
The reaction of **1b** (122 mg, 1.0 mmol), *t*-BuOK (11 mg, 0.1 mmol) and diethyl 2-benzylmalonate **4c** (250 mg, 1.0 mmol) in 2 mL of acetone afforded 283 mg (76%) of **5bc**: yellow liquid; IR (neat) 1732, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (br, 5H), 5.67–5.55 (m, 1H), 5.50 (s, 1H), 5.38 (s, 1H), 5.00–4.90 (m, 2H), 4.15–3.79 (m, 4H), 3.50–3.32 (m, 3H), 2.51–2.39 (m, 1H), 2.27–2.16 (m, 1H), 2.10 (s, 3H), 1.14 (t, $J=6.9$ Hz, 3H), 1.05 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.2, 169.3, 169.1, 142.7, 136.2, 135.4, 130.0, 127.8, 126.7, 118.5, 116.5, 64.9, 61.32, 61.27, 55.6, 40.5, 38.2, 29.2, 13.6, 13.5; MS *m/z* (%) 91 (100), 331 ($M^+-C_3H_5$, 31); HRMS *m/z* (MALDI) calcd for $C_{22}H_{28}O_5Na^+$(M^+ + Na) 395.1834. Found 395.1829.

2.1.7. 3-Butyl-4-(1′,1′-bis(ethoxycarbonyl)ethyl)-4-penten-2-one (5ca).



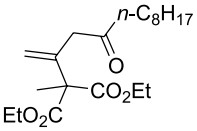
The reaction of **1c** (138 mg, 1.0 mmol), *t*-BuOK (112 mg, 1.0 mmol) and diethyl 2-methylmalonate **4a** (174 mg, 1.0 mmol) in 2 mL of acetone afforded 259 mg (83%) of **5ca**: yellow liquid; IR (neat) 1732, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.31 (s, 1H), 5.28 (s, 1H), 4.27–4.10 (m, 4H), 3.24 (dd, $J_1=8.4$ Hz, $J_2=6.0$ Hz, 1H), 2.19 (s, 3H), 1.84–1.70 (m, 1H), 1.60 (s, 3H), 1.59–1.44 (m, 1H), 1.31–1.14 (m, 10H), 0.85 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 170.5, 170.3, 144.0, 115.7, 61.21, 61.19, 60.0, 55.7, 45.7, 33.7, 29.9, 28.3, 22.4, 20.6, 13.53, 13.52; MS *m/z* (%) 239 (100), 312 (M^+, 0.82); HRMS *m/z* (EI) calcd for $C_{17}H_{28}O_5$ 312.1937. Found 312.1966.

2.1.8. 1, 3-Diphenyl-4-(1′,1′-bis(ethoxycarbonyl)ethyl)-4-penten-2-one (5da).



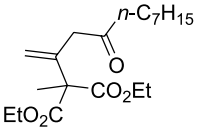
The reaction of **1d** (234 mg, 1 mmol), *t*-BuOK (11.0 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (209 mg, 1.2 mmol) in 2 mL of acetone afforded 261 mg (64%) of **5da**: yellow liquid; IR (neat) 1728, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.02 (m, 10H), 5.50 (s, 1H), 5.29 (s, 1H), 5.04 (s, 1H), 4.20 (q, $J=7.2$ Hz, 2H), 3.95 (s, 2H), 3.92–3.77 (m, 2H), 1.57 (s, 3H), 1.28 (t, $J=7.2$ Hz, 3H), 1.12 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7, 171.1, 170.7, 141.9, 137.0, 134.4, 129.7, 128.9, 128.3, 127.1, 126.7, 119.2, 61.7, 61.5, 60.3, 59.8, 48.8, 20.7, 13.9, 13.7; MS *m/z* (%) 91 (100), 408(M^+, 0.72); HRMS *m/z* (MALDI) calcd for $C_{25}H_{28}O_5Na^+$(M^+ + Na) 431.1834. Found 431.1829.

2.1.9. 2-(1′,1′-Bis(ethoxycarbonyl)ethyl)-1-dodecen-4-one (5ea).



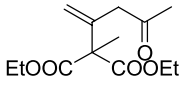
The reaction of **1e** (180 mg, 1.0 mmol), *t*-BuOK (11.0 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (174 mg, 1.0 mmol) in 2 mL of acetone afforded 234 mg (66%) of **5ea**: yellow liquid; IR (neat) 1732, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.29 (s, 1H), 5.13 (s, 1H), 4.23–4.12 (m, 4H), 3.29 (s, 2H), 2.47 (t, $J=7.5$ Hz, 2H), 1.61 (s, 3H), 1.60–1.49 (m, 2H), 1.29–1.18 (m, 16H), 0.87 (t, $J=6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.9, 170.7, 139.1, 118.0, 61.6, 59.5, 47.8, 42.0, 31.6, 29.1, 29.0, 23.7, 22.5, 20.4, 14.0, 13.9; MS *m/z* (%) 181 (100), 354 (M^+, 0.82); HRMS *m/z* (EI) calcd for $C_{20}H_{34}O_5(M^+)$ 354.2406. Found 354.2438.

2.1.10. 2-(1′,1′-Bis(ethoxycarbonyl)ethyl)-1-undecen-4-one (5fa).



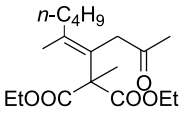
The reaction of **1f** (166 mg, 1.0 mmol), *t*-BuOK (11 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (174 mg, 1.0 mmol) in 2 mL of acetone afforded 211 mg (62%) of **5fa**: yellow liquid; IR (neat) 1732, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.30 (s, 1H), 5.13 (s, 1H), 4.24–4.12 (m, 4H), 3.30 (s, 2H), 2.48 (t, $J=6.9$ Hz, 2H), 1.62 (s, 3H), 1.60–1.49 (m, 2H), 1.38–1.20 (m, 14H), 0.88 (t, $J=6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 170.6, 139.0, 117.9, 61.5, 59.4, 47.7, 41.9, 31.7, 29.2, 29.01, 28.99, 23.6, 22.5, 20.3, 13.9, 13.8; MS *m/z* (%) 57 (100), 340 (M^+, 0.61); HRMS *m/z* (EI) calcd for $C_{19}H_{32}O_5(M^+)$ 340.2244. Found 340.2219.

2.1.11. 4-(1′,1′-Bis(ethoxycarbonyl)ethyl)-4-penten-2-one (5ga).



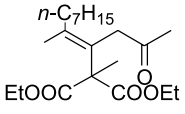
The reaction of **1g** (82 mg, 1.0 mmol), *t*-BuOK (11.0 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (209 mg, 1.2 mmol) in 2 mL of acetone afforded 113 mg (44%) of **5ga**: yellow liquid; IR (neat) 1732, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.31 (s, 1H), 5.15 (s, 1H), 4.18 (q, $J=$ 6.6 Hz, 2H), 4.19 (q, $J=6.6$ Hz, 2H), 3.31 (s, 2H), 2.19 (s, 3H) 1.62 (s, 3H), 1,26 (t, $J=6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7, 170.5, 139.0, 118.2, 61.5, 59.3, 48.7, 29.0, 20.2, 13.7; MS *m/z* (%) 43 (100), 257(M^+ +H, 0.81); HRMS *m/z* (EI) calcd for $C_{13}H_{20}O_5(M^+)$ 256.1344. Found 256.1336.

2.1.12. 4-(1′, 1′-Bis(ethoxycarbonyl)ethyl)-4-nonen-2-one ((*E*)-5ha).



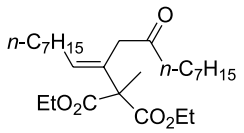
The reaction of **1h** (138 mg, 1 mmol), *t*-BuOK (12.0 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (209 mg, 1.2 mmol) in 2 mL of acetone afforded 153 mg (49%) of (*E*)-**5ha**: yellow liquid; IR (neat) 1731, 1638 cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ 5.64 (t, $J=6.9$ Hz, 1H), 4.15 (q, $J=7.2$ Hz, 2H), 4.14 (q, $J=7.2$ Hz, 2H), 3.36 (s, 2H), 2.15 (s, 3H), 1.95 (q, $J=7.2$ Hz, 2H), 1.58 (s, 3H), 1.42–1.22 (m, 4H), 1.23 (t, $J=7.2$ Hz, 6H), 0.87 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 171.2, 133.0, 129.1, 61.3, 59.8, 44.9, 31.0, 29.2, 28.5, 22.2, 20.3, 13.81, 13.78; MS *m/z* (%) 43 (100), 312 (M^+, 0.84); HRMS *m/z* (EI) calcd for $C_{17}H_{28}O_5(M^+)$ 312.1937. Found 312.1918.

2.1.13. 4-(1′,1′-Bis(ethoxycarbonyl)ethyl)-4-dodecen-2-one ((*E*)-5ia).



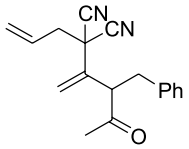
The reaction of **1i** (180 mg, 1 mmol), *t*-BuOK (11.0 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (174 mg, 1.0 mmol) in 2 mL of acetone afforded 207 mg (59%) of (*E*)-**5ia**: yellow liquid; IR (neat) 1732, 1669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.64 (t, $J=6.9$ Hz, 1H), 4.15 (q, $J=7.2$ Hz, 2H), 4.14 (q, $J=7.2$ Hz, 2H), 3.36 (s, 2H), 2.14 (s, 3H), 1.93 (q, $J=7.2$ Hz, 2H), 1.58 (s, 3H), 1.39–1.29 (m, 2H), 1.26–1.19 (m, 14H), 0.86 (t, $J=6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.0, 171.2, 133.1, 129.0, 61.4, 59.8, 44.9, 31.7, 29.3, 29.2, 29.1, 28.9, 28.8, 26.8, 22.56, 22.54, 20.3, 14.0, 13.8; MS *m/z* (%) 43 (100), 354 (M^+, 0.31); HRMS *m/z* (MALDI) calcd for $C_{20}H_{34}O_5Na^+$ (M^+ +Na) 377.2304. Found 377.2299.

2.1.14. 10-(1′,1′-Bis(ethoxycarbonyl)ethyl)-10-octadecen-8-one ((*E*)-5ja).



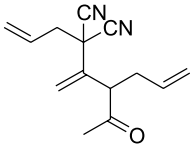
The reaction of **1j** (264 mg, 1.0 mmol), *t*-BuOK (11 mg, 0.1 mmol) and diethyl 2-methylmalonate **4a** (174 mg, 1.0 mmol) in 2 mL of acetone afforded 232 mg (53%) of *E*-**5ja**: yellow liquid; IR (neat) 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.63 (t, $J=6.9$ Hz, 1H), 4.15 (q, $J=$ 7.2 Hz, 2H), 4.14 (q, $J=7.2$ Hz, 2H), 3.35 (s, 2H), 2.41 (t, $J=7.5$ Hz, 2H), 1.92 (q, $J=6.9$ Hz, 2H), 1.58 (s, 3H), 1.57–1.50 (m, 2H), 1.42–1.18 (m, 24H), 0.87 (t, $J=6.3$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.9, 171.3, 132.9, 129.0, 61.3, 59.9, 44.1, 42.1, 31.7, 31.6, 29.2, 29.11, 29.05, 29.0, 28.92, 28.88, 23.8, 22.54, 22.51, 20.3, 13.99, 13.97, 13.8; MS *m/z* (%) 265 (100), 438 (M^+, 0.72); HRMS *m/z* (EI) calcd for $C_{26}H_{46}O_5$ 438.3345. Found 438.3343.

2.1.15. 3-Benzyl-4-methylene-5,5-biscyano-7-octen-2-one (5ad).



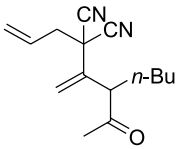
The reaction of **1a** (172 mg, 1 mmol), *t*-BuOK (11.0 mg, 0.1 mmol) and 2-allyl malononitrile (106 mg, 1.0 mmol) in 2 mL of acetone afforded 180 mg (65%) of **5ad**: yellow liquid; IR (neat) 3087, 1720, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.14 (m, 5H), 5.82 (s, 1H), 5.81–5.65 (m, 1H), 5.66 (s, 1H), 5.40 (d, $J=14.1$ Hz, 1H), 5.36 (d, $J=20.4$ Hz, 1H), 3.64 (dd, $J_1=5.7$ Hz, $J_2=9.3$ Hz, 1H), 3.24 (dd, $J_1=9.3$ Hz, $J_2=13.8$ Hz, 1H), 2.90 (dd, $J_1=5.7$ Hz, $J_2=13.8$ Hz, 1H), 2.57 (d, $J=6.9$ Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.8, 137.9, 136.0, 128.9, 128.7, 127.9, 127.0, 123.6, 120.5, 113.8, 113.5, 56.1, 44.1, 41.5, 39.7, 30.0; MS *m/z* (%) 43 (100), 279 (M^+, 1.67); HRMS *m/z* (MALDI) calcd for $C_{18}H_{19}N_2O^+$ (M^+ + H) 279.1497. Found 279.1492.

2.1.16. 3-Allyl-4-methylene-5,5-biscyano-7-octen-2-one (5bd).



The reaction of **1b** (122 mg, 1 mmol), *t*-BuOK (12.0 mg, 0.1 mmol) and 2-allyl malononitrile (106 mg, 1.0 mmol) in 2 mL of acetone afforded 143 mg (63%) of **5bd**: yellow liquid; IR (neat) 3084, 1720, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.76 (s, 1H), 5.92–5.58 (m, 2H), 5.45 (s, 1H), 5.42–5.36 (m, 2H), 5.09–5.03 (m, 2H), 3.36 (t, $J=6.9$ Hz, 1H), 2.73 (d, $J=6.6$ Hz, 2H), 2.69–2.57 (m, 1H), 2.37–2.25 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 135.8, 133.8, 127.9, 123.6, 120.3, 118.2, 113.7, 113.4, 54.0, 44.0, 41.6, 37.2, 29.1; MS *m/z* (%) 43 (100), 228 (M^+, 1.84); HRMS *m/z* (MALDI) calcd for $C_{14}H_{17}N_2O^+$(M^+ + H) 229.1341. Found 229.1335.

2.1.17. 3-Butyl-4-methylene-5,5-biscyano-7-octen-2-one (5cd).



The reaction of **1c** (138 mg, 1 mmol), *t*-BuOK (12.0 mg, 0.1 mmol) and 2-allyl malononitrile (106 mg, 1.0 mmol) in 2 mL of acetone afforded 193 mg (79%) of **5cd**: yellow liquid; IR (neat) 3088, 1720, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.92–5.77 (m, 1H), 5.76 (s, 1H), 5.49 (s, 1H), 5.46–5.36 (m, 2H), 3.28 (t, $J=6.9$ Hz, 1H), 2.39 (d, $J=7.5$ Hz, 2H), 2.26 (s, 3H), 1.99–1.86 (m, 1H), 1.63–1.49 (m, 1H), 1.33–1.23 (m, 4H), 0.87 (t, $J=6.75$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4, 136.6, 128.0, 123.6, 119.6, 113.8, 113.6, 54.6, 44.2, 41.6, 33.2, 29.9, 28.9, 22.4, 13.6; MS *m/z* (%) 43 (100), 245 (M^++H, 3.97); HRMS *m/z* (MALDI) calcd for $C_{15}H_{21}N_2O^+$ (M^++H) 245.1654. Found 245.1648.

Acknowledgements

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Synthesis of 2-methyl- and 2-methylenecyclobutane amino acids

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Abstract—An efficient and easy formal [2+2] cycloaddition (Michael–Dieckmann-type reaction) on methyl 2-acetamidoacrylate with ketene diethyl acetal gave the cyclobutane core. Two kinds of 2-substituted cyclobutane amino acids have been obtained from this compound by means of stereocontrolled interconversion of functional groups: 1-amino-2-methylcyclobutane-1-carboxylic acids (2,4-methanovalines) and 1-amino-2-methylenecyclobutane-1-carboxylic acid. The latter amino acid can be regarded as a restricted α-methyl-α-vinylglycine.

1. Introduction

1-Aminocycloalkane-1-carboxylic acids,[1] especially those with three-, five-, or six-membered rings, have attracted considerable attention, mainly due to the conformational restriction produced when they are incorporated into peptides.[2] Despite this interest, 1-aminocyclobutane-1-carboxylic acids received very little attention until 1980.[3] Since then, a number of naturally occurring cyclobutane amino acids were discovered and several derivatives were found to be potent neurotransmitters.[4] Synthetic efforts have since been extended to a whole range of cyclobutane amino acids of potential biological interest.[5]

Nevertheless, the synthesis of 2-substituted cyclobutane amino acids has not received the same attention as the preparation of other substituted cyclobutane α-amino acids[5] and, to the best of our knowledge, only a few methods for the synthesis of 1-amino-2-alkylcyclobutane-1-carboxylic acids have been described.[6] In particular, (1*S**,2*S**)-1-amino-2-methylcyclobutane-1-carboxylic acid (**1**) (2,4-methanovaline) was first synthesized by Gaoni in 1995 by the azidation of methyl 2-methyl-3-(phenylsulfonyl)bicyclo[1.1.0]butane-1-carboxylate, followed by hydrogenation, desulfonylation and hydrolysis.[5c] Later, Frahm and co-workers[7] obtained the four stereoisomers in enantiopure form by an asymmetric Strecker synthesis starting from racemic 2-methylcyclobutanone and (*R*)-phenylethylamine as a chiral auxiliary, which gave poor diastereoselectivity, followed by separation by column chromatography (Fig. 1).

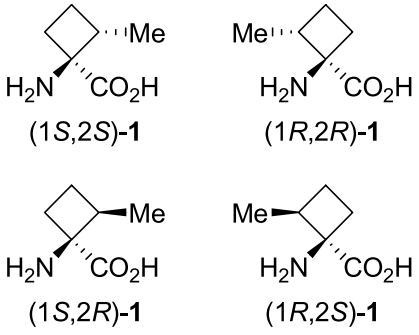
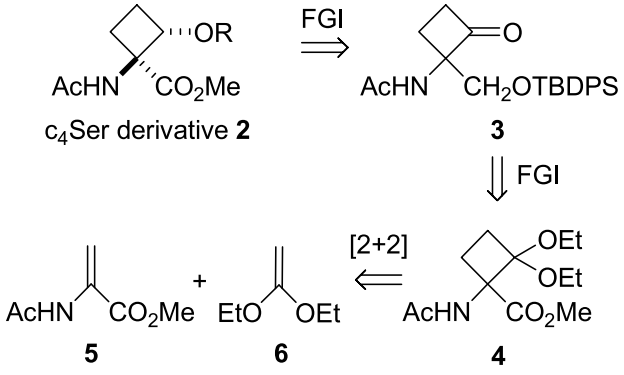


Figure 1. The all four stereoisomers of 2,4-methanovalines **1**.

As part of our research programme on the synthesis of cyclic amino acids,[8] we recently described the synthesis of the serine analogue derivative **2**, which incorporates the cyclobutane skeleton (c_4Ser).[8h] The key step in this synthesis involves a reaction of methyl 2-acetamidoacrylate **5** with ketene diethyl acetal **6** in a formal [2+2] cycloaddition (Scheme 1).



Scheme 1. Retrosynthesis of a c_4Ser derivative from methyl 2-acetamidoacrylate **5** by a [2+2] cycloaddition.

Keywords: Amino acid; Cyclobutane; Hydrogenation; Valine.
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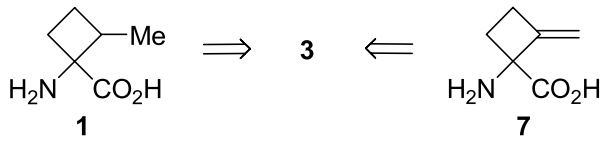
In this way, the cyclobutane skeleton was obtained by a tandem Michael–Dieckmann-type process that gave compound **4**, which was then transformed into the intermediate **3** (Scheme 1).

This pathway opens the door to important 2-substituted cyclobutane amino acids. In an effort to exemplify this feature, we decided to explore the reactivity of intermediate **3** as a building block in stereocontrolled organic synthesis in order to obtain both stereoisomers of 2,4-methanovaline **1** as well as 2-methylenecyclobutane amino acid **7** in racemic forms (Scheme 2).



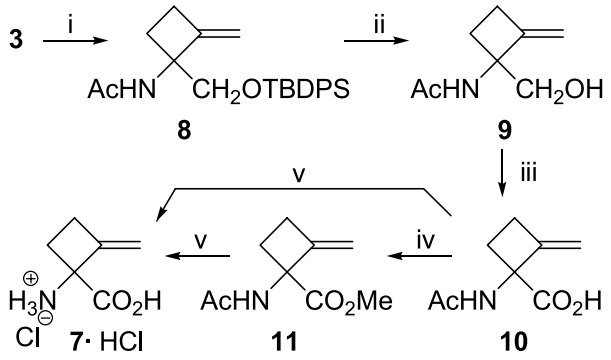
Scheme 2. Retrosynthesis of 2-substituted cyclobutane amino acids from intermediate **3**.

β,γ-Unsaturated amino acid derivatives have received a great deal of attention because they are important enzyme inhibitors.[9] For example, α-vinyl amino acids are known to inhibit pyridoxal phosphate-dependent enzymes and, in particular, amino acid decarboxylases.[10] Given this background, the interesting amino acid **7** can be regarded as a particularly restricted analogue of α-vinylalanine.[11] Moreover, it has only been synthesized on one occasion and this involved isomerization of a spiranic amino acid derivative.[12]

2. Results and discussion

2.1. Synthesis of 2-methylenecyclobutane amino acid 7

Racemic 2-methylenecyclobutane amino acid **7** was obtained as the hydrochloride salt in 22% overall yield from a four-step synthesis starting from intermediate **3** (Scheme 3). The initial step involved Wittig methylenation[13] of **3** and was carried out under salt-free Wittig conditions using methyltriphenylphosphonium bromide ($Ph_3PMe^+Br^-$) with several bases tested. The use of 2.0 equiv of potassium bis(trimethylsilyl)amide (KHMDS) at −78 °C gave 67% yield of alkene **8** but the best result was achieved with 3.0 equiv of this base, which afforded alkene **8** in 86% yield (Scheme 3).



Scheme 3. Reagents and conditions: (i) KHMDS (3.0 equiv), $Ph_3PMe^+Br^-$, THF, rt, 5 h, 86%; (ii) TBAF, THF, rt, 1 h, 91%; (iii) Jones reagent, acetone, 0 °C, 4 h, 64%; (iv) CH_2N_2, ethyl ether, rt, 30 min, 85%; (v) 3 N HCl, reflux, 3 h, 51%.

The structure of compound **8** was confirmed by X-ray analysis[†] of monocrystals and is shown in the ORTEP representation Figure 2.

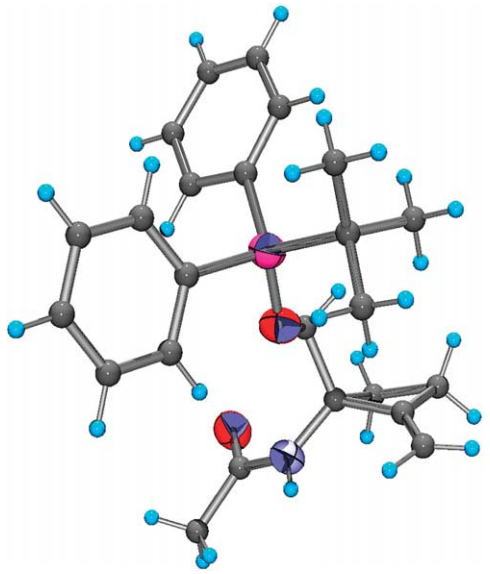


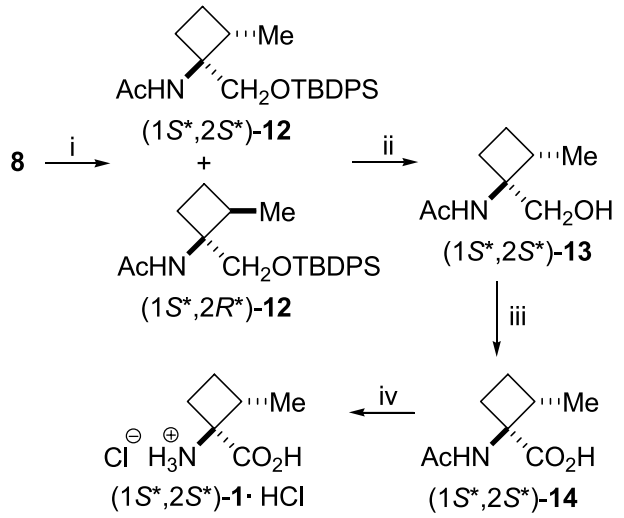
Figure 2. ORTEP representation of compound **8**.

Subsequent cleavage of the silyl group in compound **8** with tetrabutylammonium fluoride (TBAF) in THF at room temperature gave the corresponding primary alcohol **9** in excellent yield. This compound was subjected to oxidation in the presence of Jones reagent[14] to give the carboxylic acid derivative **10**. The required amino acid **7** was obtained as the hydrochloride salt by acid hydrolysis of **10** using 3 N HCl at reflux. In order to purify carboxylic acid derivative **10**, an aliquot was converted into the corresponding methyl ester by addition of diazomethane in ethyl ether at room temperature. Acid hydrolysis of compound **11** gave amino acid **7** as the hydrochloride salt with a similar yield (Scheme 3).

2.2. Synthesis of racemic 2-methylcyclobutane amino acids (1*S**,2*S**)-1

Starting from compound **8**, which in turn comes from the intermediate **3**, we envisioned a synthetic route to the

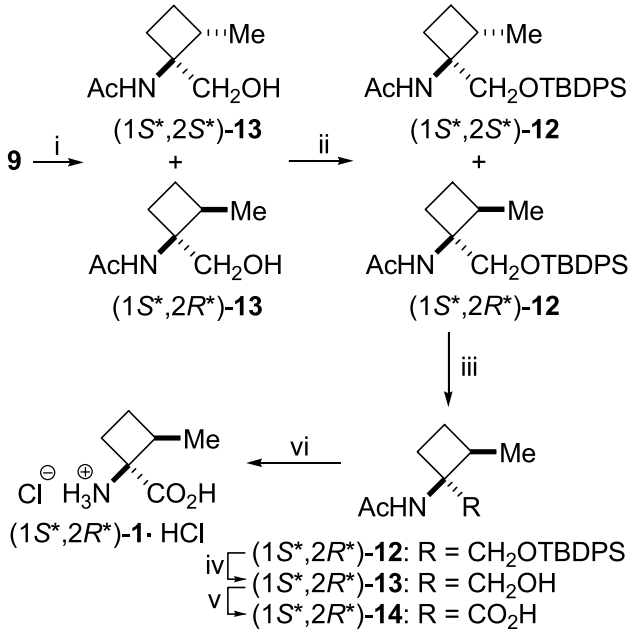
[†] The monocrystals were obtained by slowly adding octane to a solution of compound **8** in dichloromethane to form an interface. The crystal grew at the border of the two solvents. Crystal data: $C_{48}H_{62}N_2O_4Si_2$, M_w=787.18, colourless prism of 0.50×0.42×0.20 mm^3, T=223(2) K, triclinic, space group P-1, Z=2, a=9.6181(4) Å, b=14.6066(6) Å, c=16.5421(8) Å, α=79.3829(17), β=82.0665(17), γ=90.0352(13), V=2261.51(17) Å^3, d_{calc}=1.156 g cm^{-3}, $F(000)$=848, λ=0.71073 Å (Mo Kα), μ=0.12 mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.26–28.00°, 28,939 collected reflections, 10,432 unique (R_{int}=0.1694), full-matrix least-squares (SHELXL97),[15] R_1=0.1156, wR_2=0.2618, (R_1=0.2373, wR_2=0.3537 all data), goodness of fit=1.601, residual electron density between 0.870 and −1.034 e Å^{-3}. Hydrogen atoms were located from mixed methods. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number 239349.



Scheme 4. Reagents and conditions: (i) H_2, Pd–C, CH_2Cl_2, rt, 17 h, 96%; (ii) TBAF, THF, rt, 1 h, 76%; (iii) Jones reagent, acetone, 0 °C, 2 h, 73%; (iv) 3 N HCl, reflux, 6 h, 90%.

2-methylcyclobutane amino acid (1*S**,2*S**)-**1**. The reaction sequence on compound **8** starts with a selective hydrogenation followed by deprotection by removing the silyl group, oxidation and hydrolysis (Scheme 4).

Hydrogenation of the exocyclic double bond in compound **8** using palladium–carbon as a catalyst was studied in two solvents. Ethyl acetate gave an excellent yield (97%) of the mixture of hydrogenation products (1*S**,2*S**)-**12** and (1*S**,2*R**)-**12** and a stereoselectivity of 89:11 in favour of (1*S**,2*S**)-**12**. Fortunately, dichloromethane gave a similar yield (96%) but the stereoselectivity was increased to 93:7. Once separated by column chromatography, (1*S**,2*S**)-**12** was desilylated by the action of TBAF to give primary alcohol (1*S**,2*S**)-**13**, which was treated with Jones reagent to give the carboxylic acid (1*S**,2*S**)-**14**. Acid hydrolysis of this compound furnished the racemic 2,4-methanovaline (1*S**,2*S**)-**1**, as its hydrochoride salt, in which the carboxylic acid group and methyl substituent are in a *cis* disposition. This stereochemistry was confirmed by ROE experiments on compound (1*S**,2*S**)-**13** (see Section 2.4).



Scheme 5. Reagents and conditions: (i) H_2, $Pd(OH)_2$–C, CH_2Cl_2, rt, 17 h; (ii) TBDPSCl, imidazole, DMF, 50 °C, 17 h; (iii) column chromatography: hexane/ethyl acetate 65:35; 32% from **9**; (iv) TBAF, THF, rt, 1 h, 95%; (v) Jones reagent, acetone, 0 °C, 2 h, 63%; (vi) 3 N HCl, reflux, 6 h, 70%.

2.3. Synthesis of racemic 2-methylcyclobutane amino acids (1*S**,2*R**)-1

Racemic 2,4-methanovaline (1*S**,2*R**)-**1** was obtained following the same strategy as described above for 2,4-methanovaline (1*S**,2*S**)-**1**, but starting from compound **9**, which was obtained by desilylation of compound **8** (Scheme 5). The structure of the new starting compound **9** was determined by X-ray analysis[‡] in the same way as for compound **8** (Fig. 3).

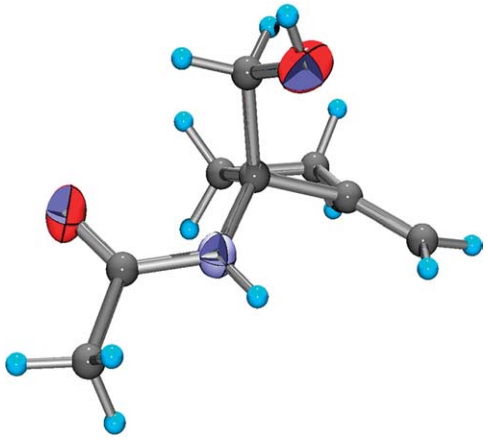


Figure 3. ORTEP structure of compound **9**.

Hydrogenation of the double bond in compound **9** was investigated under several sets of conditions. Initially, the homogeneous hydrogenation was attempted with $(Ph_3P)_3RhCl$ and after 24 h at 55 °C only a 16% of hydrogenation products (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** was obtained without selectivity. Therefore, the heterogeneous hydrogenation was assayed using palladium–carbon in three different solvents; methanol, ethyl acetate and dichloromethane. In all cases the yield was excellent (98, 96 and 95%, respectively) and the stereoselectivity of hydrogenated products (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** was as follows, 45:55, 38:62 and 37:63, respectively, always in favour of (1*S**,2*R**)-**13**. The change in the catalyst for the hydrogenation only led to a slight increase in the

[‡] Crystal data: $C_8H_{13}NO_2$, $M_w=155.19$, colourless prism of 0.50×0.37×0.25 mm^3, $T=223(2)$ K, monoclinic, space group $P\,21/c$, $Z=4$, $a=8.5399(3)$ Å, $b=10.0205(4)$ Å, $c=10.3072(4)$ Å, $\alpha=90$, $\beta=104.454(2)$, $\gamma=90$, $V=854.11(6)$ Å^3, $d_{calc}=1.207$ g cm^{-3}, $F(000)=336$, $\lambda=0.71073$ Å (Mo Kα), $\mu=0.087$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 2.03–27.88°, 6840 collected reflections, 2009 unique ($R_{int}=0.0755$), full-matrix least-squares (SHELXL97),[15] $R_1=0.0687$, w$R_2=0.2038$, ($R_1=0.0812$, w$R_2=0.2174$ all data), goodness of fit=1.068, residual electron density between 0.425 and −0.352 e Å^{-3}. Hydrogen atoms were located from mixed methods. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number 239348.

stereoselectivity; indeed, when the hydrogenation was carried out in the presence of palladium hydroxide supported on carbon and using dichloromethane as solvent, the stereoselectivity was 34:66 with a yield of 95%. This mixture of products could not be separated by column chromatography, so it was transformed into the corresponding silylated derivatives (1*S**,2*S**)-**12** and (1*S**,2*R**)-**12** with *tert*-butyldiphenylsilyl chloride (TBDPSCl). Once separated, (1*S**,2*R**)-**12** was desilylated to give pure (1*S**,2*R**)-**13**, which was oxidized to carboxylic acid (1*S**,2*R**)-**14** and hydrolysed to give the desired racemic 2,4-methanovaline (1*S**,2*R**)-**1** as its hydrochloride salt (Scheme 5).

2.4. Stereochemical outcome of the hydrogenation

The stereochemistry of the minor product (1*S**,2*S**)-**13** obtained in the heterogeneous hydrogenation reaction of compound **9** was assigned on the basis of selective gradient-enhanced 1D ROESY experiments.[16] Therefore, once the signals of the ^{1}H NMR spectra of this compound were assigned by COSY and HSQC experiments, the signal at 6.30 ppm, corresponding to the NH proton, was presaturated using a mixing time of 500 ms. As a consequence, a ROE enhancement of 2% was observed in the signal at 2.53 ppm, corresponding to proton H-2, indicating that the NHAc group is in a *cis* disposition with respect to the H-2 proton attached to C-2 of the cyclobutane ring. When the same experiment was performed on the major product (1*S**,2*R**)-**13**, a ROE enhancement was not observed on proton H-2 (Fig. 4).

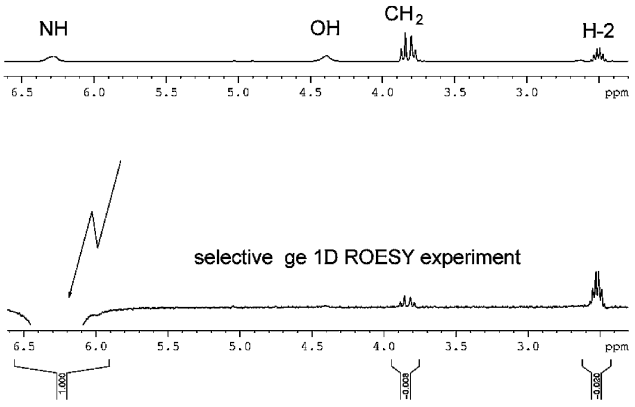


Figure 4. Selective 1D ROESY on compound (1*S**,2*S**)-**13**.

A number of calculations were performed in an effort to explain the stereochemical outcome obtained in the hydrogenation of compound **8**. First, and in order to obtain the conformational preferences of compound **8**, the initial geometry extracted from the X-ray structure of this compound was optimised by the semi-empirical PM3 method[17] with the CS MOPAC Pro 8.0 program based on MOPAC 2000, as implemented in Chem3D Ultra 8.0 software. Once other variables had been properly evaluated, the relaxed potential-energy surface (PES) scan was performed by varying the CH_2–O–Si–$C(CH_3)_3$ dihedral angle with step-sizes of 5° (Fig. 5). The global minimum was located at 290°.

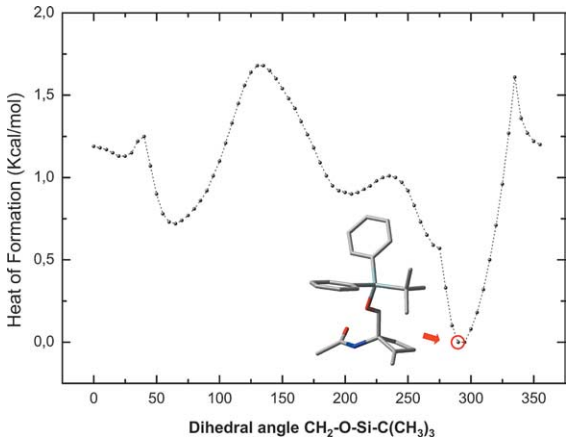


Figure 5. PES scans with PM3 method on compound **8**.

The lowest energy structure found in these preliminary calculations was fully optimised and characterised by a frequency calculation that took into account the solvent effects using the Onsager SCRF method[18] implemented in Gaussian 98. A dielectric constant of 8.93 (dichloromethane) was used in order to be consistent with the experimental conditions. The calculations were carried out at the B3LYP/6-31G(d) level[19] with the Gaussian 98 package[20] (Fig. 6).

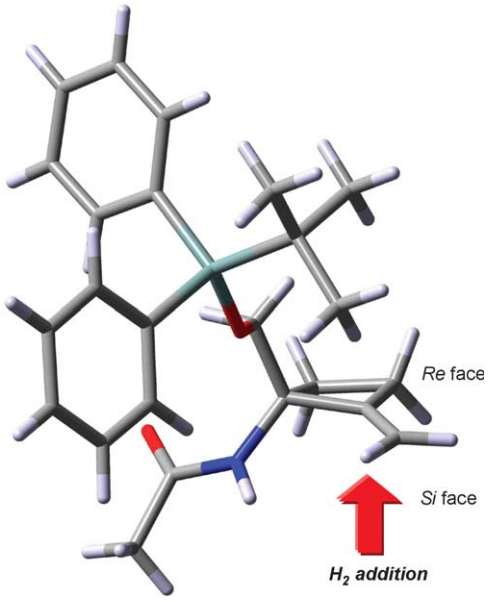


Figure 6. Optimized structure at B3LYP/6-31G(d) level considering solvent effects (Onsager) for compound **8**.

The geometry obtained from the calculations that considered the solvent effects was very similar to that obtained from the solid state. In order to confirm this feature a gradient-enhanced 2D NOESY experiment,[21] using a mixing time of 500 ms, was performed on compound **8** and a small NOE enhancement between vinylic protons and the protons of the *tert*-butyl group was observed. Therefore, it can be concluded that the conformation obtained in both the calculation and the solid state also exists in solution (Fig. 6).

In this situation the *tert*-butyl group probably shields the *re*

face of the double bond of compound **8** in such a way that the olefinic bond is forced to coordinate to the catalyst surface by the *Si* face. Consequently, the addition of hydrogen occurs at this face to give a remarkably stereochemically controlled hydrogenated product (1*S**,2*S**)-**12** (Fig. 6). In contrast, when the hydrogenation is carried out on olefin **9**, we believe that the opposite selectivity obtained is due to the presence of a coordinating function, that is, the primary alcohol, in the olefinic molecule. This group anchors itself on the catalyst surface and forces the addition of hydrogen to its own side of the molecule (*Re* face). There are numerous examples in the literature of such an anchoring effect.[22]

3. Conclusions

In summary, we have developed a new stereoselective synthetic route for 2-substituted cyclobutane-α-amino acids from the cycloadduct obtained in the formal [2+2] cycloaddition of methyl 2-acetamidoacrylate and ketene diethyl acetal. Two kinds of α-amino acid could be synthesised, 2-alkyl- and 2-alkylidenecyclobutane-α-amino acids. As an example of the first type, both stereoisomers of the well-known 2,4-methanovaline were obtained in racemic form by stereocontrolled reactions on the aforementioned cyclobutane derivative. The key step is the hydrogenation of an exocyclic double bond. This reaction is controlled by the functional groups attached to the cyclobutane skeleton. The second type of amino acid was exemplified by the synthesis of 1-amino-2-methylene-cyclobutane-1-carboxylic acid, which can be considered as a conformationally restricted analogue of an important β,γ-unsaturated α-amino acid (α-vinylalanine).

4. Experimental

4.1. General procedures

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer using $CDCl_3$ with TMS as the internal standard or using CD_3OD or D_2O with TMS as the external standard with a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants, proton–proton COSY experiments and proton–carbon HETCOR experiments on a Bruker AVANCE 400 spectrometer. This spectrometer was also used for the selective gradient-enhanced 1D ROESY and 2D NOESY experiments described in the text. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values.

4.1.1. *N*-[1-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylenecyclobutyl]acetamide 8. Methyltriphenylphosphonium bromide (1.36 g, 3.80 mmol) was suspended in THF (20 mL) at 25 °C and KHMDS (0.5 M in toluene, 7.6 mL, 3.80 mmol) was added. The resulting yellow suspension was stirred at 25 °C for 1 h, then cooled to −78 °C and a solution of ketone **3** (500 mg, 1.27 mmol) in THF (10 mL) was added dropwise. The cooling bath was removed and the mixture allowed to reach 25 °C over 5 h. The reaction was quenched with MeOH (2 mL) and the resulting mixture was poured into a saturated solution of potassium sodium tartrate and H_2O (1:1, v/v, 30 mL). Extraction with ethyl ether (2×15 mL), drying and evaporation of the solvent gave a pale yellow syrup, which was purified by column chromatography (hexane/ethyl acetate, 7:3) to give **8** (430 mg, 86%) as a white solid. Mp 114–116 °C. ^{1}H NMR ($CDCl_3$): δ 1.08 [s, 9H, $C(CH_3)_3$], 1.92 (s, 3H, CH_3CO), 1.97–2.08 (m, 1H, CH_2C–N), 2.40–2.72 (m, 3H, CH_2C–N, $CH_2C{=}CH_2$), 3.76 (d, 1H, J=9.9 Hz, CH_2O), 3.87 (d, 1H, J=10.2 Hz, CH_2O), 4.91 (s, 1H, C=CH_2), 5.05 (s, 1H, C=CH_2), 5.88 (br s, 1H, NH), 7.36–7.47 (m, 6H, Arom.), 7.64–7.68 (m, 4H, Arom.); ^{13}C NMR ($CDCl_3$): δ 19.3 [$C(CH_3)_3$], 23.9 (CH_3CO), 25.7 (CH_2C–N), 26.8 [$C(CH_3)_3$], 27.0 ($CH_2C{=}CH_2$), 63.1 (CCH_2O), 66.7 (CCH_2O), 106.5 (C=CH_2), 127.8, 129.7 (Arom.), 133.2 (C=CH_2), 135.6, 151.1 (Arom.), 169.2 (CONH); ESI$^+$ (m/z)=393.9. Anal. Calcd for $C_{24}H_{31}NO_2Si$: C, 73.24; H, 7.94; N, 3.56. Found: C, 73.54; H, 7.90; N, 3.50.

4.1.2. *N*-[1-(Hydroxymethyl)-2-methylenecyclobutyl]-acetamide 9. TBAF (1.53 mL, 1 M in THF) was added to a solution of compound **8** (500 mg, 1.53 mmol) in dry THF (15 mL) at 25 °C under an inert atmosphere and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the organic material was extracted with $CHCl_3$/^{i}PrOH (4:1) (2×20 mL). The organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (5:95), to give 180 mg (91%) of **9** as a white solid. Mp 85–87 °C. ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H, CH_3CO), 2.17–2.24 (m, 1H, CH_2C–N), 2.30–2.39 (m, 1H, CH_2C–N), 2.54–2.63 (m, 2H, $CH_2C{=}CH_2$), 3.65–3.77 (m, 2H, CH_2O), 4.86 (s, 1H, C=CH_2), 4.99 (s, 1H, C=CH_2), 6.44 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 23.5 ($CH_2C{=}CH_2$), 25.8 (CH_3CO), 28.1 (CH_2C–N), 64.7 (CCH_2O), 67.0 (CCH_2O), 106.6 (C=CH_2), 151.1 (C=CH_2), 171.2 (CONH); ESI$^+$ (m/z)=156.1. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.97; H, 8.47; N, 9.07.

4.1.3. 1-Acetamido-2-methylenecyclobutane-1-carboxylic acid 10. To a solution of compound **9** (120 mg, 0.77 mmol) in acetone (15 mL) at 0 °C was added a 2.0-fold excess of Jones reagent (0.77 mL, 2 M in water) dropwise over 5 min. The mixture was stirred at 0 °C for 4 h. The excess Jones reagent was destroyed with ^{i}PrOH. The mixture was then diluted with water (10 mL) and extracted with $CHCl_3$/^{i}PrOH (4:1) (3×15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give 77 mg (64%) of compound **10** as a white solid. This compound was used in the next step without further purification. Mp >200 °C (decomp.). ^{1}H NMR (CD_3OD): δ 1.96 (s, 3H, CH_3CO), 2.04–2.13 (m, 1H), 2.67–2.79 (m, 2H), 2.86–2.95 (m, 1H), 5.00 (s, 1H, C=CH_2), 5.23 (s, 1H, C=CH_2); ^{13}C NMR (CD_3OD): δ 21.5, 26.4, 28.7, 64.4 ($CCOO$), 109.9 (C=CH_2), 147.0

(C=CH_2), 173.9, 175.0 (COO, CONH); ESI^+ (m/z)= 170.1.

4.1.4. 1-Acetamido-2-methylenecyclobutane-1-carboxylic acid methyl ester 11. Compound **10** was purified by transforming the carboxylic acid group into the corresponding methyl ester by addition of an excess of an ethereal solution of diazomethane to a solution of the carboxylic acid **10** (12 mg, 0.07 mmol) in ethyl ether (3 mL). The mixture was stirred for 10 min, then anhydrous $CaCl_2$ was added and the solution was filtered, the solvent evaporated and the residue purified by silica gel column chromatography, eluting with hexane/ethyl acetate (3:7), to give 9 mg (85%) of methyl ester **11** as a colourless oil. ^1H NMR ($CDCl_3$): δ 2.00 (s, 3H, CH_3CO), 2.27–2.37 (m, 1H, CH_2CCOO), 2.72–2.79 (m, 2H, CH_2C=CH_2), 2.85–2.91 (m, 1H, CH_2CCOO), 3.75 ($COOCH_3$), 4.96 (s, 1H, C=CH_2), 5.09 (s, 1H, C=CH_2), 6.38 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 23.0 (CH_3CO), 26.3 (CH_2C=CH_2), 28.8 (CH_2CCOO), 52.8 ($COOCH_3$), 64.4 ($CCOO$), 108.4 (C=CH_2), 148.2 (C=CH_2), 169.4, 171.3 (COO, CONH); ESI^+ (m/z)=184.0. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.91; H, 7.22; N, 7.58.

4.1.5. 1-Amino-2-methylenecyclobutane-1-carboxylic acid hydrochloride salt 7·HCl. The white solid corresponding to carboxylic acid **10** (77 mg, 0.46 mmol) was dissolved in aqueous 3 N HCl (5 mL) and heated at 100 °C for 3 h. The solution was concentrated to give a residue, which was eluted through a C18 reverse-phase Sep-pak cartridge to give, after removal of the water, 39 mg of a white solid; yield: 51%. Mp >200 °C (decomp.). ^1H NMR (D_2O): δ 2.31–2.41 (m, 1H), 2.66–2.75 (m, 2H), 2.84–2.92 (m, 1H), 5.21–5.24 (m, 1H, C=CH_2), 5.27–5.29 (m, 1H, C=CH_2); ^{13}C NMR (D_2O): δ 25.1 (CH_2C=CH_2), 27.5 (CH_2CCOO), 63.5 ($CCOO$), 113.1 (C=CH_2), 144.8 (C=CH_2), 173.1 (COO). Anal. Calcd for $C_6H_{10}ClNO_2$: C, 44.05; H, 6.16; N, 8.56. Found: C, 44.18; H, 6.20; N, 8.61.

4.1.6. (1*S,2*S**)-*N*-[1-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*S**)-12.** A solution of olefin **8** (200 mg, 0.51 mmol) in dichloromethane (40 mL) was hydrogenated at 20 °C for 15 h with 10% palladium–carbon (40 mg) as a catalyst. Removal of the catalyst and the solvent gave a white solid corresponding to a mixture of compounds (1*S**,2*S**)-**12** and (1*S**,2*R**)-**12** in a ratio of 93:7 in favour of (1*S**,2*S**)-**12** and in 96% yield. The major compound was purified by column chromatography (hexane/ethyl acetate, 65:35) to give (1*S**,2*S**)-**12** (179 mg, 89%) as a white solid. Mp 116–117 °C. ^1H NMR ($CDCl_3$): δ 1.05–1.08 [m, 12H, CH_3CH, $C(CH_3)_3$], 1.25–1.38 (m, 1H, CH_2CH), 1.86 (s, 3H, CH_3CO), 1.91–2.04 (m, 2H, CH_2CH, CH_2C), 2.19–2.29 (m, 1H, CH_2C), 2.74–2.87 (m, 1H, CH_3CH), 3.82 (d, 1H, J=10.2 Hz, CH_2O), 3.95 (d, 1H, J=10.2 Hz, CH_2O), 5.69 (br s, 1H, NH), 7.37–7.47 (m, 6H, Arom.), 7.66–7.86 (m, 4H, Arom.); ^{13}C NMR ($CDCl_3$): δ 15.6 (CH_3CH), 19.4 [$C(CH_3)_3$], 23.0 (CH_2CH), 24.0 (CH_3CO), 26.9 [$C(CH_3)_3$], 27.1 (CH_2C), 37.9 (CH_3CH), 59.8 (CH_2C), 64.0 (CH_2O), 127.8, 129.8, 133.5, 135.6 (Arom.), 169.3 (CONH); ESI^+ (m/z)=396.4. Anal. Calcd for $C_{24}H_{33}NO_2Si$: C, 72.86; H, 8.41; N, 3.54. Found: C, 72.94; H, 8.48; N, 3.58.

4.1.7. (1*S,2*S**)-*N*-[1-(Hydroxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*S**)-13.** TBAF (0.52 mL, 1 M in THF) was added to a solution of (1*S**,2*S**)-**12** (170 mg, 0.43 mmol) in dry THF (15 mL) at 20 °C under an inert atmosphere and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (10 mL) was added and the organic material was extracted with $CHCl_3$/^{i}PrOH (4:1) (2×15 mL). The combined organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (5:95), to give 52 mg (76%) of (1*S**,2*S**)-**13** as a white solid. Mp 112–113 °C. ^1H NMR ($CDCl_3$): δ 1.08 (d, 3H, J=7.0 Hz, CH_3CH), 1.40–1.53 (m, 1H, CH_2CH), 1.87–2.10 (m, 5H, CH_3CO, CH_2CH, CH_2C), 2.21–2.29 (m, 1H, CH_2C), 2.46–2.54 (m, 1H, CH_3CH), 3.77–3.88 (m, 2H, CH_2O), 4.38 (br s, 1H, OH), 6.22 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 15.0 (CH_3CH), 23.1 (CH_2CH), 23.6 (CH_3CO), 28.4 (CH_2C), 39.8 (CH_3CH), 60.4 (CH_2C), 65.0 (CH_2O), 171.5 (CONH); ESI^+ (m/z)=158.3. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.22; H, 9.56; N, 8.88.

4.1.8. (1*S,2*S**)-1-Acetamido-2-methylcyclobutane-1-carboxylic acid (1*S**,2*S**)-14.** To a solution of (1*S**,2*S**)-**13** (49 mg, 0.32 mmol) in acetone (10 mL) at 0 °C was added a 1.5-fold excess of Jones reagent (0.23 mL, 2 M in water) dropwise over 5 min. The mixture was stirred at 20 °C for 2 h. The excess Jones reagent was destroyed with ^{i}PrOH. The mixture was then diluted with water (10 mL) and extracted with $CHCl_3$/^{i}PrOH (4:1) (3×15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give 40 mg (73%) of (1*S**,2*S**)-**14** as a white solid. This compound was used in the next step without further purification. Mp >200 °C (decomp.). ^1H NMR (CD_3OD): δ 1.03 (d, 3H, J=5.4 Hz, CH_3CH), 1.63–1.75 (m, 1H, CH_2CH), 1.87–2.07 (m, 5H, CH_3CO, CH_2CH, CH_2C), 2.61–2.82 (m, 2H, CH_2C, CH_3CH); ^{13}C NMR (CD_3OD): δ 16.9 (CH_3CH), 22.5 (CH_3CO), 24.6 (CH_2CH), 30.6 (CH_2C), 39.7 (CH_3CH), 64.0 (CH_2C), 172.9, 175.9 (COO, CONH); ESI^+ (m/z)=172.2.

4.1.9. (1*S,2*S**)-1-Amino-2-methylcyclobutane-1-carboxylic acid hydrochloride salt (1*S**,2*S**)-1·HCl.** The white solid corresponding to carboxylic acid (1*S**,2*S**)-**14** (20 mg, 0.12 mmol) was dissolved in aqueous 3 N HCl (3 mL) and heated at 100 °C for 6 h. The solution was concentrated to give 18 mg of a white solid; yield: 90%. Mp >200 °C (decomp.). Spectral data in CD_3OD agree with those published in the literature[7] for the corresponding enantiopure forms; the spectral data in D_2O are given below. ^1H NMR (D_2O): δ 1.04 (d, 3H, J=6.3 Hz, CH_3CH), 1.75–1.87 (m, 1H, CH_2CH), 2.04–2.27 (m, 2H, CH_2CH, CH_2C), 2.49–2.56 (m, 1H, CH_2C), 2.81–2.88 (m, 1H, CH_3CH); ^{13}C NMR (D_2O): δ 15.9 (CH_3CH), 23.5 (CH_2CH), 27.2 (CH_2C), 39.4 (CH_3CH), 62.5 (CH_2C), 173.7 (COO). Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.43; H, 7.37; N, 8.51.

4.1.10. (1*S,2*R**)-*N*-[1-(*tert*-Butyldiphenylsilyloxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*R**)-12.** A solution of olefin **9** (120 mg, 0.78 mmol) in dichloromethane (60 mL) was hydrogenated at 20 °C for 17 h with 10% palladium hydroxide–carbon (12 mg) as a catalyst. Removal of the catalyst and the solvent gave a white solid

corresponding to a mixture of compounds (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** in a 35:65 ratio in favour of (1*S**,2*R**)-**13** and in 95% yield. This mixture could not be separated by column chromatography and therefore the compounds were transformed into the corresponding silylated derivatives. To a solution of the mixture of (1*S**,2*S**)-**13** and (1*S**,2*R**)-**13** (90 mg, 0.57 mmol) in DMF (5 mL) were added imidazole (117 mg, 1.70 mmol) and TBDPSCl (0.43 mL, 1.80 mmol) and the mixture was stirred at 50 °C for 17 h. The solvent was evaporated under reduced pressure and 5% aqueous $NaHCO_3$ (10 mL) and ethyl acetate (15 mL) were added. The organic layer was separated and the aqueous layer was washed with ethyl acetate (3×10 mL). The combined organic layers were dried, filtered and the solvent evaporated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (65:35), to give 50 mg of (1*S**,2*R**)-**12** (32% from **9**) as a white solid. Mp 146–147 °C. ^{1}H NMR ($CDCl_3$): δ 1.07–1.12 [m, 12H, CH_3CH, C(CH_3)$_3$], 1.43–1.51 (m, 1H, CH_2CH), 1.86–1.99 (m, 4H, CH_2CH, CH_3CO), 2.09–2.13 (m, 1H, CH_2C), 2.19–2.29 (m, 1H, CH_2C), 2.40–2.44 (m, 1H, CH_3C*H*), 3.87 (d, 1H, J=10.0 Hz, CH_2O), 3.97 (d, 1H, J=10.0 Hz, CH_2O), 5.50 (br s, 1H, NH), 7.36–7.45 (m, 6H, Arom.), 7.63–7.74 (m, 4H, Arom.); ^{13}C NMR ($CDCl_3$): δ 15.8 (*C*H_3CH), 19.4 [*C*(CH_3)$_3$], 23.6 (*C*H_2CH), 23.8 (*C*H_3CO), 26.6 (*C*H_2C), 26.9 [C(*C*H_3)$_3$], 34.8 (CH_3*C*H), 59.8 (CH_2*C*), 67.0 (CH_2O), 127.7, 129.6, 129.7, 133.7, 133.8, 134.8, 135.6, 135.7 (Arom.), 169.5 (CONH); ESI$^+$ (m/z)=396.4. Anal. Calcd for $C_{24}H_{33}NO_2Si$: C, 72.86; H, 8.41; N, 3.54. Found: C, 72.92; H, 8.45; N, 3.61.

4.1.11. (1*S,2*R**)-*N*-[1-(Hydroxymethyl)-2-methylcyclobutyl]acetamide (1*S**,2*R**)-13.** TBAF (0.15 mL, 1 M in THF) was added to a solution of (1*S**,2*R**)-**12** (50 mg, 0.13 mmol) in dry THF (10 mL) at 20 °C under an inert atmosphere and the mixture was stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added and the organic material was extracted with $CHCl_3$/^{i}PrOH (4:1) (2×10 mL). The organic layers were dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (5:95), to give 20 mg (95%) of (1*S**,2*R**)-**13** as a white solid. Mp 94–95 °C. ^{1}H NMR ($CDCl_3$): δ 1.10 (d, 3H, J=7.2 Hz, CH_3CH), 1.43–1.50 (m, 1H, CH_2CH), 1.91–2.09 (m, 6H, CH_3CO, CH_2CH, CH_2C), 2.60–2.67 (m, 1H, CH_3C*H*), 3.79 (s, 2H, CH_2O), 4.79 (br s, 1H, OH), 5.83 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 16.0 (*C*H_3CH), 22.9 (*C*H_2CH), 23.4 (*C*H_3CO), 29.2 (*C*H_2C), 34.5 (CH_3*C*H), 60.4 (CH_2*C*), 69.2 (CH_2O), 171.7 (CONH); ESI$^+$ (m/z)=158.3. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.25; H, 9.70; N, 8.96.

4.1.12. (1*S,2*R**)-1-Acetamido-2-methylcyclobutane-1-carboxylic acid (1*S**,2*R**)-14.** To a solution of (1*S**,2*R**)-**13** (20 mg, 0.14 mmol) in acetone (7 mL) at 0 °C was added a 2.0-fold excess of Jones reagent (0.14 mL, 2 M in water) dropwise over 5 min. The mixture was stirred at 20 °C for 2 h. The excess Jones reagent was destroyed with ^{i}PrOH. The mixture was then diluted with water (10 mL) and extracted with $CHCl_3$/^{i}PrOH (4:1) (3× 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give 15 mg (63%) of (1*S**,2*R**)-**14** as a white solid. This compound was used in the next step without further purification. Mp > 200 °C (decomp.). ^{1}H NMR (CD_3OD): δ 1.03 (d, 3H, J= 7.2 Hz, CH_3CH), 1.44–1.54 (m, 1H, CH_2CH), 1.97 (s, 3H, CH_3CO), 2.12–2.31 (m, 3H, CH_2CH, CH_2C), 3.04–3.11 (m, 1H, CH_3C*H*); ^{13}C NMR (CD_3OD): δ 16.3 (*C*H_3CH), 22.2 (*C*H_3CO), 24.4 (*C*H_2CH), 29.9 (*C*H_2C), 37.0 (CH_3*C*H), 61.8 (CH_2*C*), 173.5, 177.4 (COO, CONH); ESI$^+$ (m/z)=172.2.

4.1.13. (1*S,2*R**)-1-Amino-2-methylcyclobutane-1-carboxylic acid hydrochloride salt (1*S**,2*R**)-1·HCl.** The white solid corresponding to carboxylic acid (1*S**,2*R**)-**14** (10 mg, 0.06 mmol) was dissolved in aqueous 3 N HCl (2 mL) and heated at 100 °C for 6 h. The solution was concentrated to give 7 mg of a white solid; yield: 70%. Mp >200 °C (decomp.). Spectral data in CD_3OD agree with those published in the literature[7] for the corresponding enantiopure forms; the spectral data in D_2O are given below. ^{1}H NMR (D_2O): δ 1.14 (d, 3H, J=7.5 Hz, CH_3CH), 1.75–1.88 (m, 1H, CH_2CH), 2.17–2.35 (m, 2H, CH_2CH, CH_2C), 2.61–2.71 (m, 1H, CH_2C), 3.03–3.15 (m, 1H, CH_3C*H*); ^{13}C NMR (D_2O): δ 15.4 (*C*H_3CH), 24.1 (*C*H_2CH), 27.9 (*C*H_2C), 37.0 (CH_3*C*H), 62.3 (CH_2*C*), 175.2 (COO). Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46. Found: C, 43.41; H, 7.41; N, 8.53.

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Corrigendum

Corrigendum to "Reaction of 3/2-formylindoles with TOSMIC: formation of indolyloxazoles and stable indolyl primary enamines"

[Tetrahedron 61 (2005) 1793]

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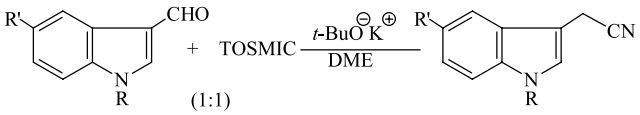

R=H, Me, Bn; R'=H, OMe

Scheme 2.

Scheme 2 contained errors and should be replaced by the corrected version as shown above.

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