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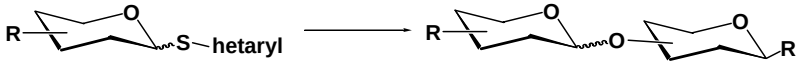

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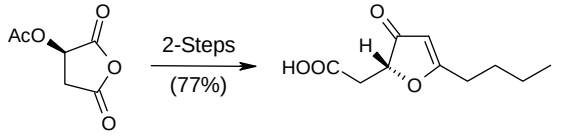

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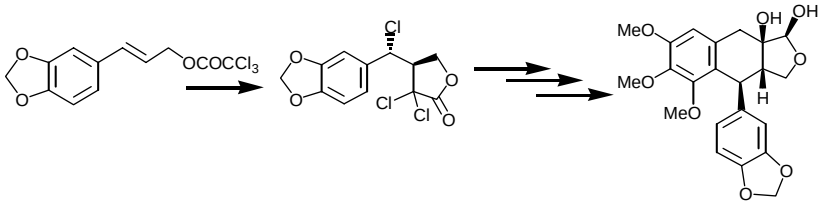

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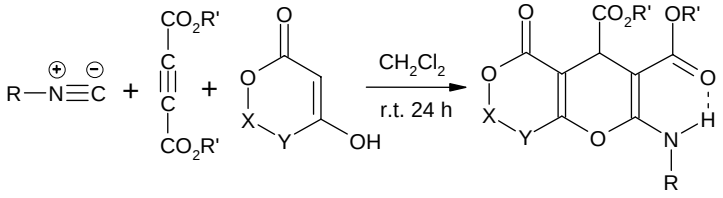

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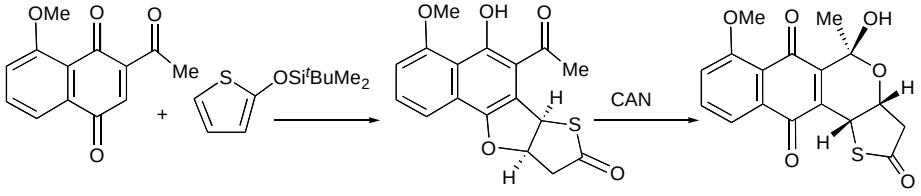

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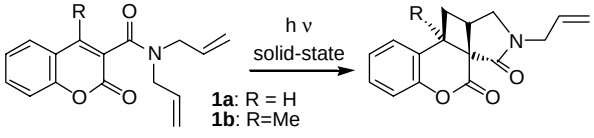

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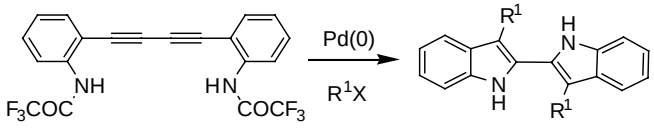

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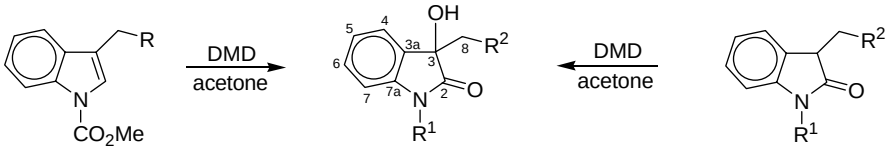

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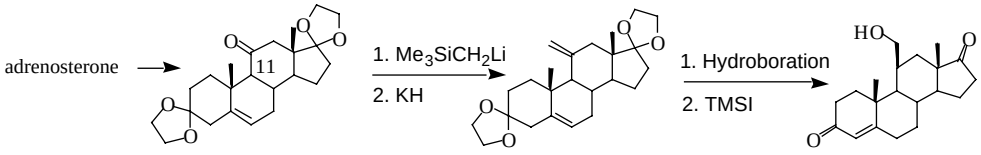

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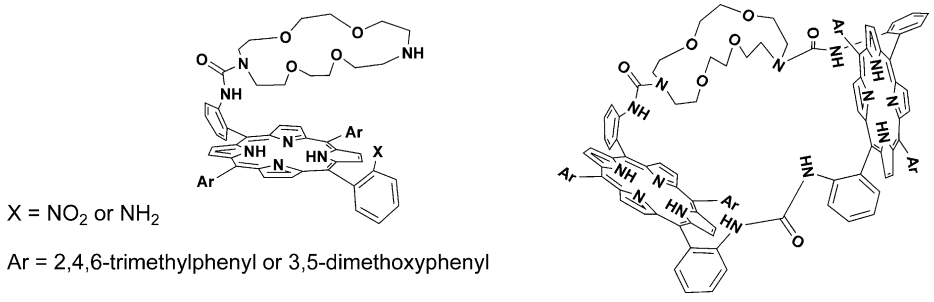

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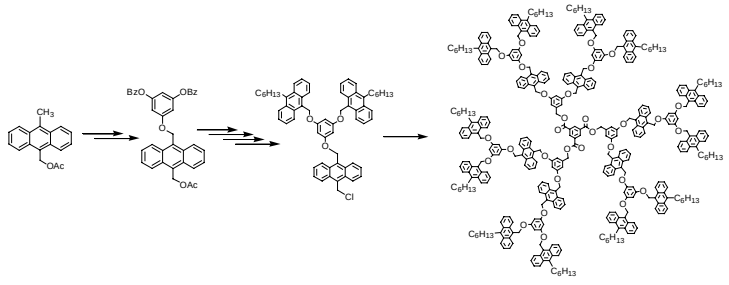

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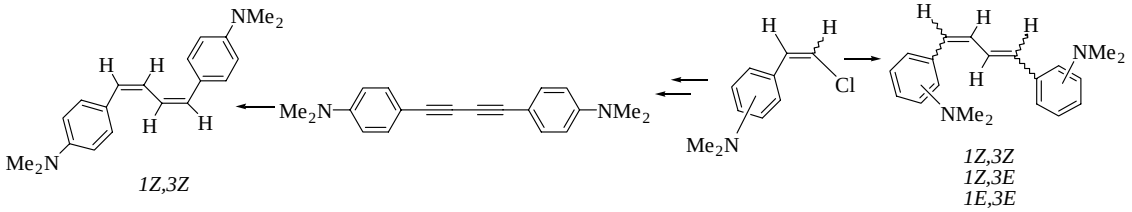

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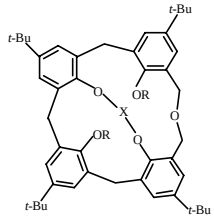

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2 R = CH_2–
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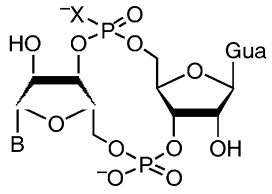

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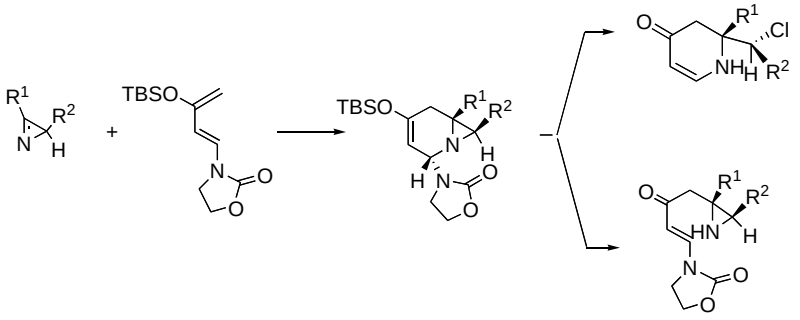

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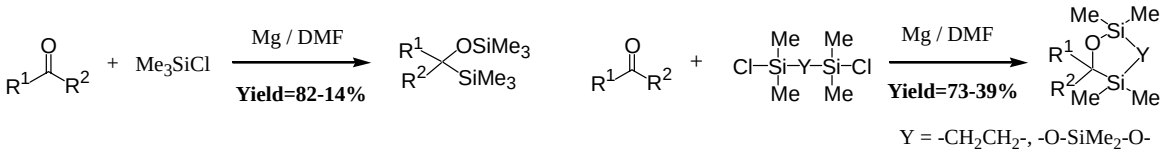

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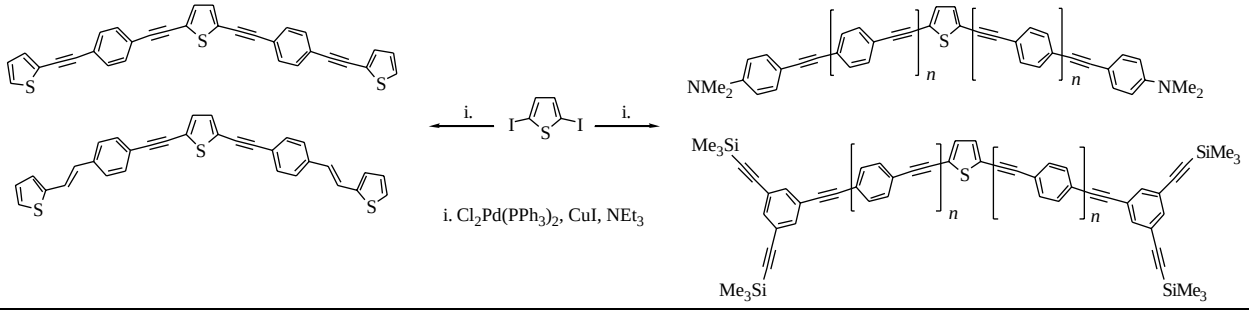

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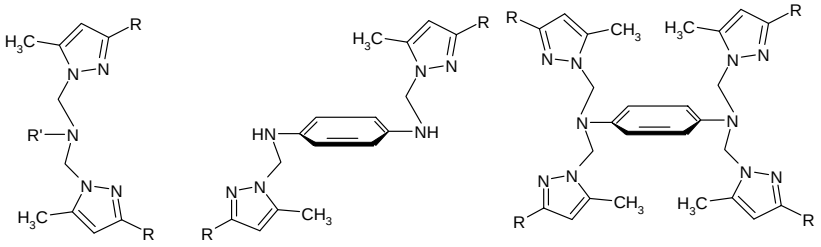

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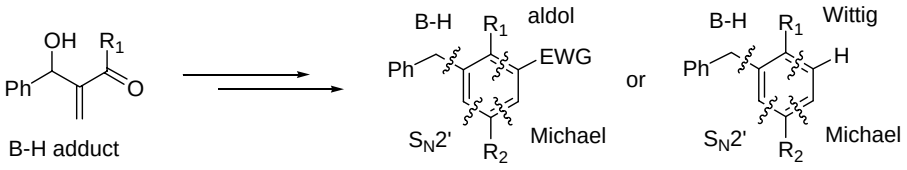

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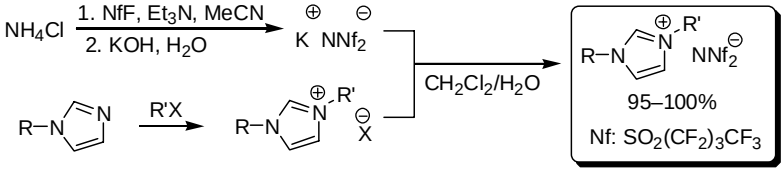

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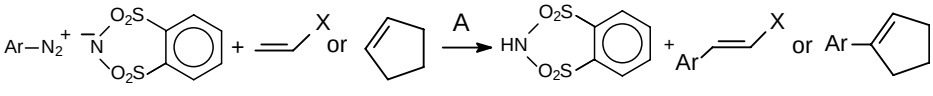

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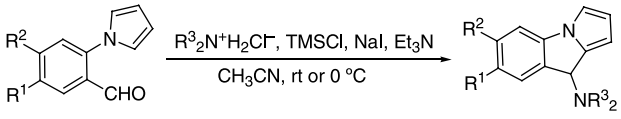

*Corresponding author
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Synthesis and role of glycosylthio heterocycles in carbohydrate chemistry

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Keywords: Thioglycoside; Glycosidation reaction; Glycosylating agents; Heterocycles; *O*-Glycosides; C-Glycosidation; Leaving groups; Anomeric centers.
Abbreviations: SPy, thiopyridyl; SQu, thioquinolinyl; SIm, thioimdazolyl; STh, thiothiazolyl; SBth, thiobenzothiazolyl; SBox, thiobenzoxazolyl; STr, thiotriazolyl; SOxd, thiooxadiazolyl; SThd, thiothiadiazolyl; STe, thiotetrazolyl; SPd, thiopyridazinyl; SPm, thiopyrimidinyl; SPz, thiopyrazinyl; SQz, thioquinazolinyl; SBtz, thiobenzothiazinyl; SQx, thioquinoxalinyl; STz, thiotriazinyl; HMDS, hexamethyldisilazane; TMSOTf, trimethylsilyltriflate; TBAHS, tetrabutylammonium hydrogen sulfate; TBAB, tetrabutylammonium bromide; $BnSOCl_2$, benzylsulfonyl chloride; BnBr, benzyl bromide; DMF, dimethyl formamide; MS, molecular sieves; NIS, *N*-iodosuccinimide; AgOTf, silver triflate; THOf, trifloromethane sulfonic acid; TBDMSOTf, *t*-butyldimethylsilyltriflate.

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1. Introduction

The majority of carbohydrates found in nature or biological systems exist as polysaccharides and/or glycoconjugates in which the monosaccharide units are joined via *O*- or *N*-glycosidic bonds. The necessity to form either a 1,2-*cis* or 1,2-*trans* glycosidic bond with complete stereoselectivity is the main concern during chemical *O*-glycosylations, which is one of the most challenging problems of modern synthetic chemistry. A strong demand still remains, however, to develop simple, mild and efficient methods for stereoselective glycosylations.

Thioglycosides have received considerable attention, because they are widely employed as biological inhibitors,[1–5] inducers[6–8] and ligands[9–12] for affinity chromatography of carbohydrate-processing enzymes and proteins. Moreover, they are promising candidates in synthetic carbohydrate chemistry as convenient and versatile glycosyl donors. Among these glycosyl donors are the thioglycosyl heterocycles that are sufficiently stable under a variety of reaction conditions and have the ability to be readily converted into a variety of other functionalities.[13–15] Most interesting is the divergent use of a number of thioglycosyl heterocycles as glycosyl acceptors and, subsequently, as donors which have been employed for the stereoselective synthesis of oligosaccharides.[13,14,16–20] There is, however, a lack of reviews in the literature on glycosylthio heterocycles, in spite of the fact that thioglycosides in general have been surveyed. Consequently, the present article reviews the literature on thioglycosyl heterocycles, particularly their synthesis and potential in carbohydrate chemistry, as well as their use as biological inhibitors.

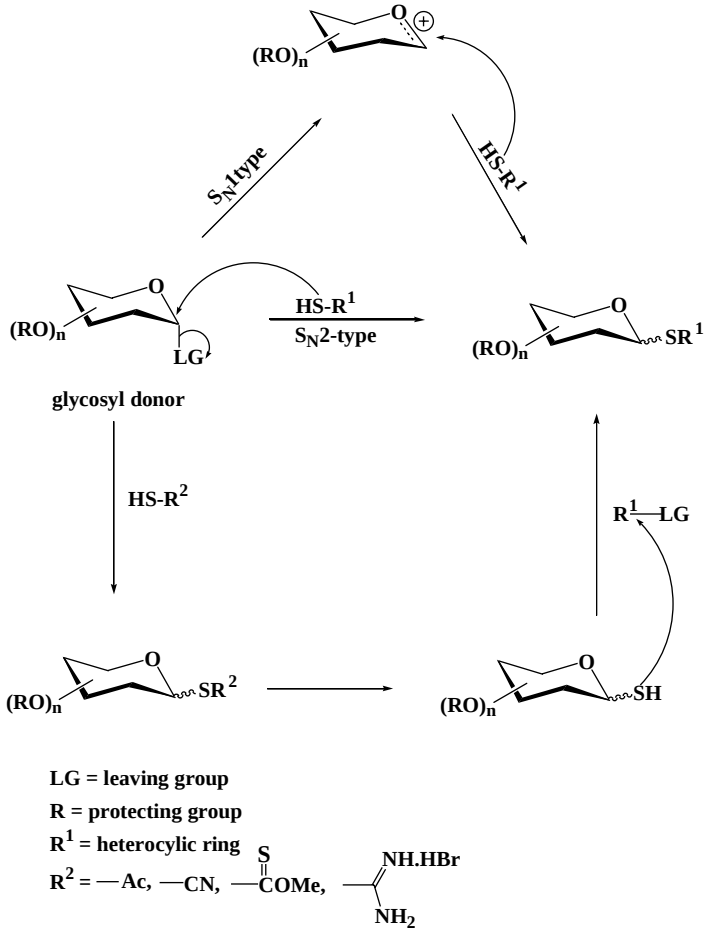
2. Synthesis of glycosylthio heterocycles

The general approaches to the synthesis of thioglycosides may proceed via the direct introduction of the heterocyclic thiol part, either by an S_N^1 or S_N^2 mechanism through a displacement reaction of an anomeric leaving group, sometimes aided by a promoter, in a manner similar to *O*-glycosylation reactions. Alternatively, a two- (or more) step procedure may be employed in which a thiol group is first introduced on the anomeric center, which is then reacted with an electrophile to give the target thioglycoside; the thiol functionality can be generated from the thioglycosyl derivatives having readily cleavable groups, in a selective manner, on the sulfur atom. The generation of α- and/or β-thioglycosyl heterocycles is dependent on all the factors involved in the reaction, particularly the protecting groups on the sugar portion of the glycosyl donor (Scheme 1). Consequently, the available synthetic approaches can be classified according to the structure of the glycosylating agent, and then according to the heterocycle and, in each case, according to the promoter or the catalyst.

2.1. Per-*O*-acylated sugars as glycosylating agents

The anomeric acetoxy group in a glycosyl donor can be efficiently displaced by a thiol group linked to a heterocycle under the influence of an acidic catalyst. The standard procedure is to react a per-*O*-acetylated aldose with a slight excess of thiol using a hard Lewis acid as promoter, which generally gives predominantly a high yield of the 1,2-*trans* product.[21] Various Lewis-acid catalysts have been employed, for example, $BF_3 \cdot Et_2O$, zinc chloride, stannic chloride and ferric chloride.[22–24] Thus, the reaction of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose **1** with 2-mercaptopyridine **2** in the presence of $BF_3 \cdot Et_2O$ in dichloroethane at 0 °C yielded the β-ribofuranoside **3** in 85% yield.[25] Using 4-mercaptopyridine **5** instead of **2**, however, under the same reaction conditions, a 2:1 mixture of the α- and β-anomers of thioribofuranoside **6** was obtained.[25] The trimethylsilyl derivatives of heterocyclic thiols were also used for generating the thioglycosyl heterocycles. Thus, the trimethylsilylated derivative **4** of 2-mercaptopyridine was reacted with **1** in the presence of TMSOTf to give **3**[26] (Scheme 2).

Stannic chloride in acetonitrile was used for the coupling of trimethylsilylated pyridine **9** with **7** or **8** to give the β-thioglycosides[27] **10** and **11**, respectively (Scheme 2).



Scheme 1.

The reaction of polyfunctionalized pyridine-2(1*H*)-thiones **12** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **13**, in the presence of hexamethyldisilazane (HMDS) and ammonium sulphate in methylene chloride containing a catalytic amount of TMSOTf, gave the β-thioribosides **14**.[28]

2-Pyridyl 1-thiogluco- and 1-thiogalacto-pyranosides **15** and **16** were also prepared in 79 and 73% yield, respectively, when glucose or galactose pentaacetates **7** and **8** were reacted with 2-mercaptopyridine **2** in the presence of $ZrCl_4$ in 1,2-dichloroethane[29] (Scheme 2). Deacetylation of **15** followed by tritylation and then benzylation gave **17**.

The reaction of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose **18** with 1-aminoimidazole 2(3*H*)-thione derivatives **19** was catalyzed by *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and TMSOTf at 40 °C to give **20**, exclusively in the β-anomeric configuration, in 66–84% yield.[30] Under the same conditions, D-glucose pentaacetate **7** was coupled with **19** to afford the β-thioglucoside **21** (65% yield).[30] The coupling of **19** (R=4-ClC_6H_4) with **13** was also carried out in the presence of NaH in DMF as a solvent to give **20** (R=4-ClC_6H_4) in low yield (38%)[31] (Scheme 3).

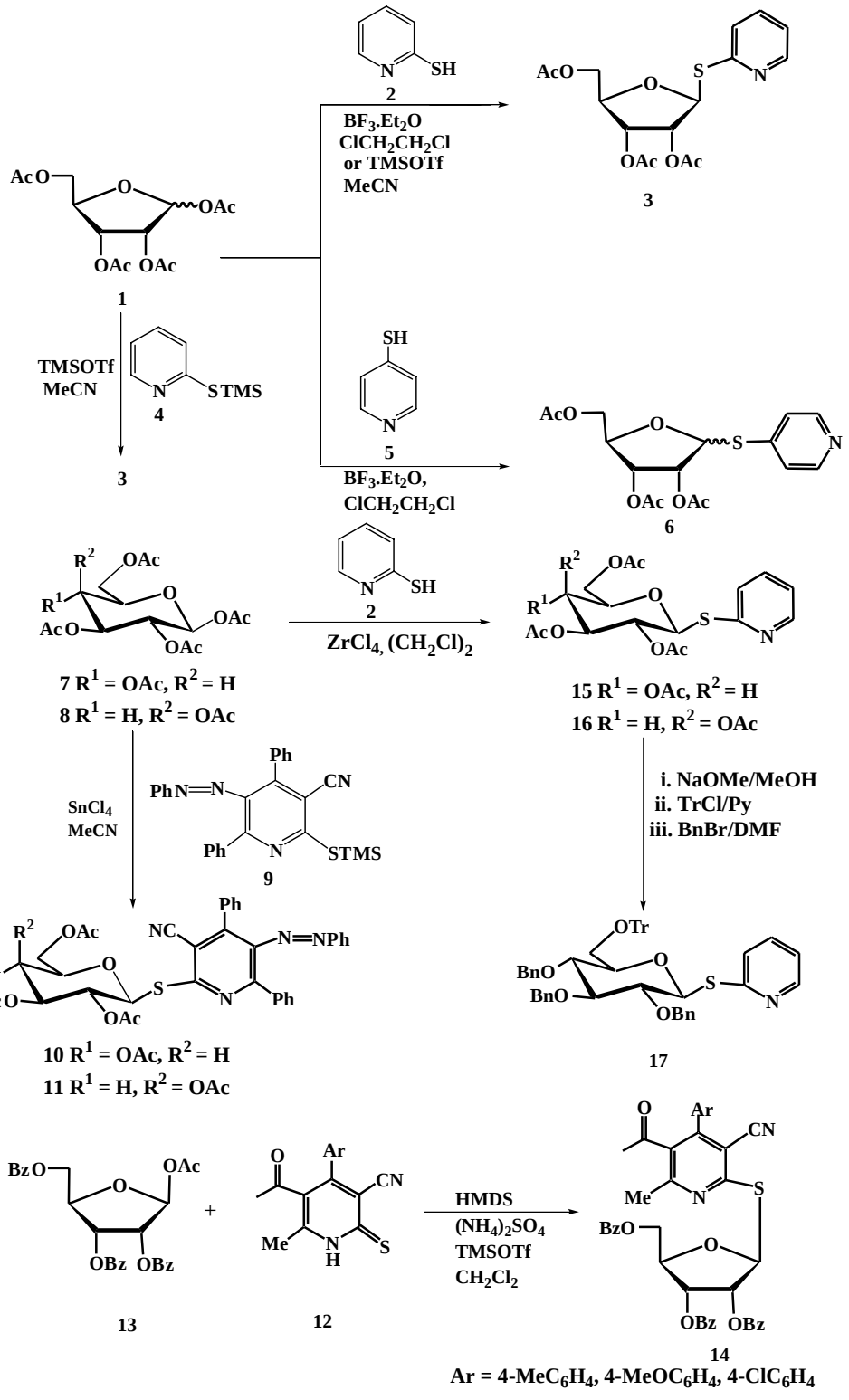
The coupling of **7** with a silylated benzylidene of the thiohydantoin **22** was catalyzed by TMSOTf to afford the β-thioglucoside **23** in 58% yield[32] (Scheme 4). Catalysis of the thioglycosylation with $BF_3\cdot Et_2O$ was used for reacting penta-*O*-acetyl-D-galactofuranose **24** with heterocyclic thiols **25** to give the β-thiofuranosides **26**[33] (Scheme 4).

Coupling of the β-anomer **13** with 5,6-dichloro-2-mercaptobenzimidazole **27** in the presence of TMSOTf at room temperature gave the β-thioriboside[34] **28**.

In the presence of $BF_3\cdot Et_2O$, D-glucose pentaacetate **7** was reacted with 2-mercaptobenzoxazole (**30**, HSBox) to afford **32** as an anomeric mixture (α:β=1:3.5) in 79% yield.[35] On the other hand, when 1,2,4,6-tetra-*O*-acetyl-3-*O*-methyl-D-glucopyranose **29** was coupled with 2-mercaptobenzothiazole **31** under the same reaction conditions, it afforded only the β-thioglucopyranoside derivative **33**.[36] Similarly, 1-thio D-galactofuranoside derivative **26** was obtained when penta-*O*-acetyl-D-galactofuranose **24** was reacted with **31**.[33]

The trimethylsilyl derivative **35** was reacted with **34**β in presence of TMSOTf to afford the β-thioriboside derivative **36** in 78% yield[26] (Scheme 5).

The β-thioglucuronopyranosides **40** and **41** were obtained from the coupling of methyl 1,2,3,4-tetra-*O*-acetyl-β-D-glucuronate **37** with 5-halogenated 2- and 4-mercaptouracils



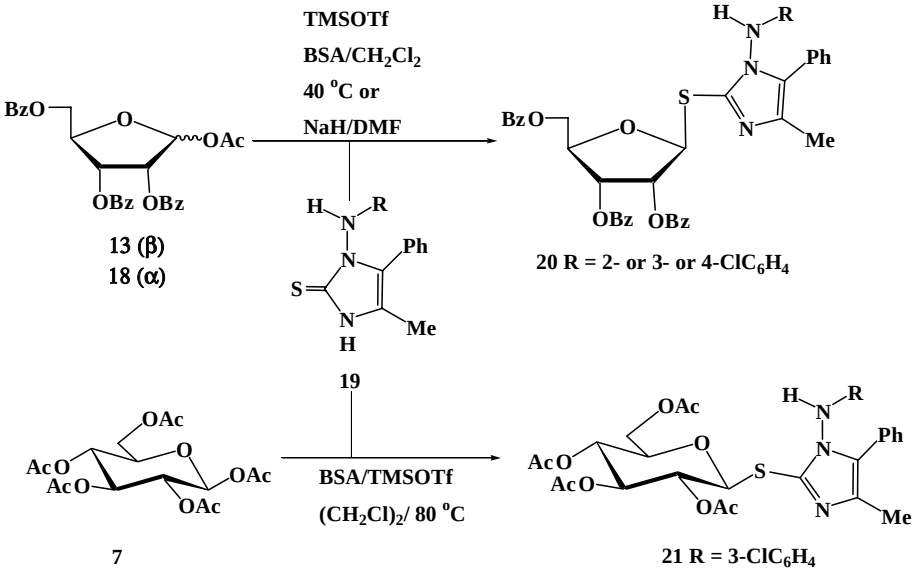
Scheme 2.

38 and **39**, respectively, in the presence of $SnCl_4$ in acetonitrile.[37]

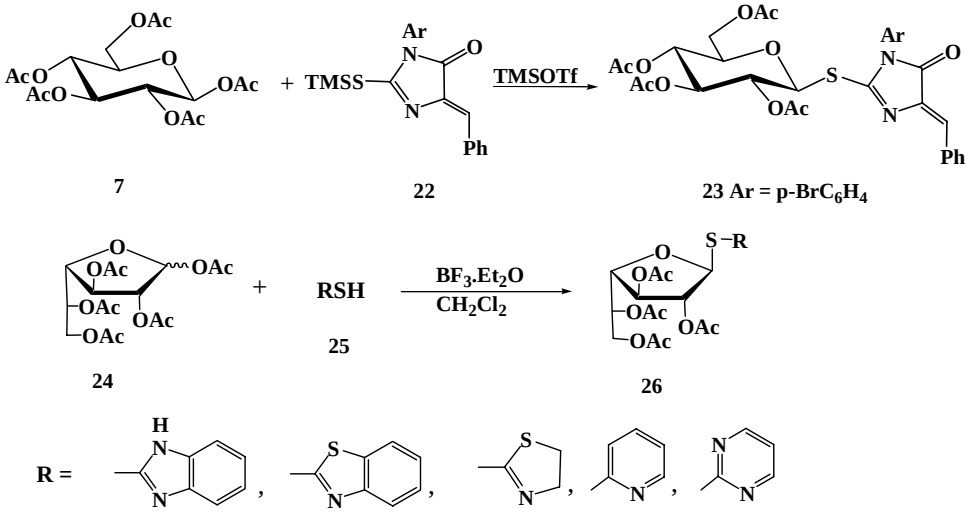
Similarly, 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose **1** was coupled with 4-mercapto-2-methylthiopyrimidine **42**, but in the presence of $BF_3 \cdot Et_2O$, to give the thio-β-D-ribofuranoside **43**[38] (Scheme 6).

2.2. Glycosyl halides as glycosylating agents

A classical route to thioglycosides is the reaction between an acetohalosugar and a thiolate anion. The high nucleophilicity of sulfur towards the anomeric position combined with its rather low basicity make it possible to perform the reaction in acetone or methanol or even in an acetone-water



Scheme 3.



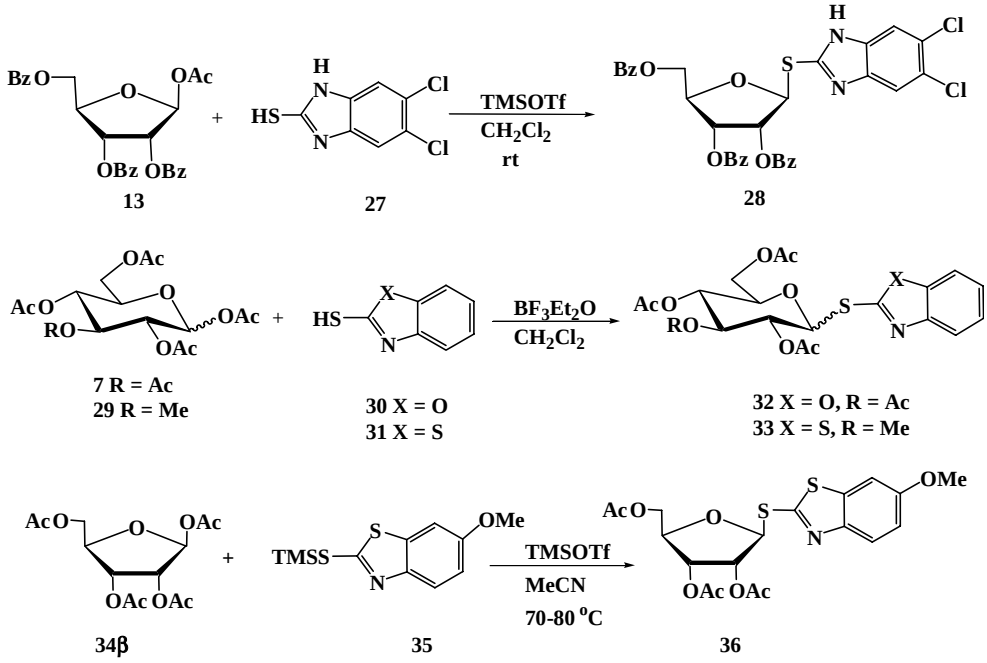
Scheme 4.

mixture. Usually, a 1,2-*trans* product is obtained, possibly through the participation of the 2-*O*-acetyl group, but, if the conditions are carefully selected, a direct S_N^2 displacement reaction can take place.[39] The thiolate anion can be generated from heterocyclic thiols in situ with the aid of bases such as sodium or potassium hydroxide, sodium hydride or potassium carbonate. There are many examples that can be included under this title. Consequently, herein they have been subdivided according to the heterocyclic ring system; heterocycles with one heteroatom come first, followed by those with increasing size and complexity of the ring. Each heterocycle has been denoted by an abbreviation, as reported in the literature, and others were developed for the purpose of this review.

2.2.1. Heterocycles with one heteroatom. Although, thioglycosides of the six-membered ring heterocycle, pyridine, were extensively reported, no examples have been given of the synthesis of the respective thioglycosides of five-membered ring heterocycles with one heteroatom.

2.2.1.1. Thiopyridyl (SPy) glycosides. Thiopyridyl glycosides are the most extensively studied thioglycosyl heterocycles, particularly because of their potential as glycosyl donors. Treatment of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -α-D-galacto-pyranosyl bromide **44** and **45** or 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride **46** with 2-mercaptopyridine **2** in the presence of K_2CO_3 in acetone afforded the respective pyrid-2-yl 1-thio-β-D-glycopyranoside derivatives **15**, **16** and **47**, respectively, in 86 and 72% yield.[14,40,41] The thioglucoside **15** and the thiogalactoside **16** can be obtained in 77 and 86% yield when the coupling was carried out in the presence of NaH in acetonitrile.[26] In the presence of K_2CO_3 in hot toluene–acetone as the solvent, 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl bromide was reacted with **2** to give the thioribofuranoside **48**, which, on debenzoylation and subsequent benzylation, afforded the benzylated derivative[42] **49**.

2-Mercaptopyridine **2** was coupled with α-acetobromo-rhamnose, α-acetobromomaltose and α-acetobromolactose



13 27 28

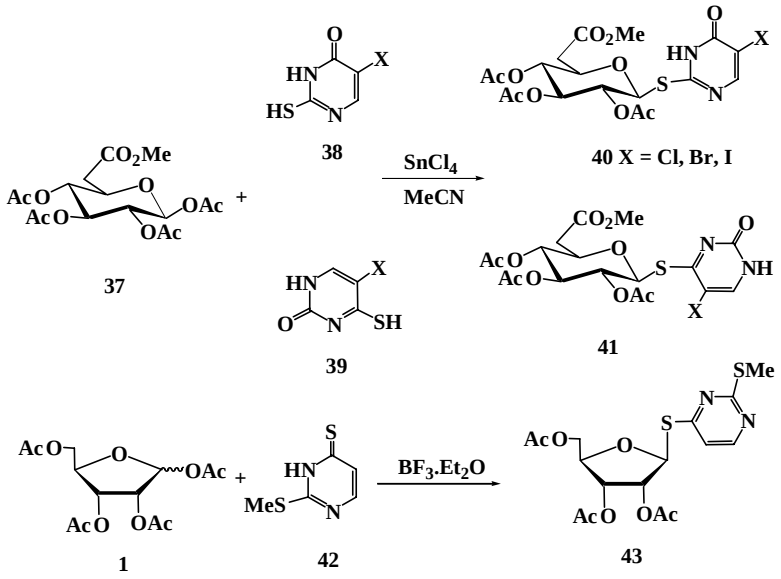
7 R = Ac
29 R = Me

30 X = O
31 X = S

32 X = O, R = Ac
33 X = S, R = Me

34β 35 36

Scheme 5.



37 38 39 40 X = Cl, Br, I 41 1 42 43

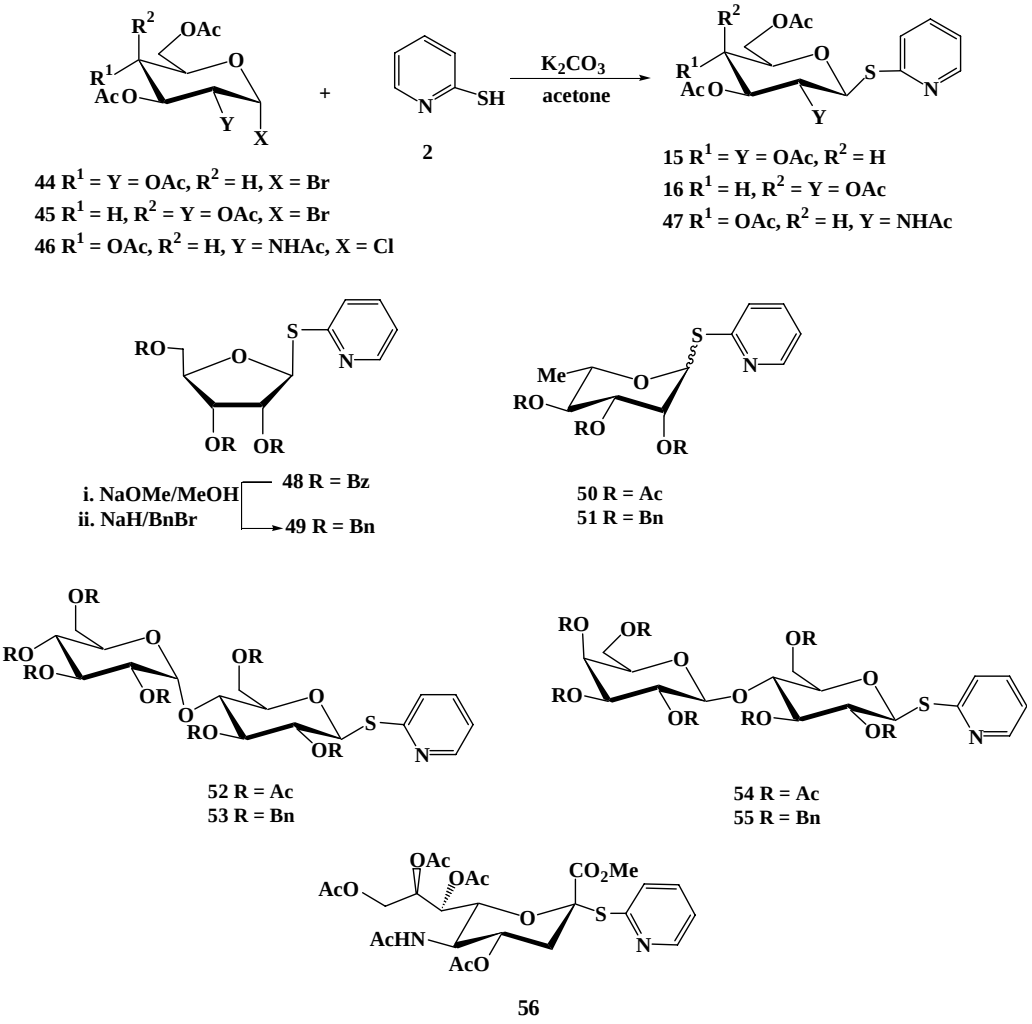
Scheme 6.

to give 1-thio-L-rhamnopyranoside **50**, in an α:β ratio of 1:1, 1-thio-β-maltoside **52** and 1-thio-β-lactoside **54**, respectively.[43,44] Deacetylation followed by benzylation of these thioglycosides gave the benzyl derivatives **51**, **53** and **55**, respectively.[43,44]

Coupling of per-*O*-acetyl β-acetochloroneuraminic ester with **2** at room temperature in the presence of tetra-*n*-butylammonium hydrogen sulfate (TBAHS) and a 1 M solution of sodium carbonate under phase-transfer conditions in either methylene chloride or ethyl acetate afforded the α-thiopyridyl derivative[45] **56** (Scheme 7).

The reaction of sodium salts of 5-arylazo-3-cyano-2-mercaptopyridines **58**, obtained from the reaction of cyanothioacetamide with 2-arylhydrazono-1,3-diphenyl-propane-1,3-diones in the presence of sodium ethoxide, with acetobromoglucose **44** or acetobromogalactose **45** in acetone gave the respective *S*-glycosylated pyridine derivatives **59** and **60** in 67–74% yield (Scheme 8).[27]

Piperidinium salts of dihydropyridine thiolates **61** were also coupled with glucosyl or galactosyl bromide **44** and **45** in dry acetone at 0 °C[46,47] to give the 1,4-dihydro-3-cyanopyridine thioglycosides **62** and **63**, respectively, in good yields. On the other hand, when the reaction was carried out at 30 °C in dry acetone, the corresponding aromatized pyridine thioglycosides **64** and **65**, respectively,[46] were obtained that alternatively resulted from heating **62** and **63** in ethanol (Scheme 8).[48]



Scheme 7.

The synthesis of (2-pyridyl *N*-oxide) thioglycosides **67** and **68** has been achieved by condensation of the sodium salt **66** of 2-pyridinethiol *N*-oxide with acetobromoglucose **44** or methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl bromide uronate **57**. The reaction was dependent on the solvent; when DMF was used, the reaction of **44** with **66** gave **67** in high yield and high purity, whereas the reaction of **57** with **66** in DMF gave **68** in high yields, but in low purity. In methanol, however, **68** was obtained in low yield, but in much higher purity[49] (Scheme 8).

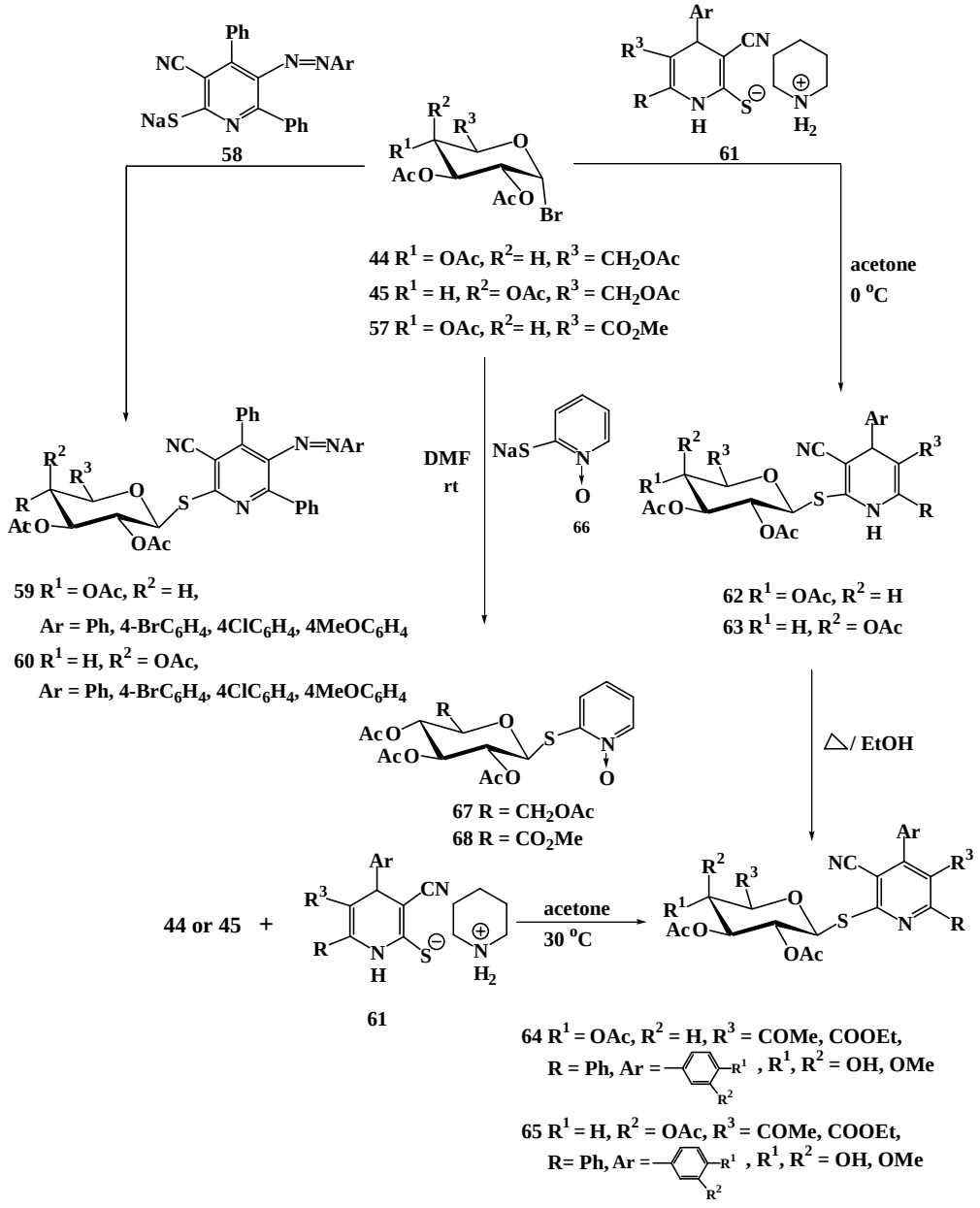
2.2.1.2. Thioquinolinyl (SQu) glycosides. 4-Quinolinyl thioglycosides **70** and **71** were obtained when an alcoholic potassium hydroxide solution of 4-mercaptoquinolines **69** was treated with acetobromoglucose or acetobromolactose.[50] Similarly, the thioglycosides **73** and **74** were obtained from cycloalkanopyridine thiones **72** in aqueous acetone[51,52] (Scheme 9).

2.2.2. Five-membered heterocycles with two heteroatoms.

2.2.2.1. Thioimidazolyl (SIm) glycosides. Glycosylation of 2-mercapto-4,5-diphenylimidazole **75** or 2-mercapto-1,4,5-triphenylimidazole **76** with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -α-D-galacto-pyranosyl bromides or 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride in acetone–DMF in the presence of triethylamine at room temperature gave the β-thioglycosides **77**, **78** and **79**, respectively, in 74–86% yield.[53] The reaction has been accelerated by microwave irradiation to give higher yields (88–94%) within 2–4 min.[53]

Ribosylation of 1-(4-chlorophenyl)amino-2,3,-dihydro-4-methyl-5-phenyl-1*H*-imidazole-2-thione with 2-deoxyribofuranosyl chloride **80** in the presence of NaH in DMF afforded only the β-anomer thioglycoside[31] **82**.

5-Alkylidenes and 5-arylidenes of 3-aryl-2-thiohydantoins have been glycosylated with glycosyl halides in the presence of NaH in acetonitrile to give the *S*-glycosylated hydantoins of the gluco-, galacto- and ribo- analogues.[32,54,55] Similarly, compounds **84** (R^3=H, R^4=naphthyl) were also obtained when **44** or **45** were coupled with the hydantoin derivatives in aqueous potassium hydroxide or potassium carbonate in acetone.[55] When **44** was reacted with the *N*-3-unsubstituted hydantoin derivative under the same conditions, it gave the thioglycoside **84** (R=H) and the thio and *N*-3 diglycosyl derivative **85**.[54] The reaction has been explained to take place at the sulfur followed by further reaction at the nitrogen, when available, to give the diglycosylated derivative that could



Scheme 8.

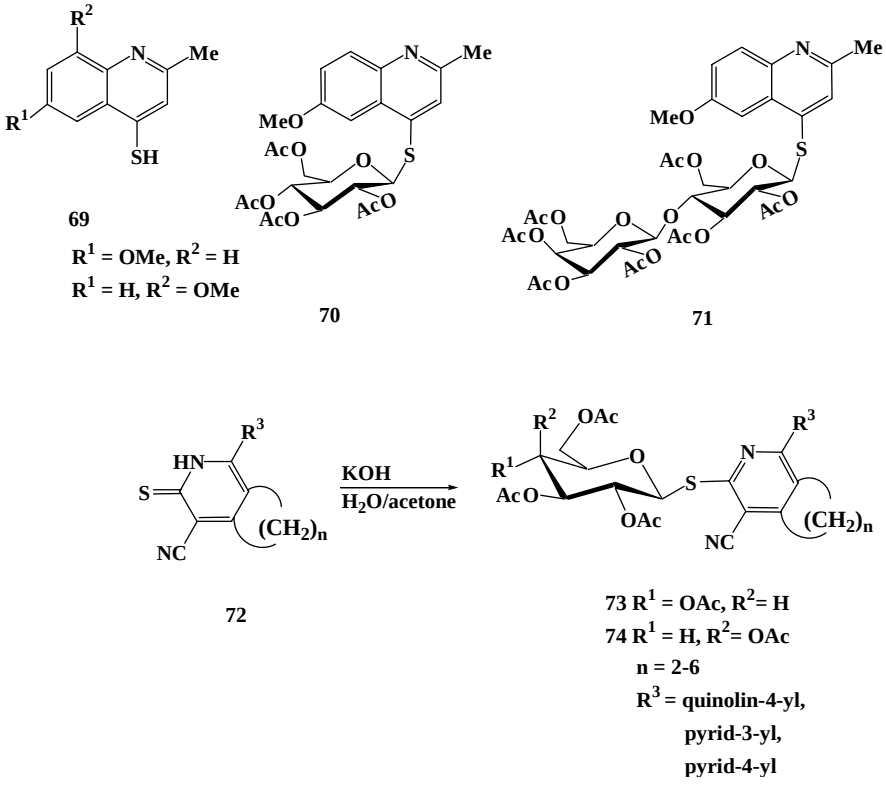
be the only product in the presence of an excess of the glycosylating agent.[55] In one pot, **84** was prepared by coupling 3-aryl-2-thiohydantoin with benzaldehyde in the presence of ethanolic potassium hydroxide followed by subsequent reaction with acetobromoglucose in aqueous acetone.[32]

Under phase-transfer catalysis, imidazolyl-2-α-thio-neura minic ester **87** was obtained in 68% yield when β-aceto-chloroneuraminic ester **86** was reacted with 1-methyl-2-mercaptoimidazole in the presence of TBAHS and a 1 M solution of sodium carbonate in either methylene chloride or ethyl acetate[45] (Scheme 10).

2.2.2.2. Thiobenzimidazolyl (SBim) glycosides. Potassium 1-methylbenzimidazole-2-thiolate **88** gave, upon glucosylation with acetobromoglucose **44** in acetone, 1-methyl-2-(tetra-*O*-acetyl-β-D-glucopyranosylthio)benzimidazole **90** and a small amount of the respective β-*N*-benzimidazole glucoside analogue **92**.[56] Using 5-nitrobenzimidazole **89** in the coupling with **44**, however, afforded only the 5-nitrobenzimidazolyl thioglucoside derivative **91** in 74% yield[41] (Scheme 11).

2.2.2.3. Thiothiazolyl (STh) glycosides. Thiazolin-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **93** has been prepared by the reaction of acetobromoglucose with 2-mercaptothiazoline (**25**, R=thiazolinyl) in the presence of NaH in acetonitrile followed by deacetylation and benzylation[57] to give **94** (Scheme 12).

2.2.2.4. Thiobenzothiazolyl (SBth) glycosides. Conversion of 2-mercaptobenzothiazole **31** into the respective sodium salt with sodium hydride in dry acetonitrile, followed by reaction with acetobromoglucose **44** afforded the β-thioglucoside **96** as the major product (84%) and the β-nucleoside **100** as the minor product (4%).[26] Under the



Scheme 9.

same conditions, the coupling of **44** with 5-methoxy-2-mercaptobenzothiazole **95** gave only the β-thioglucoside **97** in 83% yield.[26] On the other hand, only the thiogalactoside **98** was obtained in 90% yield by reacting the acetylated galactopyranosyl bromide **45** with **31**, whereas, with **95**, the thiogalactoside **99** resulted as the major isomer (60%) and nucleoside **101** as the minor isomer (22%).[26]

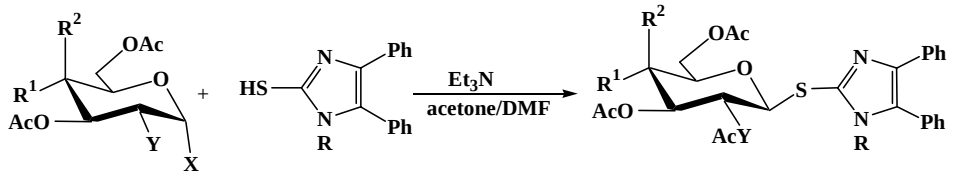
Thiobenzothiazolyl glycoside derivative **102** has been prepared by glycosidation of 2-mercaptobenzothiazole **31** with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride in the presence of 1,8-bis-(dimethylamino)naphthalene in dichloromethane[58] (Scheme 12).

2.2.2.5. Thiobenzoxazolyl (SBox) glycosides. The reaction of 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranosyl bromide **103** with 2-mercaptobenzoxazole (**30**, HSBox) in the presence of potassium carbonate in acetone afforded the β-anomer, benzoxazolyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-thio-β-D-glucopyranoside **108** in high yield.[57] Similarly, the D-galactoside derivative **109** was prepared from **104**. Under the same reaction conditions, **30** was coupled with acetobromoglucose to give the benzoxazolyl thio-β-glucoside **32**.[35,41,57] Prolonged reaction times were required for the transformation of the less reactive benzoyl D-gluco- **105**, D-galacto- **106** and D-manno- **107** bromide derivatives into the respective thioglycosides[35] **110**, **111** and **112**. The synthesis of an SBox glycoside having nonparticipating groups was achieved by deacetylation and subsequent benzylation of **32** to afford the respective thioglucoside **113**.[57] Alternatively, compound **113** was obtained in 75% yield when 2,3,4,6-tetra-*O*-benzyl-α,β-D-glucpyranosyl bromide was treated with HSBox **30** in CH_2Cl_2 in the presence of 1,8-bis(dimethylamino)naphthalene.[41] An alternative method for the synthesis of the thioglycosides **110**, **111** and **112** in 90–97% yields was developed by reacting KSBox with benzoylated glycosyl bromides **105**, **106** and **107**, respectively, in the presence of 18-crown-6 in acetone; the mannoside **112** was accompanied by its α-anomer as an α,β-anomeric mixture (1:1).[35] The glucoside benzoate **110** was also obtained when **30** was treated with NaH followed by **105** in acetonitrile,[26] whereas the galactopyranosyl bromide derivative **45**, under the same reaction conditions, gave the thiogalactoside, 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-thiobenzoxazole, in addition to the respective galactonucleoside derivative, in 45 and 38% yield, respectively[26] (Scheme 13).

2.2.3. Five-membered heterocycles with three heteroatoms.

2.2.3.1. Thiotriazolyl (STr) glycosides. The coupling of a 3-mercapto-5-substituted-1*H*-1,2,4-triazole **114** with acetohalosugars was studied under various reaction conditions. Thus, the reaction of **114** with **44**–**46** in the presence of K_2CO_3 in DMF at room temperature overnight followed by heating for 2–4 h afforded the *N*,*S*-di-β-glycosides **115**–**117** in 72–75% yields. On the other hand, a regioselective formation of the respective β-thioglycosides **118**–**120** was achieved in 73–78% yields by performing the reaction in the presence of triethylamine.[59] Alternatively, compounds **115**–**117** and **118**–**120** were obtained under microwave irradiation within 3–5 min in better yields[59] than using conventional heating (Scheme 14).

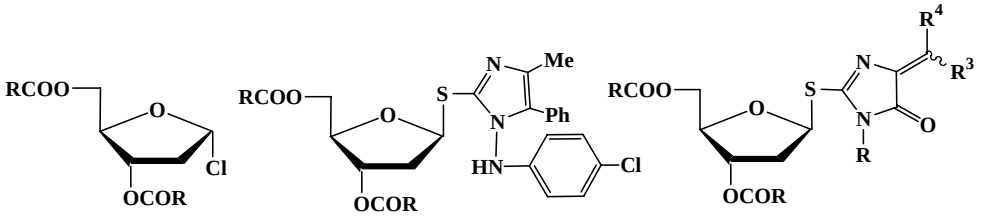
3-Phenyl-1,2,4-triazolin-5-thione **122** was reacted with acetobromoglucose **44** or acetobromoxylose **121** in the presence of sodium hydroxide to give the thioglucopyranoside



44 R^1 = Y = OAc, R^2 = H, X = Br
45 R^1 = H, R^2 = Y = OAc, X = Br
46 R^1 = OAc, R^2 = H, Y = NHAc, X = Cl

75 R = H
76 R = Ph

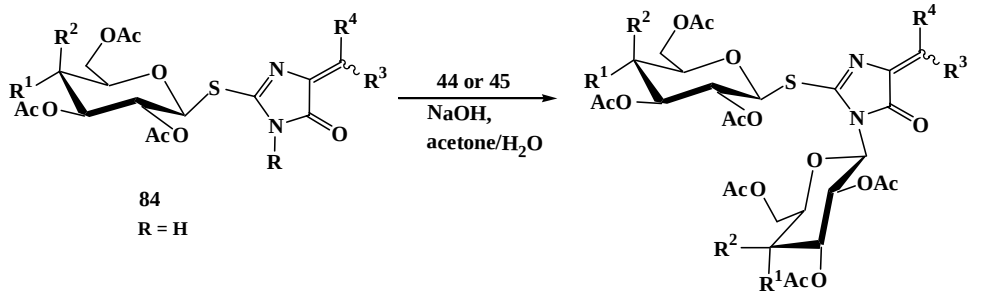
77 R^1 = OAc, R^2 = H, Y = O, R = H or Ph
78 R^1 = H, R^2 = OAc, Y = O, R = H or Ph
79 R^1 = H, R^2 = OAc, Y = NH, R = H or Ph



80 R = 4-ClC_6H_4
81 R = 4-MeC_6H_4

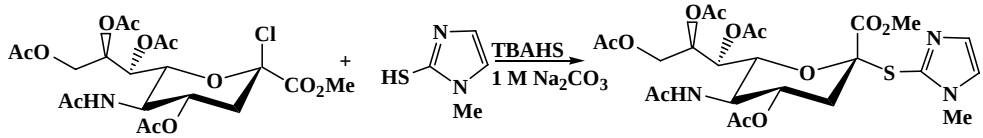
82 R = 4-ClC_6H_4

83 R = 4-MeC_6H_4
R^3 = H, R^4 = Ph, 2-thienyl, 3-indolyl



84
R = H

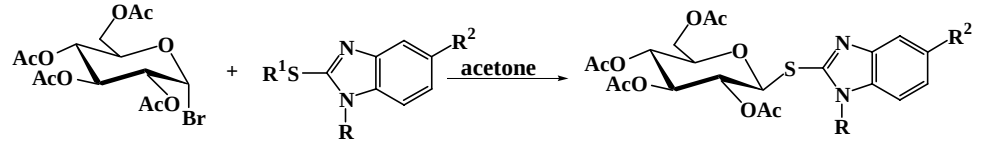
85
R^1 = OAc, R^2 = H



86

87

Scheme 10.

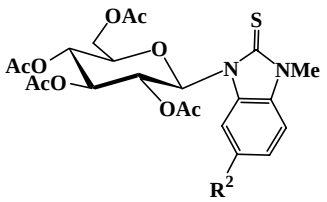


44

88 R = Me, R^1 = K, R^2 = H
89 R = R^1 = H, R^2 = NO_2

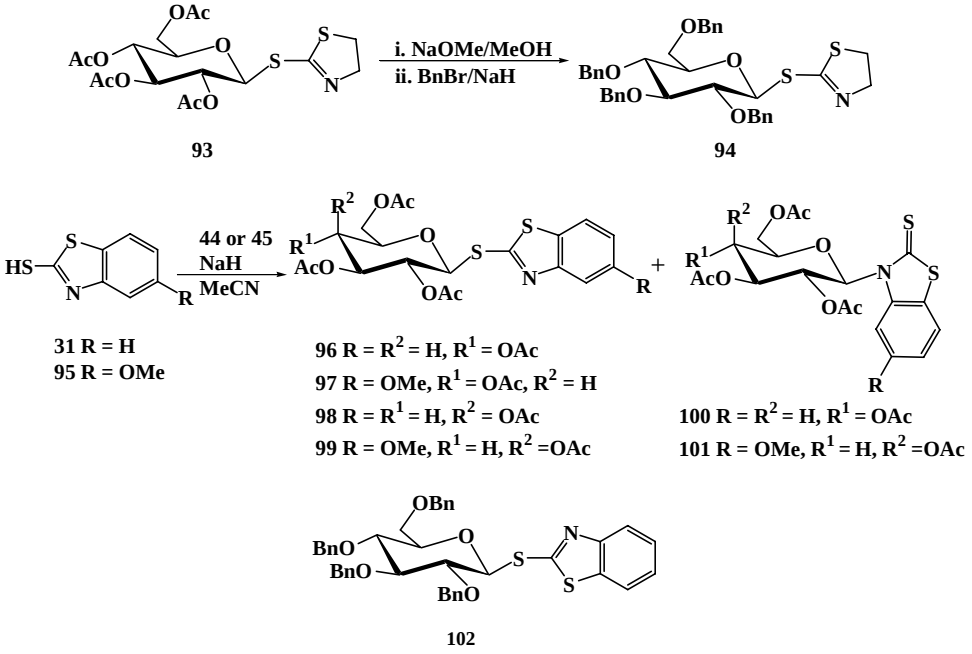
90 R = Me, R^2 = H
91 R = H, R^2 = NO_2

+



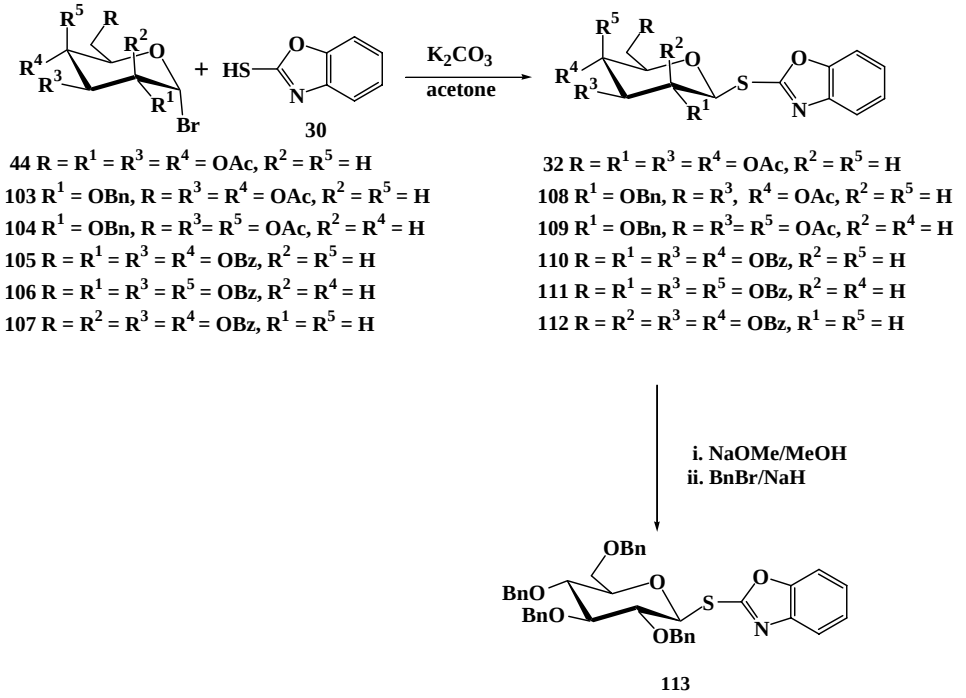
92 R^2 = H

Scheme 11.



93 94 102

Scheme 12.

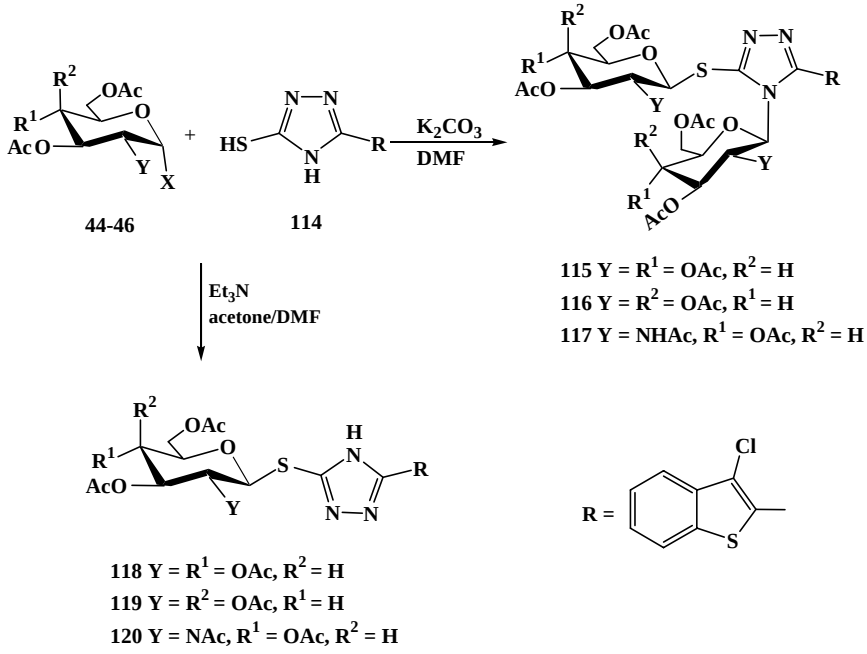


30 113

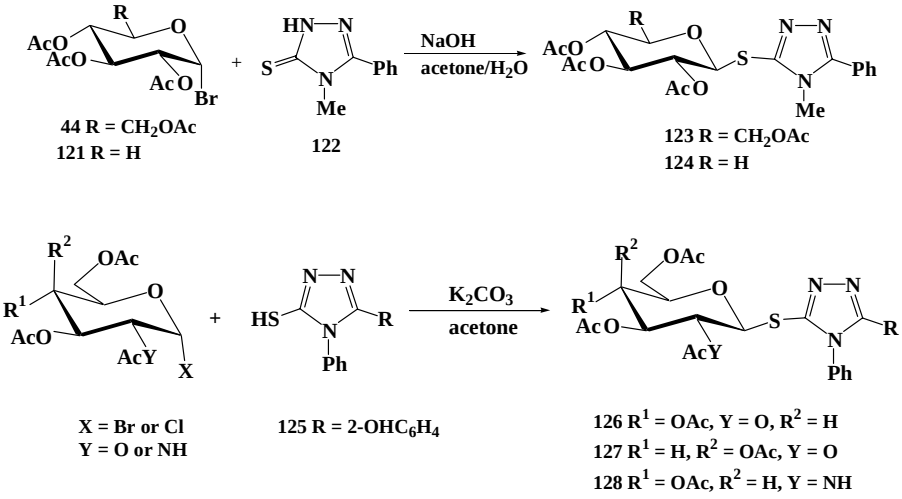
Scheme 13.

123 and thioxylopyranoside **124**, respectively.[60] Reaction of 3-(2-hydroxyphenyl)-5-mercapto-4-phenyl-1,2,4-triazole **125** with acetohalosugars in acetone in the presence of potassium carbonate at room temperature afforded the respective β-thioglycosides **126**–**128**[53] (Scheme 15). Better yields were obtained in shorter reaction times when the microwave technique was applied to these reactions.[53]

2.2.3.2. Thiooxadiazolyl (SOxd) and thiothiadiazolyl (SThd) glycosides. Condensation of acetobromoglucose **44** with 5-aryl-1,3,4-oxadiazoline- or thiadiazolin-2-thiones in the presence of potassium hydroxide in acetone gave the thioglucosides **129**, and the *N*-glucosyl derivatives **130** in poor yield.[61] When 5-phenyl-1,3,4-oxa or thiadiazolin-2-thione was, however, coupled with **44** or acetobromoxylose **121** in the presence of sodium hydroxide in acetone, they gave only the *S*-glycoside derivatives **129** or **131** (Ar=Ph).[60,62] Treatment of **129** or **131** with mercuric bromide in toluene afforded the *N*-nucleosides **130** and **132**, respectively.[61,62]



Scheme 14.



Scheme 15.

Reaction of 1,3,4-thiadiazolidine-2,5-dithione **133** with acetobromoglucose **44** gave a mixture of the dithioglucoside **134** and the *N*,*S*-diglucoside **135**, whereas, when **133** was used in excess, the product was the monothioglucoside **139**. Similarly, the methylthio analogue **136** gave the respective thioglucoside **137** and the *N*-glucoside **138**.[63]

The potassium salts of 2-mercapto-4-methyl- or 2-mercapto-4-phenyl-5-thiono-1,3,4-thiadiazoline were reacted with acetobromoglucose **44** under various conditions to give 4-methyl- or 4-phenyl-5-thiono-1,3,4-thiadiazolinyl-2-(tetra-*O*-acetyl-β-D-thioglucopyranoside) **140** or **141**, respectively.[64] The acetyl–thioglucoside **141** has been oxidized to the corresponding sulphone **142**, either by hydrogen peroxide or potassium permanganate[64] (Scheme 16).

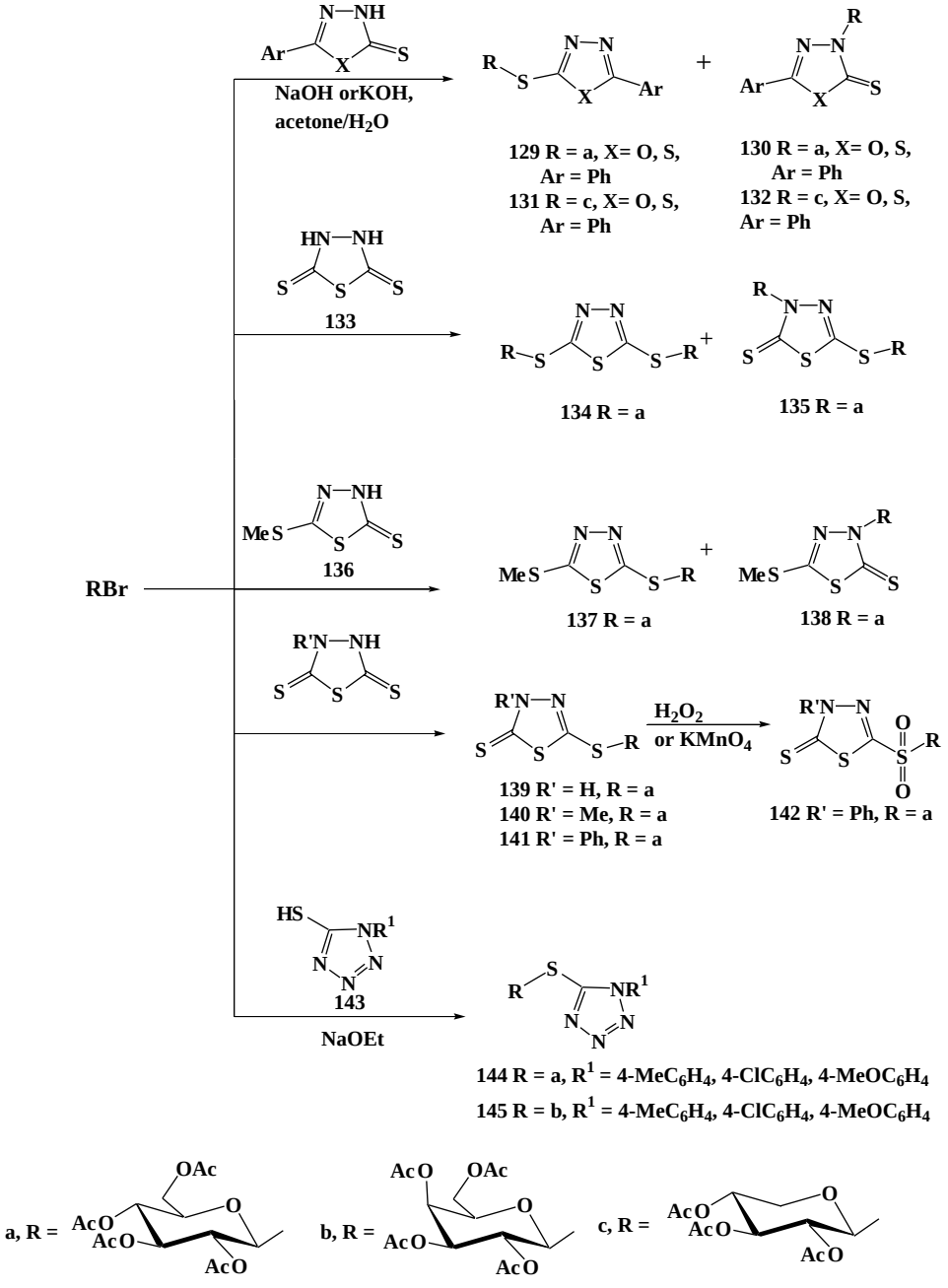
2.2.4. Five-membered heterocycles with four heteroatoms.

2.2.4.1. Thiotetrazolyl (STe) glycosides. The (tetrazol-5-yl) 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucosides **144** and -galactosides **145** were obtained by the reaction of 1-substituted-5-mercaptotetrazoles **143** with acetobromoglucose **44** or acetobromogalactose **45**, respectively, in the presence of sodium ethoxide[65] (Scheme 16).

2.2.5. Six-membered heterocycles with two heteroatoms.

2.2.5.1. Thiopyridazinyl (SPd) glycosides. Condensation of 4-mercaptopyridazine with acetobromoglucose **44** in the presence of potassium hydroxide in acetone afforded a mixture of *S*- and *N*-glycosides **146** and **147**, respectively.[66]

When ribofuranosyl chloride **81** was reacted with thiopyridazine derivatives **148** in the presence of pyridine, the



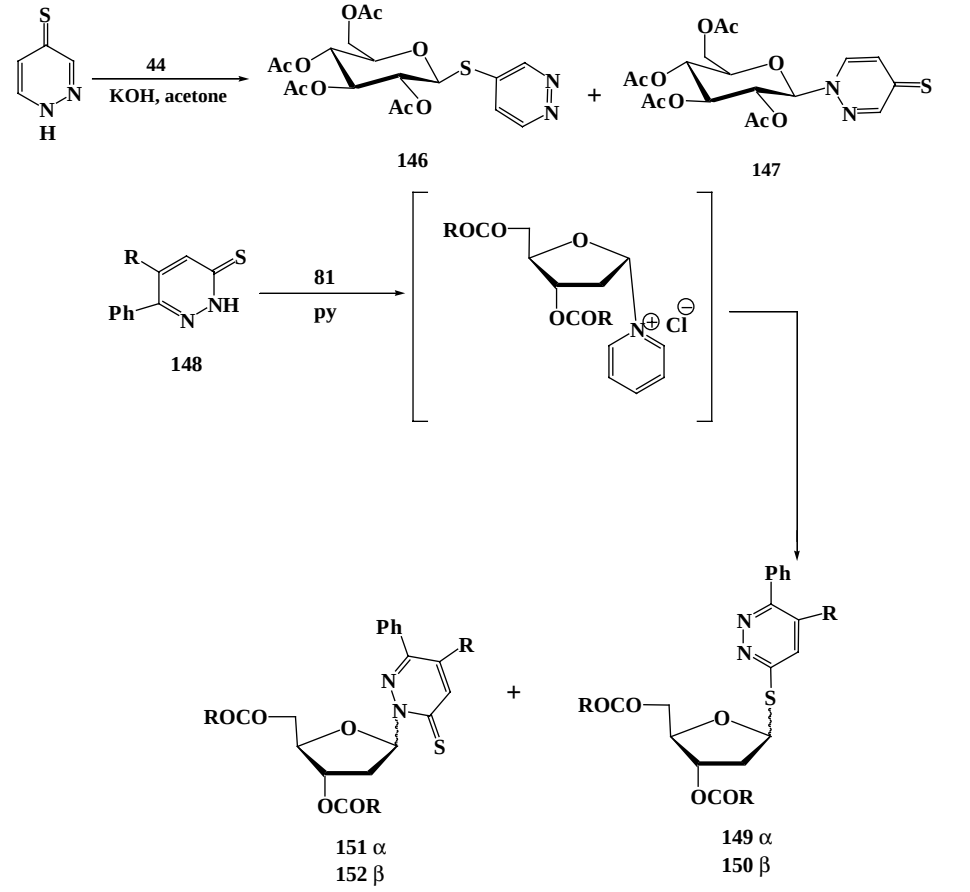
Scheme 16.

simultaneous formation of a pyridinium chloride as an intermediate was formed, which coupled with **148** to give a mixture of the α and β *S*- and *N*-glycosides **149–152**[67,68] (Scheme 17).

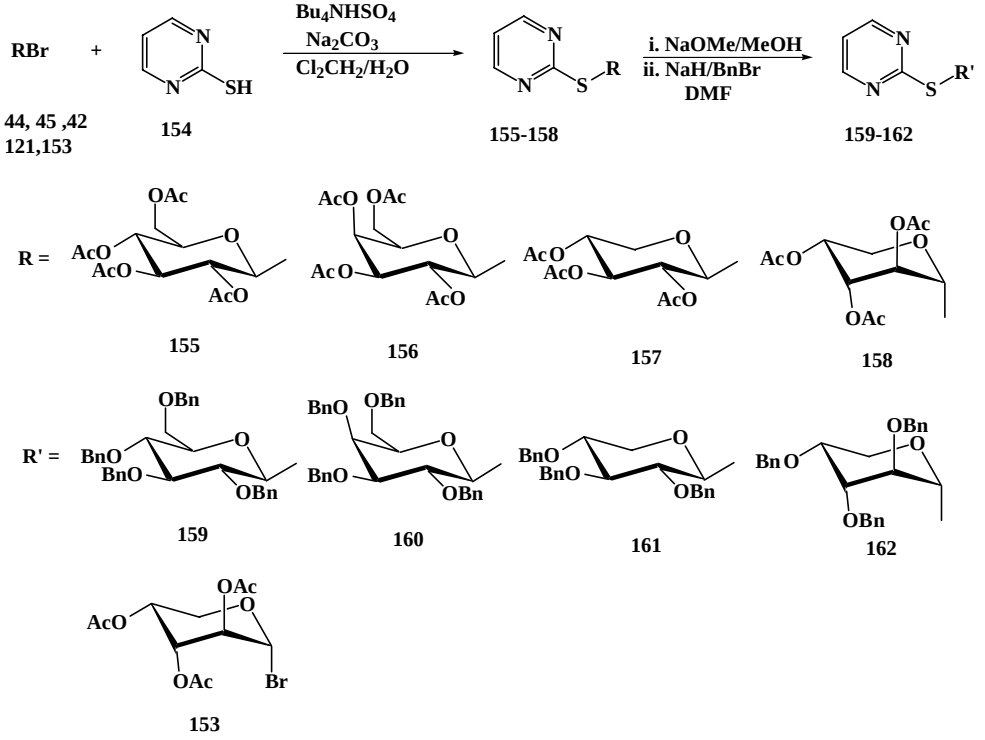
2.2.5.2. Thiopyrimidinyl (SPm) glycosides. Phase-transfer reaction conditions allowed the use of the free thiol and non-polar solvents[69–71] to give high yields of the corresponding 1,2-*trans*-thioglycosides from acetylated bromosugars. Thus, treatment of acetobromosugars **44**, **45**, **121** and **153** with 2-mercaptopyrimidine **154** in the presence of tetrabutylammonium hydrogen sulfate and sodium carbonate in a mixture of dichloromethane and water afforded the corresponding thioglycopyranosides **155–158**. Increasing the molar ratio of **154** to 3 mol equiv gave an almost quantitative yield of **155** and **156**.[13] Deacetylation followed by benzylation with benzyl bromide afforded the respective benzyl derivatives **159–162**[13] (Scheme 18).

Similarly, 2,3,4,6-tetra-*O*-acetyl-β-L-fucopyranosyl bromide **163** under phase-transfer conditions afforded the β-L-fucothiopyranoside derivative **164**, which, upon deacetylation followed by isopropylidenation, formed **165** that benzylated and hydrolyzed to give **166**. Selective benzylation of **166** with benzyl bromide via its dibutyltin complex gave **167**. Acylation of **167** by acetic anhydride or stearoyl chloride gave the respective 4-*O*-acetyl **168** or 4-*O*-stearoyl **169** derivatives[72] (Scheme 19).

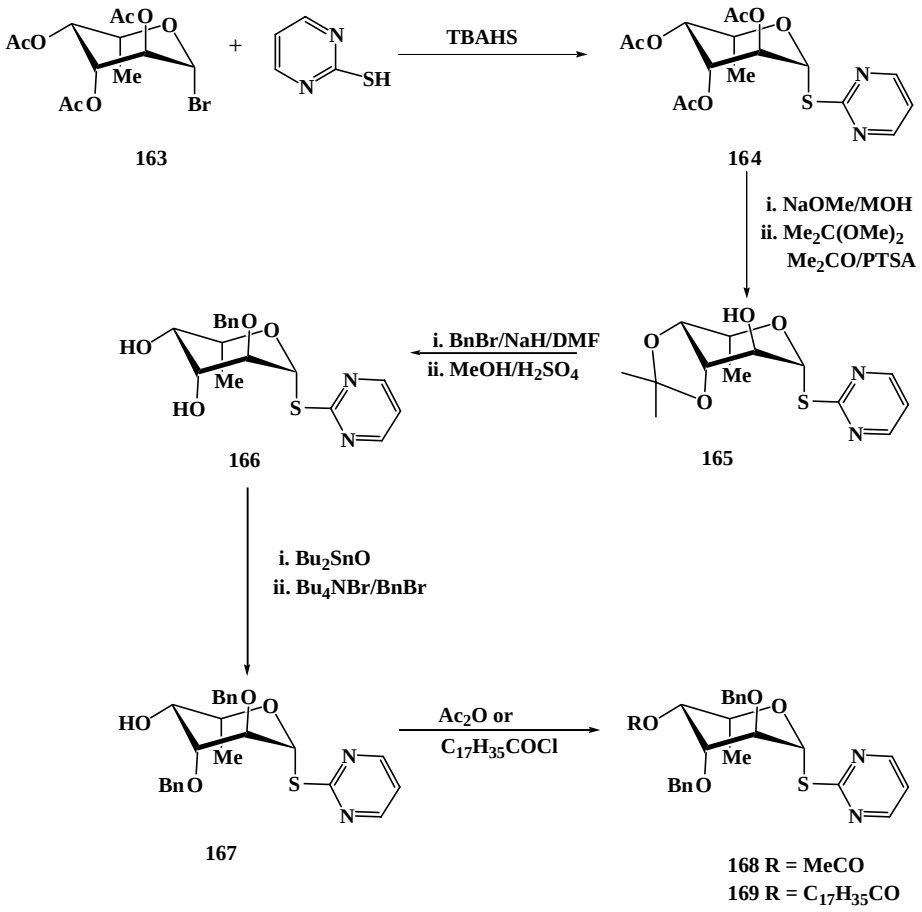
Reaction of 2-deoxy-ribofuranosyl chloride **81** with bis(trimethysilyl)-2-thiouracil **170** in 1,2-dichloroethane at room temperature afforded the respective



Scheme 17.



Scheme 18.



Scheme 19.

β-thioribfuranoside **171**. When the reaction was catalyzed with $SnCl_4$ in CH_2Cl_2 at −78 °C, it afforded the α-anomer **172** in 90% purity (remainder **171**).[73] Thioglycosides **43** and **174** were prepared by reacting 4-mercapto-2-methylthiopyrimidine with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide **173** (R=Ac, X=Br) and acetobromoglucose **44**, respectively, in the presence of K_2CO_3 in acetone.[38]

Reaction of acetobromoglucose with 6-mercaptouracil took place in aqueous acetone in the presence of sodium hydroxide to give **175** and with 6-mercaptocytosine in the presence of potassium carbonate to give **176**.[74]

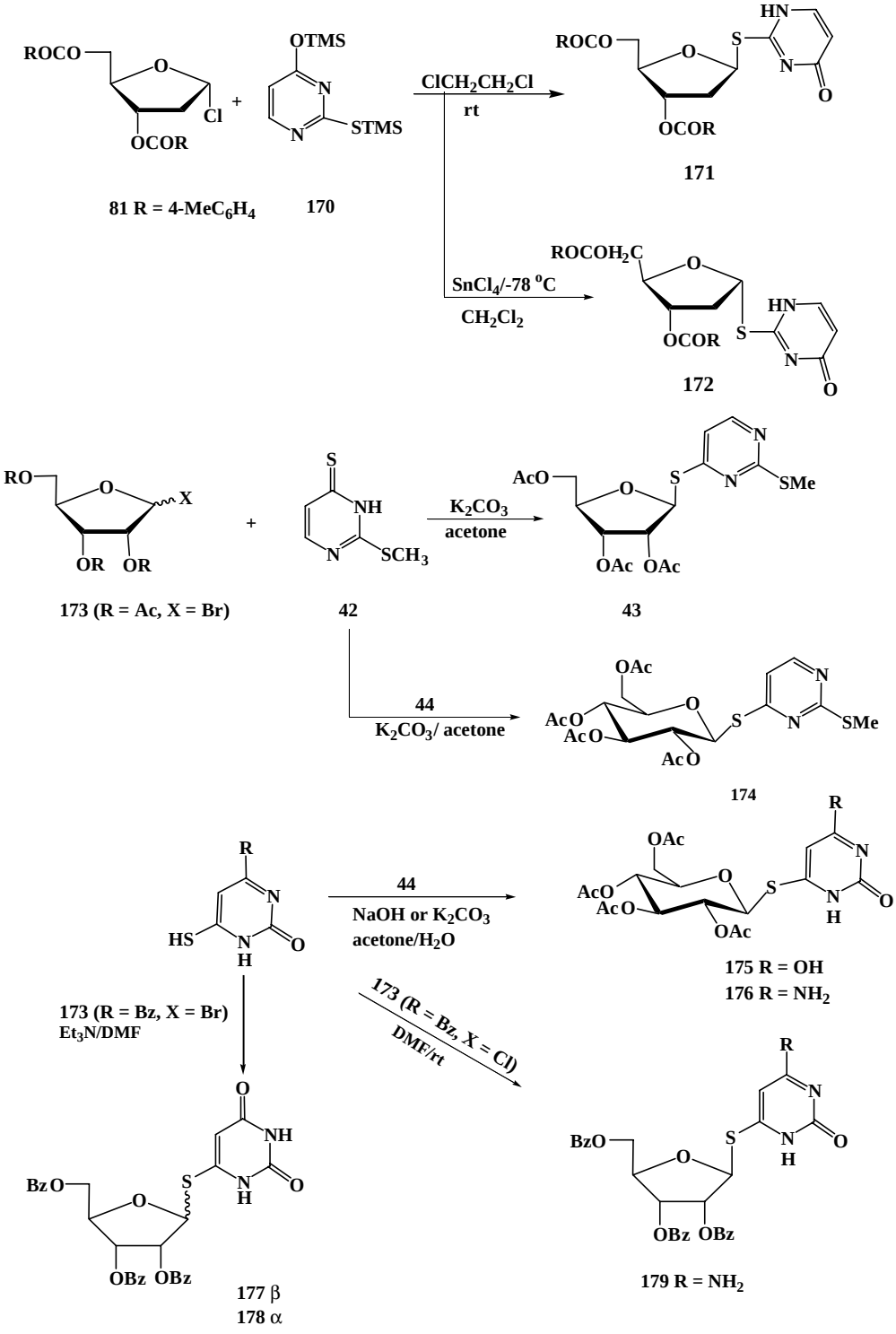
The reaction of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide **173** (R=Bz, X=Br) with 5-mercaptouracil in DMF in the presence of Et_3N as a catalyst yielded a mixture of the β-anomer **177** as a major product (31.5%) and the α-anomer **178** as a minor product (14.6%).[75] When 2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl chloride **173** (R=Bz, X=Cl) was coupled with the sodium salt of 6-mercaptouracil in DMF at room temperature, it gave the β-thioriboside[74] **179** (Scheme 20).

Reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or -α-D-galacto-pyranosyl bromides (**44** and **45**) with thiopyrimidin-4-one derivatives **180** in the presence of aqueous KOH in acetone or with the sodium salts of **180** in DMSO gave the corresponding bisglycosides **181**. Deacetylation of **181** with ammonia in methanol cleaved the *S*-glycosyl residue to give the N^3-glycosylated analogues[76a] **182**. When the piperidinium salts of **183** were coupled with **44** or **45** in aqueous acetone,[76b] gave a mixture of nucleosides **184** and **185**, resulted.

Coupling of the potassium salts of 4-aryl-7-(substituted benzylidene)-tetrahydrocyclopentapyrimidine-2(3*H*)-thiones **186** with acetobromoglucose **44** or acetobromogalactose **45** in aqueous potassium hydroxide afforded the thioglucosides **187** and thiogalactosides **188**, respectively[77] (Scheme 21).

2.2.5.3. Thiopyrazinyl (SPz) glycosides. Reaction of the sodium salts of mercaptopyrazine derivatives **189** with acetobromoglucose **44** in the presence of sodium hydroxide in acetone gave the corresponding *S*- and *N*-glucosides[78] **190** and **191** (Scheme 22).

2.2.5.4. Thioquinazolinlyl (SQz) glycosides. A series of acetylated glycosides of 2-thio-4(3*H*)-quinazolinones and their thiono analogues, including D-glucose, D-galactose, D-xylose and L-arabinose derivatives, have been synthesized by the reaction of 6,8-disubstituted 3-aryl-2-thio-4(*H*)-quinazolinones and quinazolinethiones **192** with tetra-*O*-acetylglycopyranosyl bromides in the presence of potassium hydroxide or potassium carbonate in acetone to yield the corresponding *S*-glycosides **193**.[79] 3-Phenylamino-2-thioxo-3*H*-quinazolin-4-ones were also reacted with acetylglycosyl bromides in the presence of NaH in DMF at room temperature to yield the *S*-glycoside derivatives **194**[80]



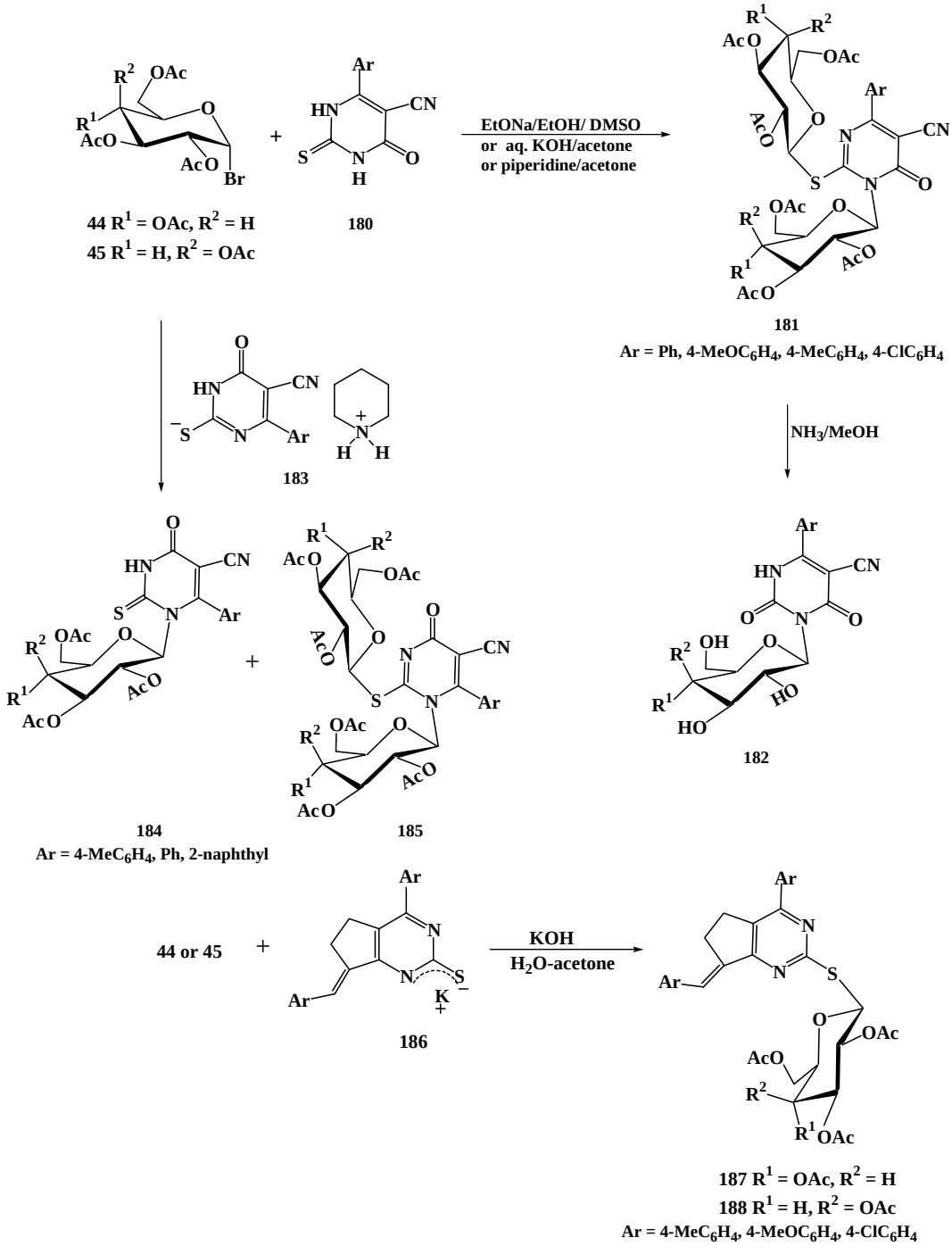
Scheme 20.

(Scheme 23). Oxidation of **193** and **194** with potassium permanganate or hydrogen peroxide in acetic acid gave the respective sulphones **195**.[80]

On the other hand, 6-substituted-2-aryl-4(3*H*)-quinazolinethiones **196** were coupled with acetobromoglucose **44** in the presence of potassium hydroxide in aqueous acetone to give the *N*- and *S*-glucosides **197** and **198** in poor yield[81] (Scheme 24). Oxidation of the thioglucosides **198** with potassium permanganate in acetic acid afforded the sulphones **199**.[79–81]

Treatment of 3-(4-thioxo-3,4-dihydroquinazolin-2-yl)-acrylic acid with glucopyranosyl bromide in an alkaline medium afforded the respective *S*- and *N*-glucosides.[82]

2.2.5.5. Thiobenzothiazinyl (SBtz) glycosides. When **44** or **45** were reacted with 3,1-benzothiazin-2,4-dithione



44 R^1 = OAc, R^2 = H
45 R^1 = H, R^2 = OAc

180

181
Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4

183

182

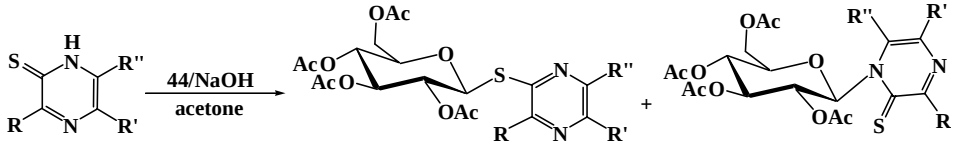
184
Ar = 4-MeC_6H_4, Ph, 2-naphthyl

185

186

187 R^1 = OAc, R^2 = H
188 R^1 = H, R^2 = OAc
Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 21.

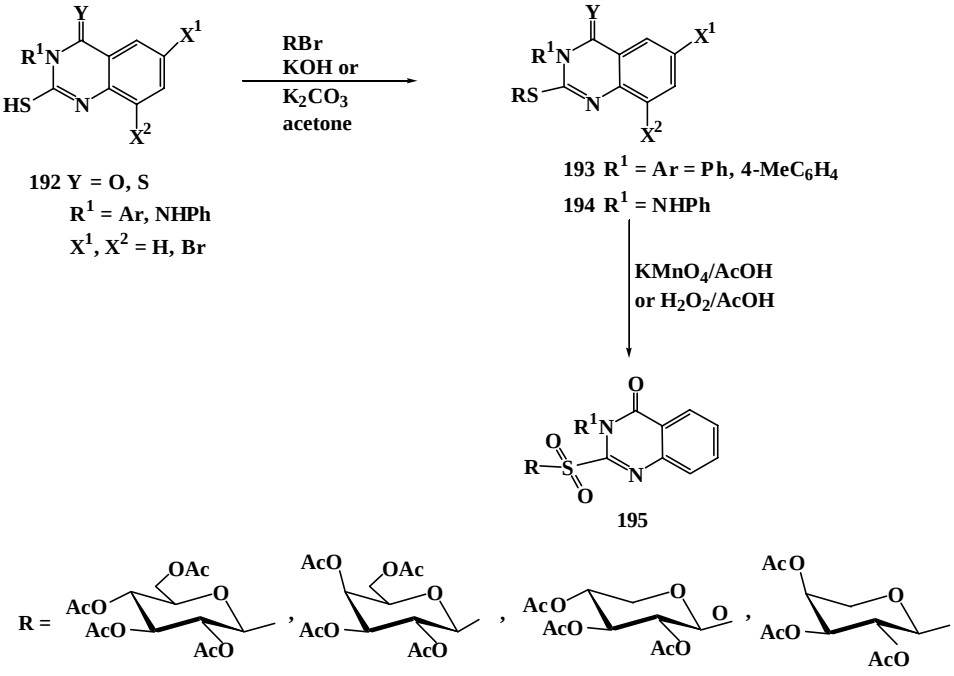


189

190

191
R = H, Ph
R` = H, Ph
R`` = H, Ph

Scheme 22.



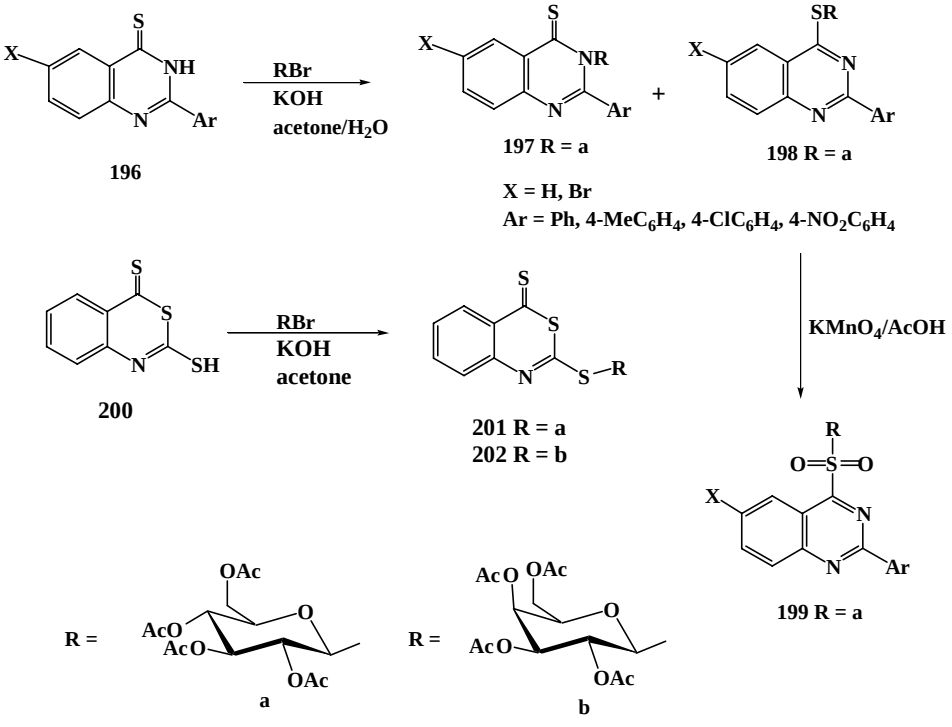
Scheme 23.

200, (tetra-*O*-acetyl-β-D-gluco- or -β-D-galacto-pyranosyl)-thio-3,1-benzothiazine-4-thione[79] **201** and **202**, respectively, were obtained (Scheme 24).

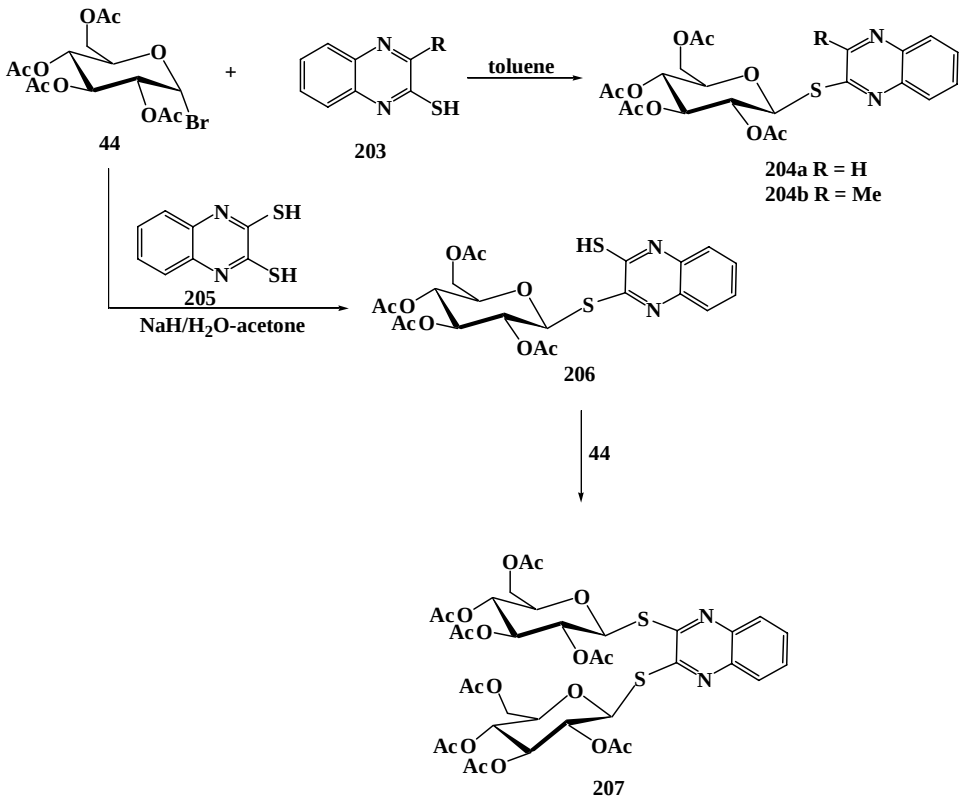
2.2.5.6. Thioquinoxalinyl (SQx) glycosides. Reaction of 2-mercaptoquinoxaline derivatives **203** with acetobromoglucose **44** in toluene afforded the quinoxaline β-thioglucosides **204**. Coupling of equimolar amounts of 2,3-dimercaptoquinoxaline **205** and **44** in the presence of sodium hydride in aqueous acetone gave the β-monothioglucoside **206**, while the bisthioglucoside **207** was obtained when **205** was reacted with two molar equivalents of **44** under the same reaction conditions[83] (Scheme 25).

2.2.6. Six-membered heterocycles with three heteroatoms.

2.2.6.1. Thiotriazinyl (STz) glycosides. Glycosylation of 3-mercapto-1,2,4-triazine **208** with **44** was achieved in aqueous acetone containing sodium hydroxide to give **209** in 98% yield.[84]



Scheme 24.

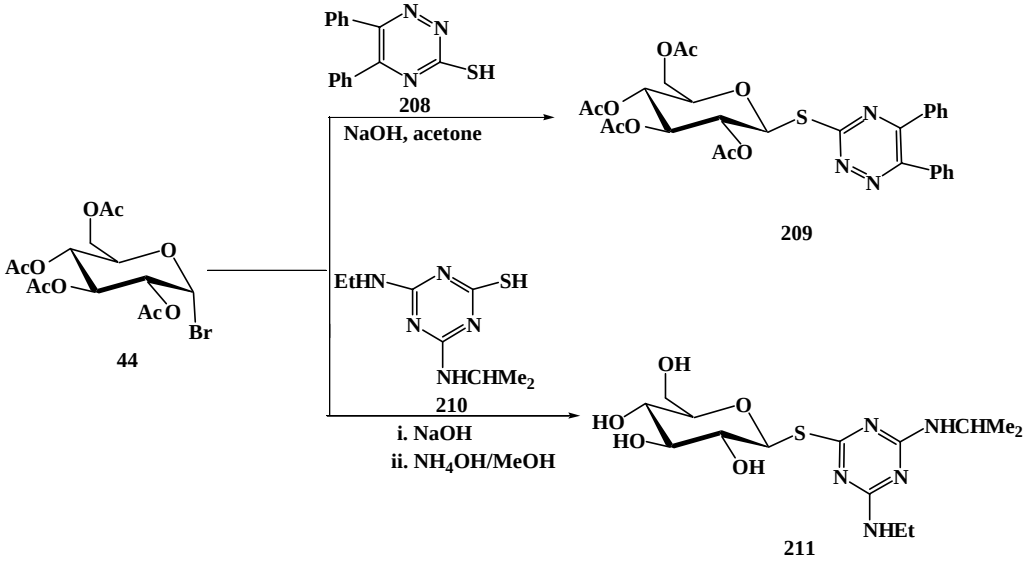


Scheme 25.

Acetobromoglucose **44** was also reacted with 2-mercaptotriazine **210** in the presence of sodium hydroxide in acetone at reflux, followed by deacetylation using ammonium hydroxide, to give the thioglucoside **211**[85] (Scheme 26).

2.2.7. Biheterocycles. Simultaneous glycosylation and deacetylation have taken place when 6-mercaptopurine **212** was condensed with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or -α-D-galacto-pyranosyl chloride in the presence of ammonium hydroxide to give 6-purinyl β-D-gluco or β-D-galactopyranoside[86,87] **213** and **214**, respectively. Similarly, 1-chloro-2,3,4-tri-*O*-acetyl-L-rhamnopyranose **215** gave 6-purinyl thiorhamnopyranoside **216**,[87] and **217** gave the ammonium salt of 6-purinyl thioglucofuranuronide **218**.[87]

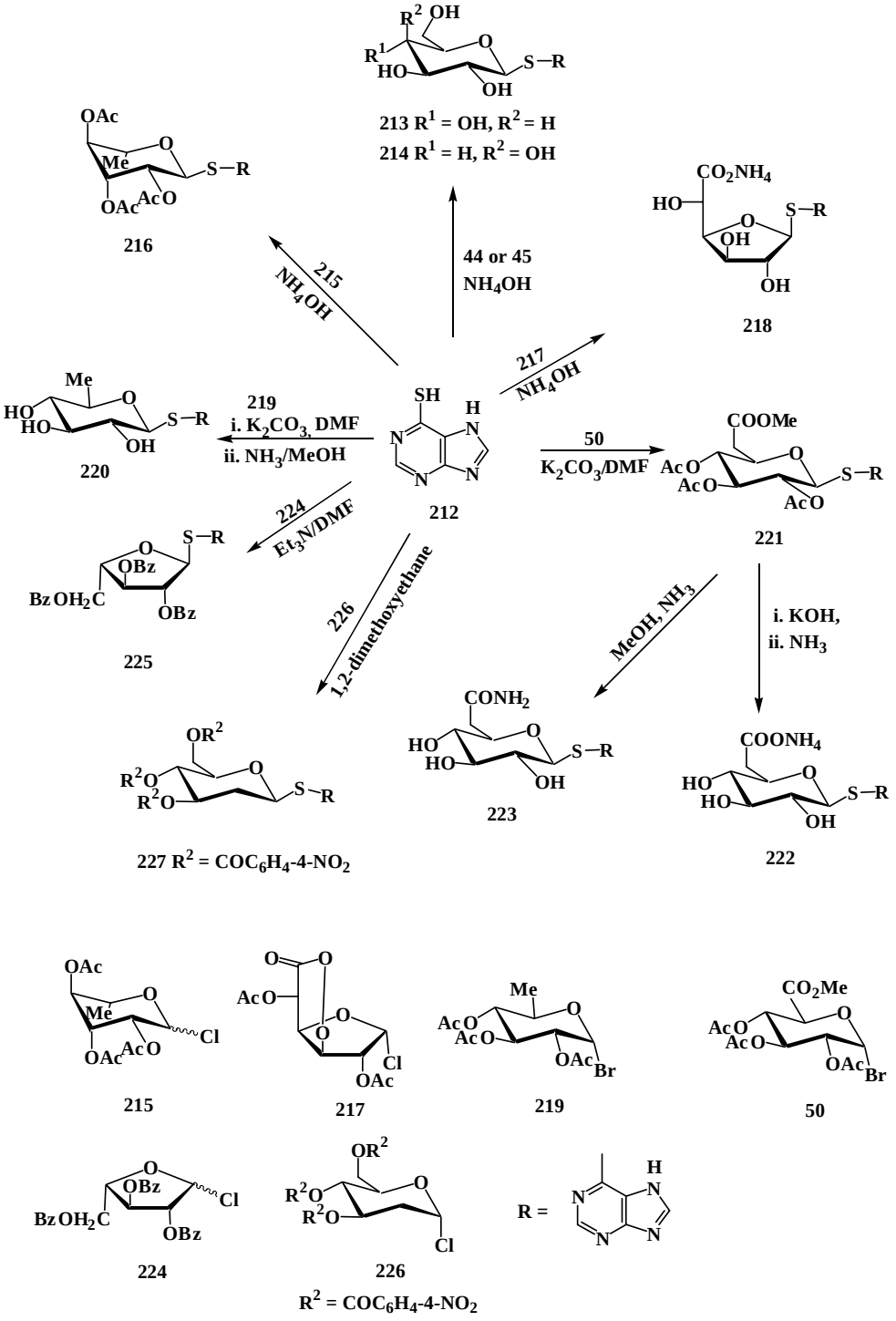
Purin-6-yl 6-deoxy-1-thio-β-D-glucopyranoside **220** was obtained from the reaction of **212** with 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-glucopyranosyl bromide **219** in the presence of potassium carbonate, followed by deacetylation using ammonia in methanol.[88] Similarly, treatment of **212** with



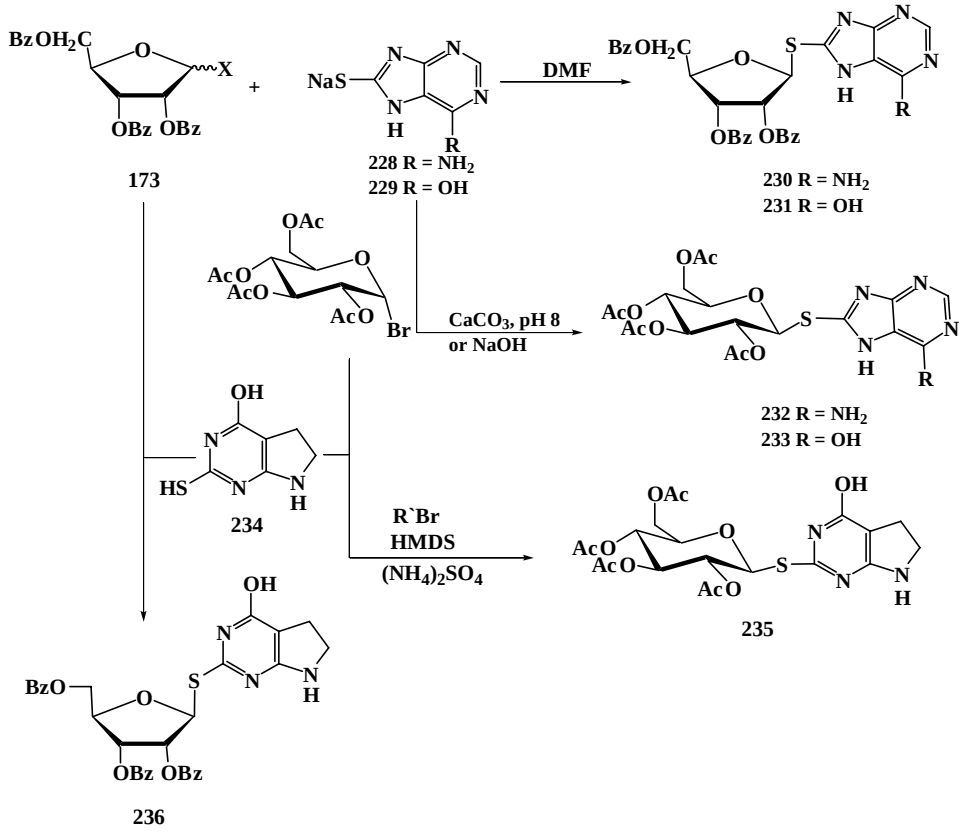
Scheme 26.

methyl 1-deoxy-1-bromo-2,3,4-tri-*O*-acetyl-α-glucopyranosyluronate (**50**), yielded the corresponding purine thioglucoside **221**, which in turn, was transformed into the ammonium salt **222** and the amide **223**.[89] Base-catalyzed glycosylation of **212** with tri-*O*-benzoyl-L-arabinofuranosyl chloride **224** was carried out in the presence of triethylamine in DMF to afford α-L-arabinothiofuranoside **225** in 28% yield.[90] The sodium salt of 6-mercaptopurine was coupled with 2-deoxy-3,4,6-tri-*O*-(*p*-nitrobenzoyl)-α-D-arabinohexopyranosyl chloride **226** in 1,2-dimethoxyethane to give **227**[91] (Scheme 27).

A series of 8-adenine thioglycosides were obtained from condensation of the sodium salt of 8-mercapto-adenine **228** and -hypoxanthine **229** with glycosyl halides. Thus, the reaction of **228** or **229** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride **173** (R=Bz, X=Cl) in DMF afforded the β-thioribfuranosides **230** and **231**, respectively. Reaction of acetobromoglucose with **228** was carried out in the presence of $CaCO_3$ at pH 8 to give **232**, whereas 8-mercaptohypoxanthine **229** was coupled with acetobromoglucose in the presence of NaOH to give the β-thioglucopyranoside **233**[74] (Scheme 28).



Scheme 27.



Scheme 28.

Glycosylation of mercaptopyrrolopyrimidine **234** with either tetra-*O*-acetyl-α-D-glucopyranosyl bromide or tri-*O*-benzoyl-D-ribofuranosyl bromide in the presence of $(Me_3Si)_2NH$ containing $(NH_4)_2SO_4$ gave the β-glycosides **235** and **236**, in 62 and 73% yield,[92] respectively, (Scheme 28).

The reaction of 4-aryl-1-thioxo[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones (**237**) with acetylated glycosyl bromides (D-gluco-, D-galacto- and D-xylo-) in the presence of potassium carbonate in acetone at room temperature afforded a mixture of the corresponding β-*S*-glycoside derivatives **238** and β-*N*-glycoside derivatives **239**. Oxidation with *m*-chloroperbenzoic acid (CPBA) of **238** yielded the corresponding sulphones **240**, whereas the *N*-glycosyl derivatives **239** yielded the 1-oxo-derivatives **241**[93] (Scheme 29).

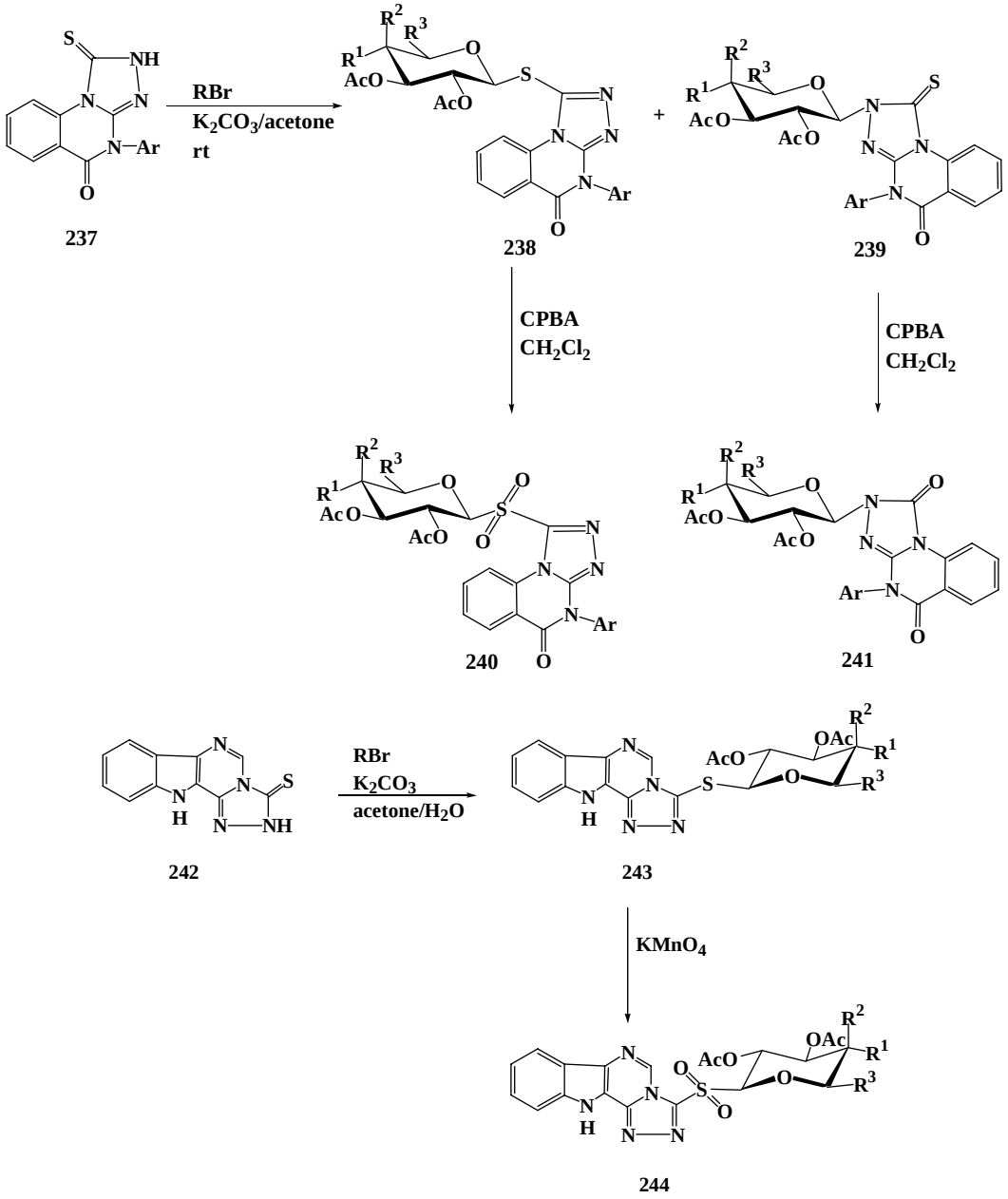
Similarly, reaction of 3-thioxo-11*H*-1,2,4-triazolo[4,3-*c*]-pyrimido[5,4-*b*]indole **242** with per-*O*-acetylglycopyranosyl halides gave the respective β-thioglycosides **243**, oxidation of which with potassium permanganate yielded the corresponding sulfones **244**[94] (Scheme 29).

2.3. 1-*O*-Trichloroacetimidates as glycosylating agents

Thioglycosides can be effectively synthesized from trichloroacetamidates as glycosyl donors using hard Lewis acids such as $BF_3 \cdot Et_2O$ or TMSOTf as promoters.[95] The α-anomer thioglucoside **248** was synthesized from 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose **245** by transformation into the β-trichloroacetimidate **246**, which, upon treatment with 2-mercaptopyridine **2** in the presence of $BF_3 \cdot Et_2O$, gave the α-2-pyridyl thioglucoside **247**. Subsequent reduction of the azide and acetylation gave **248**, oxidation of which with MCPBA led to the glycosyl 2-pyridyl sulfone **249**[96] (Scheme 30).

2.4. Hemiacetals as glycosylation agents

In recent years, a number of methods to synthesize thioglycosides from hemiacetals have been reported. Hence, the 2-pyridyl 2,3,4-tri-*O*-benzyl-α,β-L-rhamnopyranoside **51** and α,β-L-fucopyranoside **253**[97] were synthesized from **250** and **252**, respectively, using bis(2-pyridyl)disulfide (**251**) in the presence of Bu_3P. Treatment of a fully protected hemiacetal monosaccharide such as 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **254** with **251** in the presence of triethylphosphine in acetonitrile gave an α:β mixture of 2′-pyridyl 2,3:5,6-di-*O*-isopropylidene-1-thio-D-mannofuranoside **255** in 8 and 79% yield, respectively. Under the same reaction conditions, 2,3-*O*-isopropylidene-D-ribofuranose **256** afforded only the α-anomer **257**.[98] On the other hand, the thioriboside derivatives **259** and **261** were obtained as α:β mixtures (1:1 and 3:1) when **258** and **260** were reacted under the same conditions,[99] and for the reaction of **259** in the presence of *p*-toluenesulfonic acid.[99] The 2-pyridyl 2,3:5,6-di-*O*-isopropylidene-1-thio-β-mannofuranoside **255**, 2-pyridyl-3,5-di-*O*-benzoyl-2-deoxy-1-thio-D-ribofuranoside **263** and 2-pyridyl 2,6-dideoxy-3-methoxy-4-*O*-acetyl-1-thio-L-arabinopyranoside **265** were also synthesized from **262**

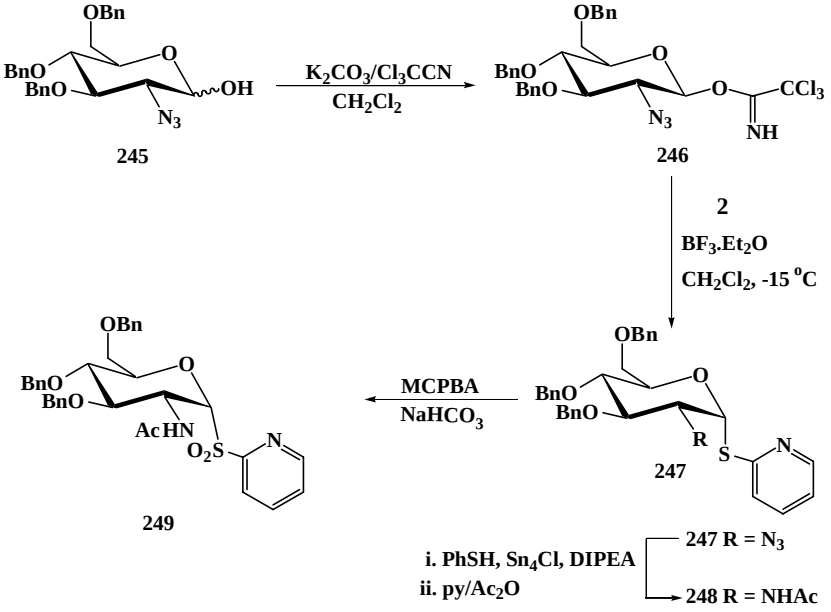


Scheme 29.

and **264**, respectively.[42] Per-*O*-benzylated 2-pyridyl 1-thio-α/β-D-gluco- **269**, galacto- **270** and manno- **271** pyranosides were prepared from the corresponding 2,3,4,6-tetra-*O*-benzyl-D-glycopyranose derivatives **266–268** with 2,2′-dipyridyl disulfide **251** in the presence of a trialkylphosphine. Thus, 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α/β-D-glucopyranoside **269** was obtained in a 1:3 α:β mixture when triethylphosphine was used,[98] whereas, with tri-*n*-butylphosphine in methylene chloride, a 2:3 α:β mixture was obtained.[43,97] It was reported,[99] however that, under the same reaction conditions, only the β-isomer was isolated. Using $^{n}Bu_3P$ in the coupling of benzylated galactopyranose **267** and mannopyranose **268** with **251**, afforded the thiopyridyl derivatives **270–271** in 1:1 α:β mixtures.[43]

Alternatively, compounds **269** and **270** were obtained by deacetylation of the corresponding per-*O*-acetyl derivatives followed by benzylation.[43]

2-Pyridyl 1-thio-α/β-L-arabinopyranoside **273** was obtained by acid hydrolysis of methyl β-L-arabinoside **272** followed by treatment with dipyridyl disulfide in the presence of Bu_3P in CH_2Cl_2[100] (Scheme 31).



Scheme 30.

2′-Benzothiazolyl 2,3:5,6-di-*O*-isopropylidene-1-thio-β-D-mannofuranoside **275** was obtained in good yield when 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose **254** was treated with bis(2-benzothiazolyl)disulfide **274** and Et_3P in acetonitrile.[98] On the other hand, under the same reaction conditions 3,4-*O*-isopropylidene-L-arabinose **276** afforded a mixture of the α,β anomers of **277**[98] (Scheme 32).

Under phase-transfer conditions, an α,β mixture (1:3) of thioglucoside **278** was obtained when 2-mercaptobenzothiazole was reacted with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **266** in the presence of tosyl chloride and tetrabutylammonium chloride (TBAC) in benzene and 50% aqueous sodium hydroxide.[101] In this method, a good leaving group was generated from the anomeric hydroxyl group by reaction with TsCl. Under the same reaction conditions, the α,β mixture of 2-benzothiazolyl-1-thio-xyloside **279** was prepared from the respective sugar[101] (Scheme 32).

Treatment of **266** with 5,5′-bis(1-phenyl-1*H*-tetrazol-5′-yl)dithiocarbonate in the presence of triethylamine or 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in acetonitrile afforded the *S*-glucosides **280** and **281** as the main products and a trace of **282**. DMAP was superior to triethylamine as a catalyst (Scheme 33).[102]

2.5. 1-Thiosugars as glycosylating agents

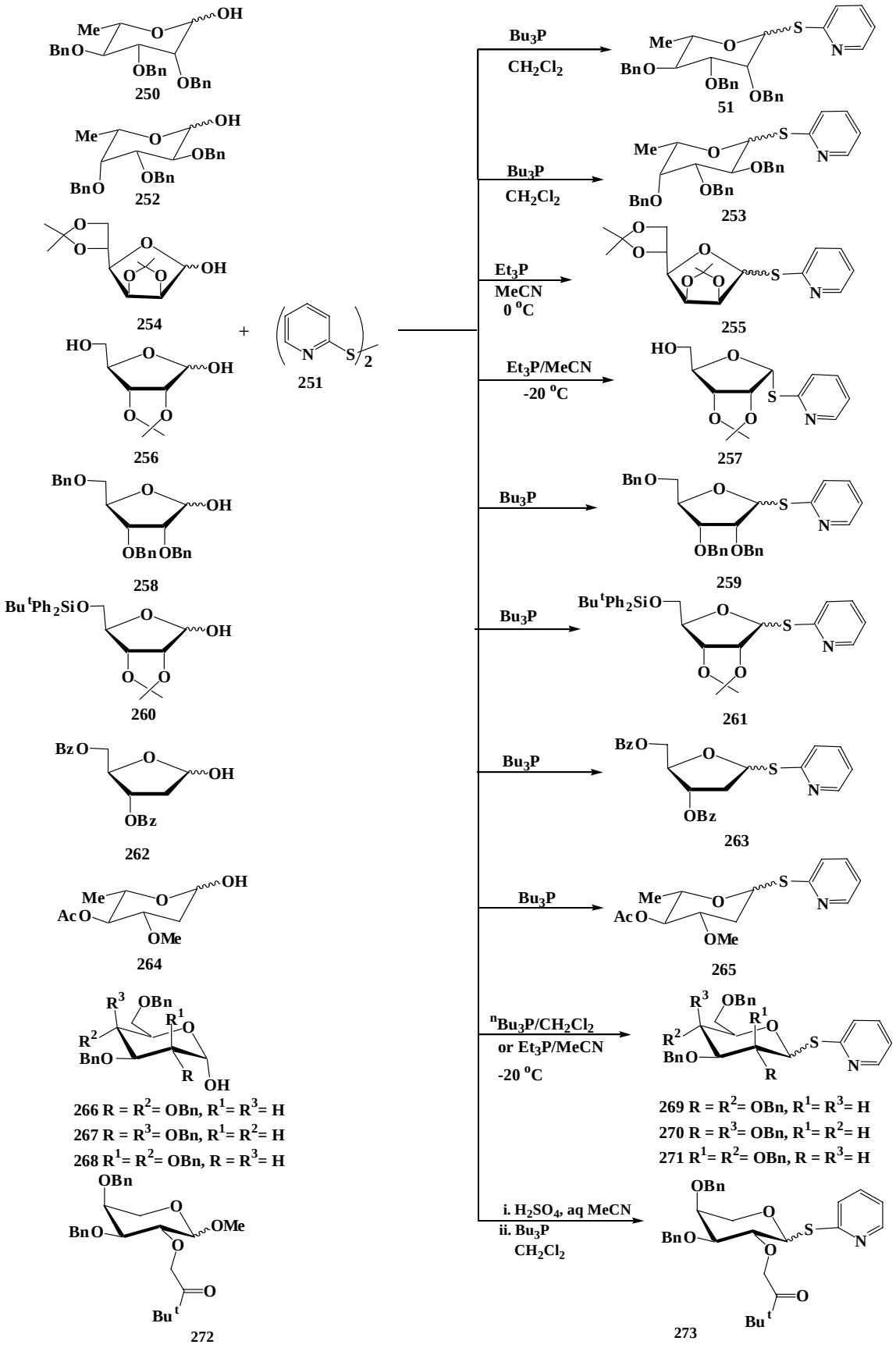
A method for the synthesis of thioglycosides has been based on the reaction of 1-thiosugars with halogenated heterocyclic compounds. Thus, direct displacement of one or two chloro atoms in halogenated maleimides **284** or **285**, by reaction with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **283** in the presence of triethylamine in anhydrous dioxane at room temperature, gave **286** and **287**, respectively[103] (Scheme 34).

Similarly, nitroimidazolyl 1-thioglycosides were obtained in good yield from per-*O*-acetyl 1-thiosugars and bromonitroimidazole derivatives.[104] An efficient synthesis of 2-pyridyl thioglycoside derivatives has been achieved by the reaction of 1-thiosugar derivatives with either 2-bromopyridine *N*-oxide[105] or 2-chloro-nitropyridine.[106]

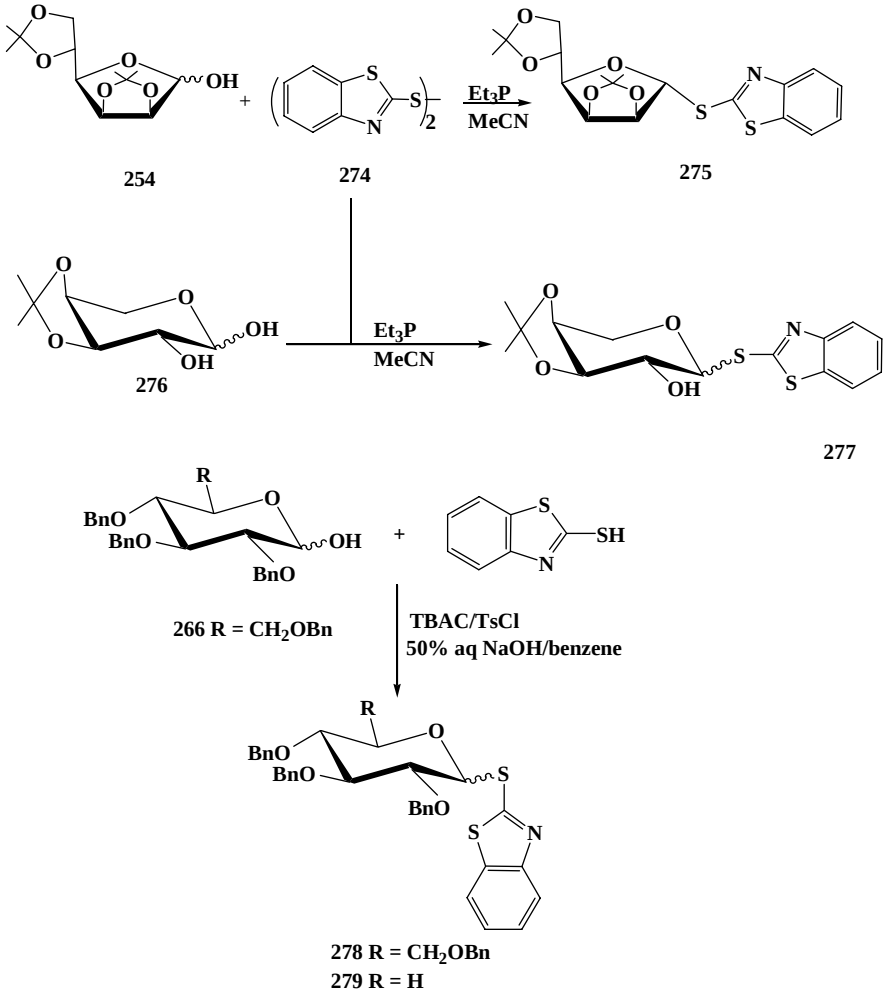
2,4,6-Trichloro-1,3,5-triazine **288** showed a high reactivity towards reaction with three equivalents of 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **283** in the presence of Et_3N in acetonirile to give the tris-thioglucoside **289**.[107] On the other hand, reaction of **288** with 1 equiv of **283** to form the corresponding monoglycosylated derivative was unsuccessful, owing to the high reactivity of the product and its decomposition.[107] 1-Thio-D-glucose **283** was also treated with the nitrogen- and oxygen-linked spin-labeled triazine compounds **290** and **291** in acetone in the presence of $NaHCO_3$ at room temperature to form, respectively, the mono- **292** and **293** as well as the bis-thiosugar **294** and **295** derivatives[107] (Scheme 35).

Condensation of 5-chloro-3-methylmercapto-1,2,4-thiadiazole **296** with **283** in the presence of sodium hydroxide in acetone gave the thioglucoside **297**.[108] The 6-purinyl β-D-glucothiopyranoside **300** was synthesized from the sodium thiolate resulting from acetylthio 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose **298** by deacetylation upon reaction with 6-chloropurine **299**.[86] Similarly, coupling of 6-chloropurine with 1-acetylthiohepta-*O*-acetyl lactose **301** in the presence of sodium in methanol afforded the respective thiolactoside **302**[87] (Scheme 36).

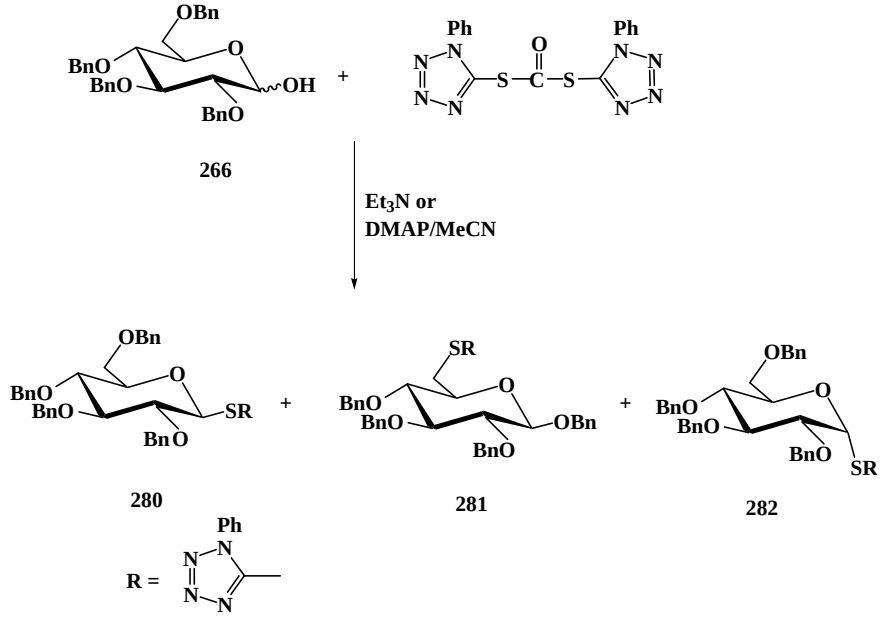
An alternative approach to the synthesis of thioglycosyl heterocycles was attempted by constructing the heterocycle in functionalized thiosugar hydrazones. Thus, 1,5-diarylpyrazol-3-yl 1-thioglycosides were synthesized by the reaction of miscellaneous per-*O*-acetylated glycosylmercaptans **303** with cinnamohydrazonoyl bromides in the presence of Et_3N and methylene chloride–ether as the solvent to afford styryl-type 1-*S*-glycopyranosyl thiohydrazonates **304** in high yield, cyclization of which with iodine or *N*-bromosuccinimide in methylene chloride gave the pyrazol-3-yl-thioglycosides **305**[109] (Scheme 37).


250
252
254
256
258
260
262
264
266 R = R2= OBn, R1= R3= H
267 R = R3= OBn, R1= R2= H
268 R1= R2= OBn, R = R3= H
272
251
Bu3P
CH2Cl2
51
253
Et3P
MeCN
0 °C
255
Et3P/MeCN
-20 °C
257
259
261
263
265
nBu3P/CH2Cl2
or Et3P/MeCN
-20 °C
269 R = R2= OBn, R1= R3= H
270 R = R3= OBn, R1= R2= H
271 R1= R2= OBn, R = R3= H
i. H2SO4, aq MeCN
ii. Bu3P
CH2Cl2
273

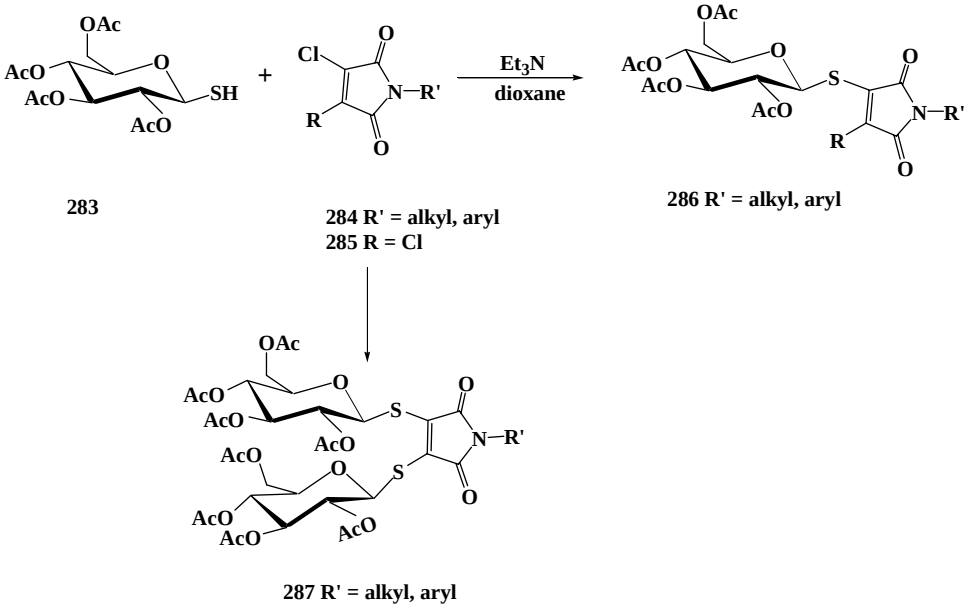
Scheme 31.



Scheme 32.



Scheme 33.



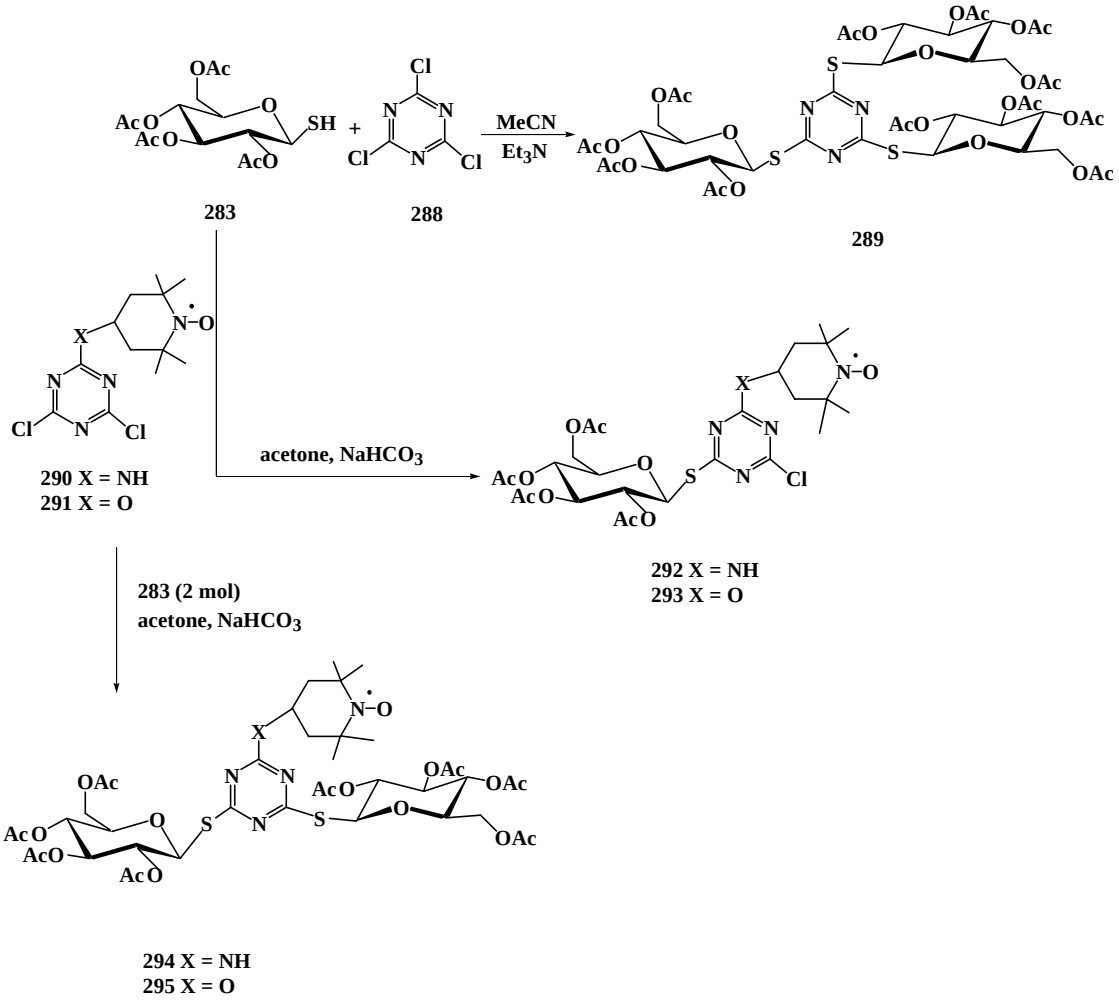
283

284 R' = alkyl, aryl
285 R = Cl

286 R' = alkyl, aryl

287 R' = alkyl, aryl

Scheme 34.



283

288

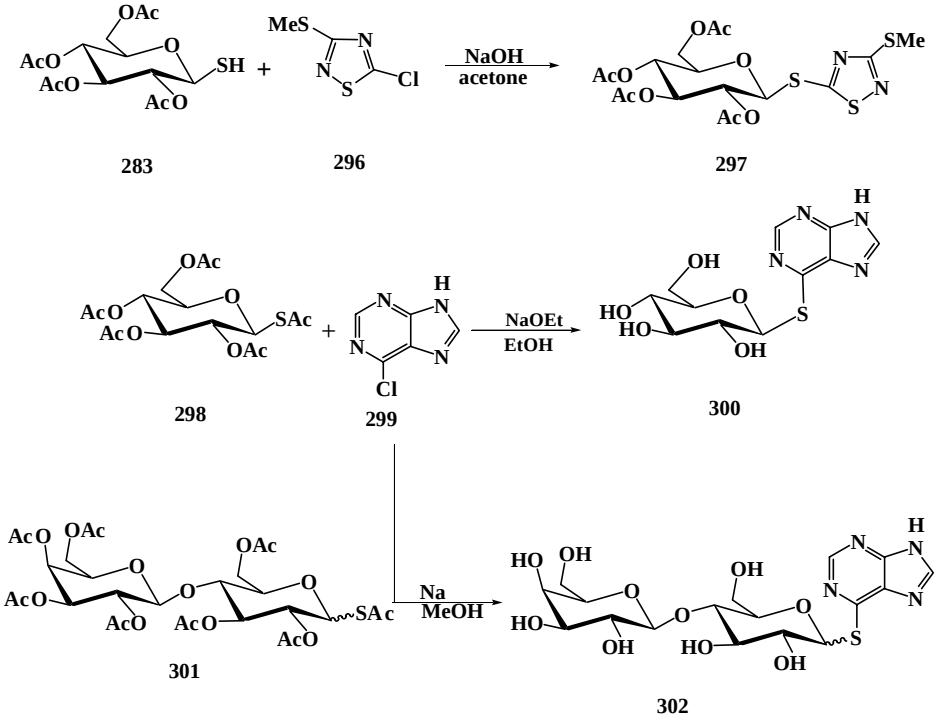
289

290 X = NH
291 X = O

292 X = NH
293 X = O

294 X = NH
295 X = O

Scheme 35.

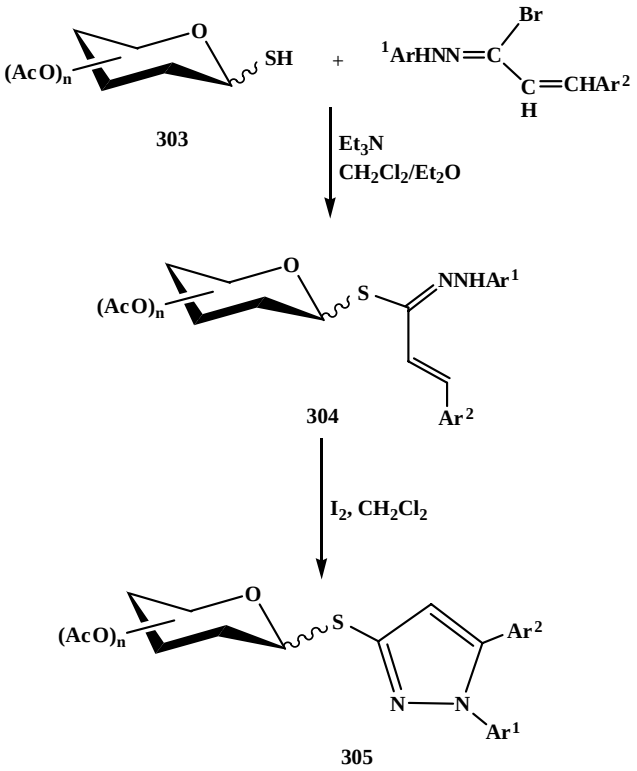


283 296 297 298 299 300 301 302

Scheme 36.

2.6. Isothiouronium salts as glycosylating agents

One of the most convenient and simple methods for the preparation of thioglycosides has utilized isothiourea derivatives of sugars as the starting materials, which are readily available from the reaction of glycosyl halides with thiourea.[63,110] With this method, thioglycosides can be synthesized under very mild reaction conditions. The



303 304 305

n = 3-4

Ar^1, Ar^2 = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

Scheme 37.

synthetic procedure involved cleavage of a glycosyl isothiouronium salt by treatment with potassium carbonate, sodium hydrogen sulfide or metabisulfite in water/acetone media, followed by reaction of the resulting 1-thioglycopyranose with alkyl or aryl and glycosyl halides. Triethylamine has been found to react readily with isothiouronium salts to form 1-thioglycoses and can successfully be used for the activation of the resulting 1-thioglycosides by converting them into the more nucleophilic thiolate anions.[110]

Thus, thioglycosides **309–312** with a nitropyridyl moiety at position 3 or 5 have been synthesized when the isothiouronium salts **306** and **307** were treated with 2-chloro-3-nitropyridine **308** ($R^1=H$, $R=NO_2$) or 2-chloro-5-nitropyridine **308** ($R^1=NO_2$, $R=H$) in acetonitrile and in the presence of triethylamine under MWI for 2–3 min in 60, 85, 80 and 88% yield, respectively. On the other hand, compounds **309–312** were traditionally obtained within 6–8 h in 40, 60, 68 and 68% yield, respectively.[111]

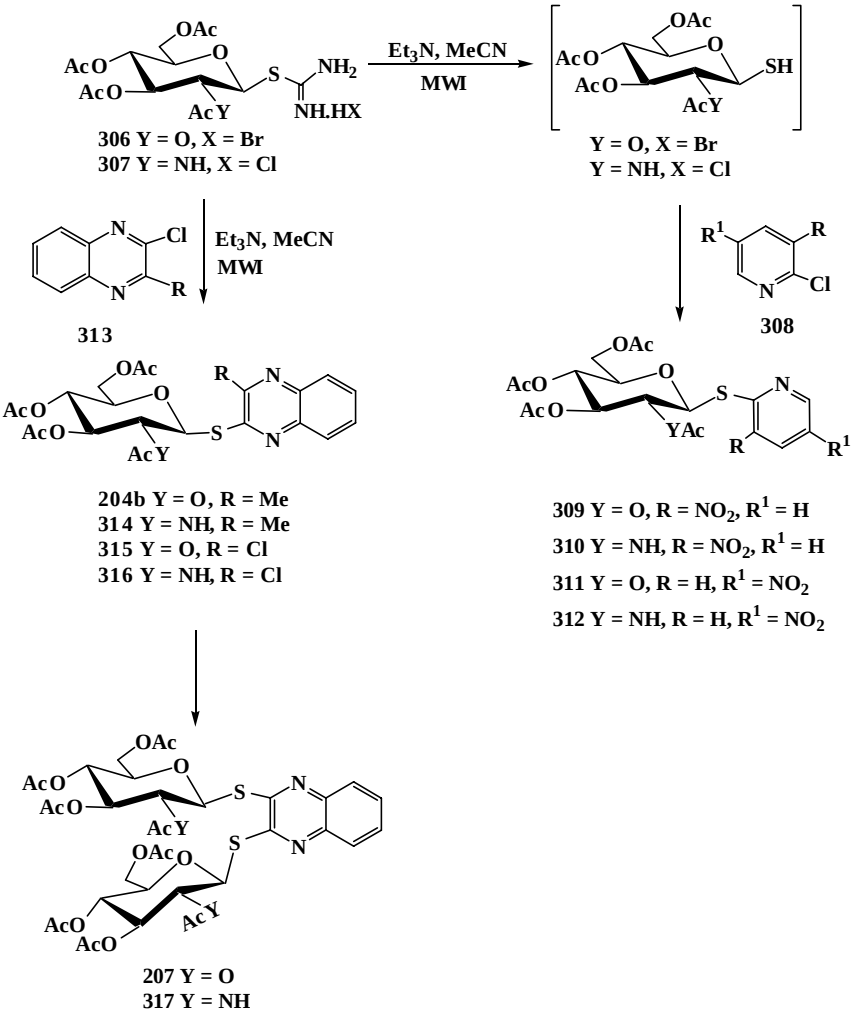
Under the same conditions, the isothiouronium salts **306** and **307** were coupled with 2-chloro-3-methylquinoxaline **313** ($R=Me$) to give the thioglycosides **204** and **314**, respectively, in 60 and 66% yield within 3 min under MWI. Similarly, 2,3-dichloroquinoxaline **313** ($R=Cl$) was reacted with 1 mol equiv of **306** and **307** to afford the monothioglycosides **315** and **316** in 48–50% yield, whereas, with 2 equiv, the bis analogues **207** and **317** were obtained. Conventionally, compounds **314–316** were obtained in 40–48% yield within 10 h[111] (Scheme 38).

2.7. Glycals as glycosylating agents

Acid-catalyzed addition of thiols to glycals gave the 2-deoxythioglycosides. Thus, 3,4,6-tri-*O*-acetyl-D-glucal **318**, -D-galactal **319**, and 3,4-di-*O*-acetyl-L-rhamanal **322**, were reacted with 2-mercaptopyridine (**2**), either with or without anhydrous *p*-toluenesulfonic acid (PTSA) in dichloromethane, to afford α,β mixtures of the 1,2-addition products **320**, **321** and **323**, respectively.[112,113] Similarly, glycal disaccharides **324** and **325** were treated with **2** in the presence of PTSA in CH_2Cl_2 at 5 °C to afford α/β mixtures of 2-deoxy-thioglycosides **326** and **327**, respectively.[113]

When the reaction of **318** was carried out in the presence of $BF_3\cdot Et_2O$ as a catalyst, an allylic displacement took place, with the formation of the 2,3-dideoxy-1-thioglycoside **328**.[112]

On the other hand, when the reaction of **318** or **319** with **2** was carried out in the presence of $SnCl_4$ as a catalyst, it was found to be dependent on the molar ratio of the thiol and



Scheme 38.

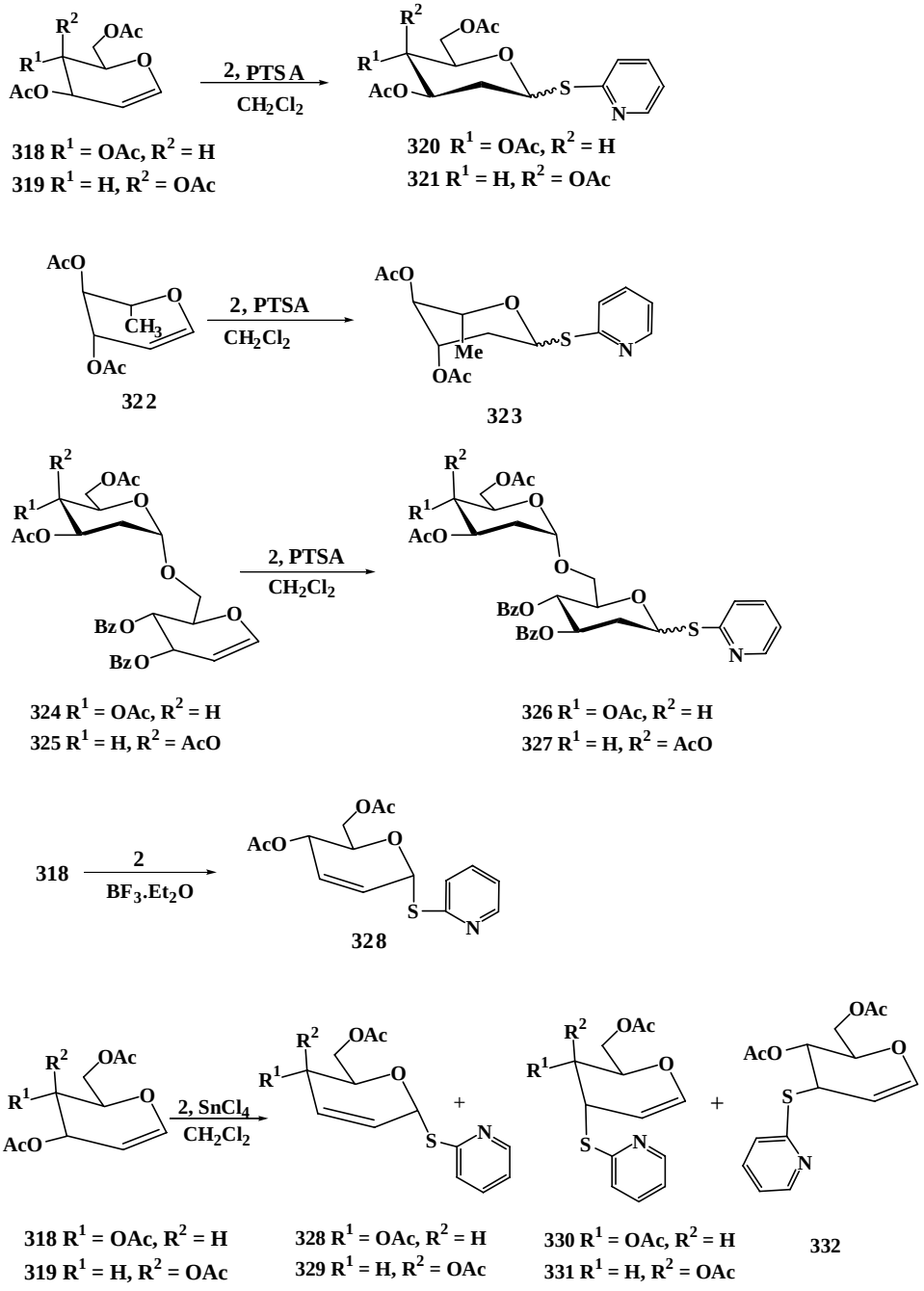
catalyst as well as the temperature.[114] Thus, when **318** was reacted with 1.1 mol equiv of **2** and $SnCl_4$ in dichloromethane at room temperature for 20 min, it gave a mixture of the allylic displacement products **328** (25%), **330** (37%) and **332** (29%), whereas, with 1.5 mol equiv of **2** at −20 °C for 3 h, **328** (69%) was only obtained. When 3,4,6-tri-*O*-acetyl-D-galactal **319** was reacted with 1.1 mol equiv of **2** and 1.0 mol equiv of $SnCl_4$ at −20 °C, a minor product **329** (24%) and traces of **331** were obtained, with the recovery of the starting product **319**. Increasing the molar equivalents of **2** to 1.2 and $SnCl_4$ to 1.5 and the reaction time to 24 h at 0 °C to room temperature afforded **331** as the major product (65%) and **329** as the minor product (15%) with recovered starting material **319** (6%)[114] (Scheme 39).

2.8. Glycosides as glycosylating agents

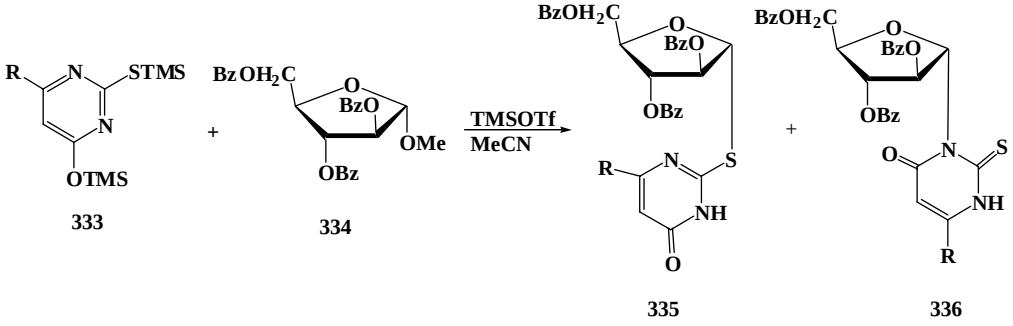
O-Glycosides can be converted into *S*-glycosides in quite acceptable yields by treatment with a thiol or a thiotrimethylsilane and a Lewis acid. The silylated 6-substituted thiouracil **333** was readily reacted with methyl 2,3,5-tri-*O*-benzoyl-α-D-arabinofuranoside **334** in acetonitrile in the presence of trimethylsilyl triflate (TMSOTf) to give the thioglycoside **335** as a minor product while the nucleoside **336** was the major product[115] (Scheme 40).

2.9. Orthoesters as glycosylating agents

Protected 1,2-*O*-methoxyethylidene β-D-mannopyranose **337** (R′=OAc, OBn) were coupled with 2-mercaptopyrimidine in



Scheme 39.



Scheme 40.

dry acetonitrile in presence of mercuric bromide to give the respective 1,2-*trans* thioglycosides, pyrimidin-2-yl 1-thio-α-D-mannopyranosides **338** and **339** in excellent yields.[116] Selective 6-*O*-debenzylation of **339** with trimethylsilyl triflate in acetic anhydride at −50 °C afforded the pyrimidin-2-yl 2,6-di-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside.[116] On the other hand, the fully benzylated thiopyrimidinyl derivative **340** was obtained by deacetylation of **338a** followed by benzylation.[116]

Treatment of 3,4,6-tri-*O*-benzyl-β-D-mannopyranose orthoacetate **337** ($R'=Bn$) with 2-mercaptopyridine, 2-mercaptopyrimidine, 2-mercaptobenzoxazole, or 2-mercaptobenzothiazole in acetonitrile in the presence of $HgBr_2$ afforded the 1-thio-α-mannopyranosides **339a–d** in 87–93% yield,[117] deacetylation of which gave **340a–d**. Treatment of **340b** with benzylsulfonyl chloride in pyridine afforded the 2-pyridyl 3,4,6-tri-*O*-benzyl-2-*O*-benzylsulfonyl-α-D-mannopyranoside **341**.[118]

Under the same reaction conditions, compound **337** was coupled with 2,5-dimercapto-1,3,4-thiadiazole to give the bis-thiomannoside **342** in 88% yield.[117] The reaction of 1,2-*O*-methoxyethylidene β-L-rhamnopyranose **343** with 2-mercaptopyrimidine under similar conditions as above gave **344** or **345**.[116] Deacetylation of **345** followed by benzylation gave **345a** (Scheme 41).

Treatment of **340b** with isophthaloyl chloride in dry toluene and in the presence of a catalytic amount of dry pyridine afforded **346**, which, on treatment with methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **347** in the presence of dibutyltin oxide and tetrabutylammonium iodide (TBAI), afforded **348**.[117] Under the same reaction conditions, the thioglycosides **340a–d** were treated with α,α′-dibromo-*m*-xylene (**349**) followed by coupling with **347** to give the respective mannosides **350a–d** (Scheme 42).[117]

3. Role of thioglycosyl heterocycles in *O*-glycoside synthesis

One of the hot topics in organic synthesis and, in particular, carbohydrate chemistry is the exploration of methods for the synthesis of glycosides. Their formation normally requires a glycosyl donor and an acceptor, which may proceed in an intermolecular or intramolecular fashion, as shown in Scheme 43.

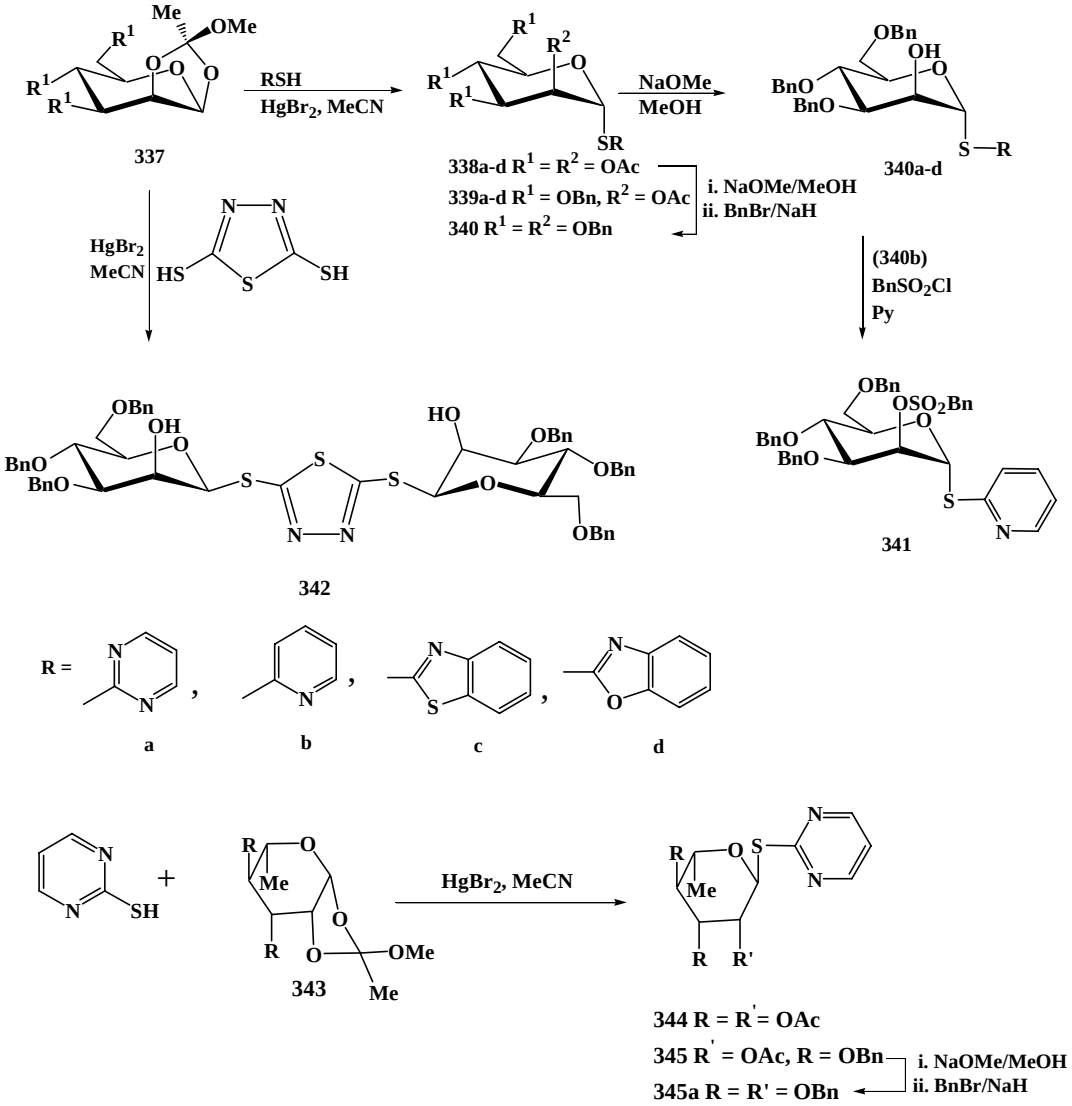
Thioglycosides and, more recently, thioglycosyl heterocycles have become promising candidates as glycosyl donors, which sometimes provide an interesting entry for complex oligosaccharides. Since the thioglycosyl heterocycles are stable towards replacement with alcohols, it has been found that, upon activation, they provide excellent glycosyl donors. This activation of the anomeric center, usually carried out with a promoter, has attracted much attention and, consequently, much research has become available in the literature. In order to review work, it is convenient to classify according to the promoter utilized in the glycosidation step.

3.1. Methyl iodide as promoter

In addition to the selection of a promoter for activating the anomeric center, the protection on the hydroxyl groups has frequently played an important and/or decisive role on the diastereoselectivity of the glycosidation process. This has been exemplified by using participating groups such as acetyl groups and nonparticipating groups such benzyl groups.

Glycosidation reactions of 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-β-D-gluco- **269** and -β-D-galacto-pyranosides **270** were investigated with different alcohols in different solvents using alkyl halides as activators to give the alkyl glycosides **351a** and **352a**, respectively.[43,118] As expected, methanol was more reactive than isopropyl and *t*-butyl alcohols, but *t*-butyl alcohol showed a higher α-diastereoselectivity. The α-distereoselectivity was higher for galactosides **352**, compared to glucosides **351**. Methyl iodide was found to be the ideal activator in terms of the rate of reaction and distereoselectivity. Using *n*-butyl iodide resulted in the recovery of 55% of the glycosyl donor **269** with 30% yield of **351** ($R={}^{i}Pr$), whereas, using *n*-butyl bromide, **269** was completely recovered. Dichloromethane was found to be a suitable solvent in terms of solubility and providing good yields as well as stereoselectivity[43] (Table 1).

With 2-azidoethanol, **17**, **269** and **270** under the same reaction conditions afforded only the α-glycosides **351**, **352** and **353** in 68–72% yield.[44] 2-Pyridyl thioglycosides **49**, **51** and **55** gave the α-*O*-glycosides **354–356** in 70, 56 and 66% yield, respectively. Stereoselective α-glycosylation was also observed when an anomeric mixture of 2-pyridyl thioglycosides **269–271**, **51**, **253** and **53** was used in the glycosylation with various acceptors in the presence of methyl iodide as an activator and 4 Å molecular sieves in CH_2Cl_2 to



Scheme 41.

afford the α-glycosides **351** (R=c,d,e,f), **352** (R=c,e), **357** (R=c), **358** and **359**, respectively[43,97] (Scheme 44).

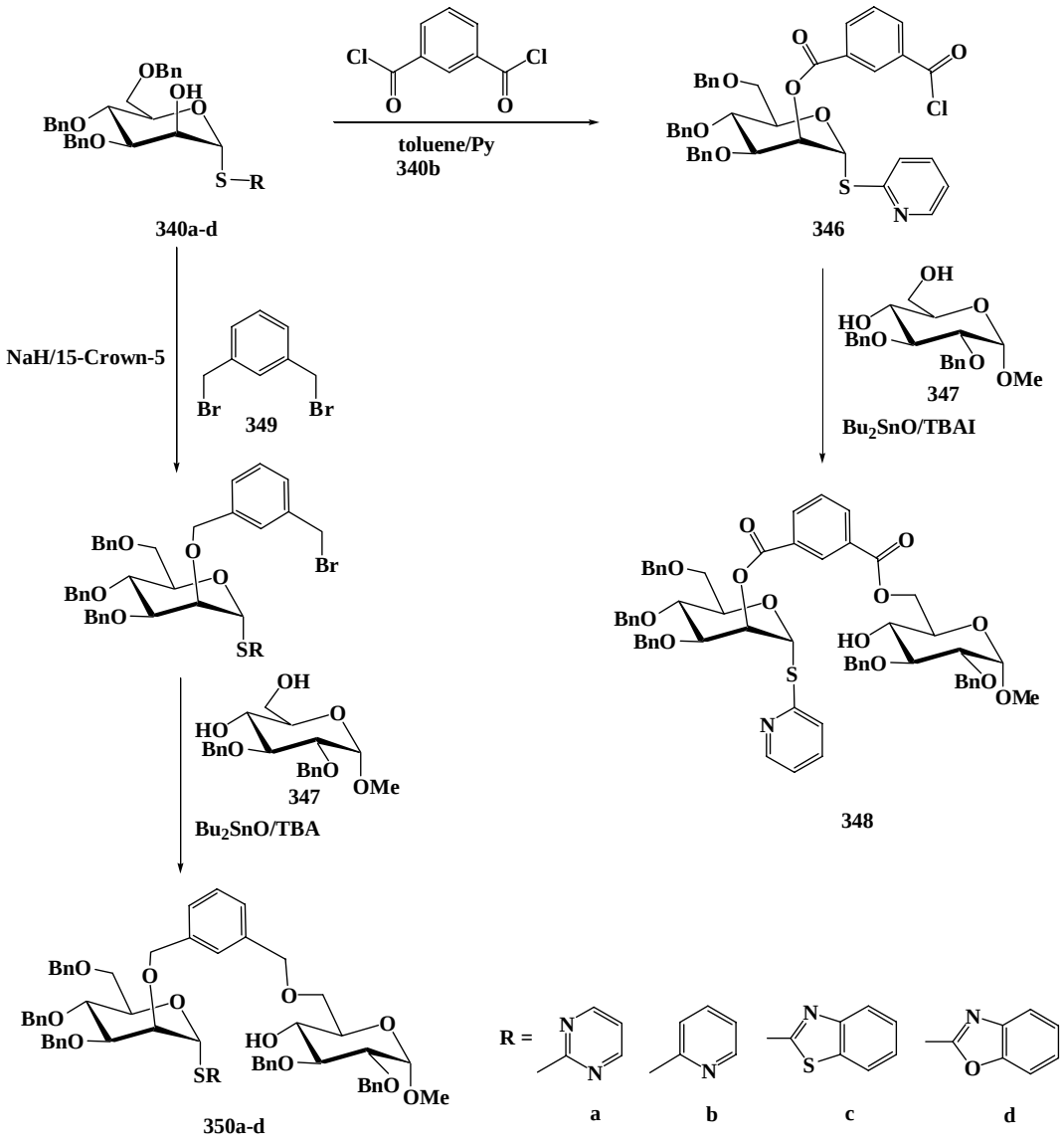
The reaction of per-*O*-benzyl 2-pyridyl-1-thio-β-D-ribofuranoside **49** and 2-pyridyl 2,3:5,6-di-*O*-isopropylidene-1-thio-β-D-mannofuranoside **255** with the acceptors, 1,2:5,6-di-*O*-isopropylidene-D-glucopyranose and methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside, using methyl iodide as an activator afforded the respective α-disaccharides **354** and **360** in 67–81% yield[42] (Scheme 44).

The thiopyridyl sialoside **56** and its thio-*N*-methylimidazolyl analogue, however, failed to react with glycosyl acceptors when either MeI or NBS were used as promoters.[45]

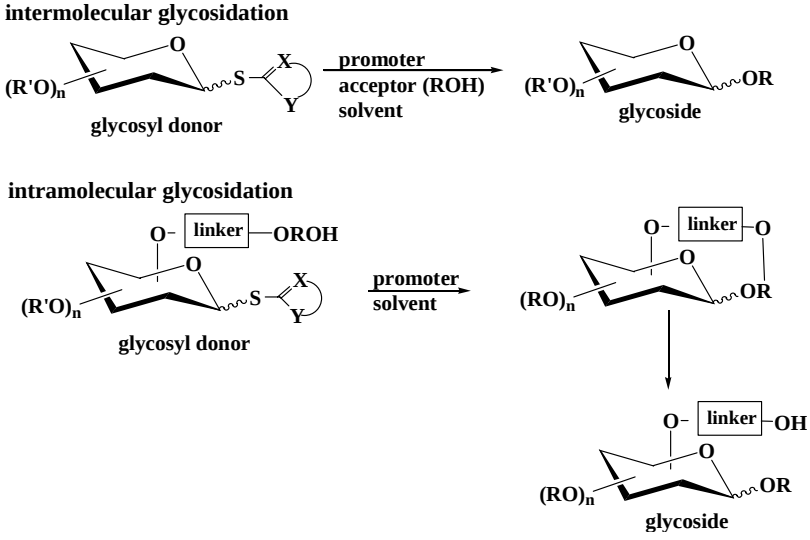
On the other hand, only a few examples were reported on thioglycosyl donors with acetyl groups. This can be attributed to the high success in achieving high diastereoselectivies encountered using acetyl derivatives and different leaving groups at the anomeric center. Under the same reaction conditions, the acetylated derivative, 2-pyridyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside **15**, with methanol or ethanol resulted in the recovery of 90% of **15**,[119] whereas 2-pyridyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside **47** afforded the β-glucosides **363**, **364**, **365** and **366** in 72–81% yield, respectively.[40,119] Similarly, the benzoylated derivative **361** afforded the β-glucoside **362** (Scheme 45).[119] With the glycosyl acceptors, 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose and 4-*O*-(2,3-di-*O*-acetyl-α-D-glucopyranosyl)-1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose, the thiopyridyl donor **47** afforded the β-glucosides **367** and **368**, respectively, (Scheme 45).[40]

Methyl iodide as a promoter was used for the synthesis of complex oligosaccharides. Thus, the glycosyl donor **369** was coupled with 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose to give the tetrasaccharide[119] **370** (Scheme 46).

Methyl iodide was evaluated as a promoter for the coupling of 2-pyridyl 2-deoxy-1-thio-α/β-D-glycopyranosides with several acceptors in CH_2Cl_2 to give the α-linked disaccharides[42,113] **371** and **372**, respectively, in 65–87% yield, except for the disaccharide **371** (R=**a**), which was obtained as an α:β mixture with a ratio of 85:15.[42] The reaction was



Scheme 42.



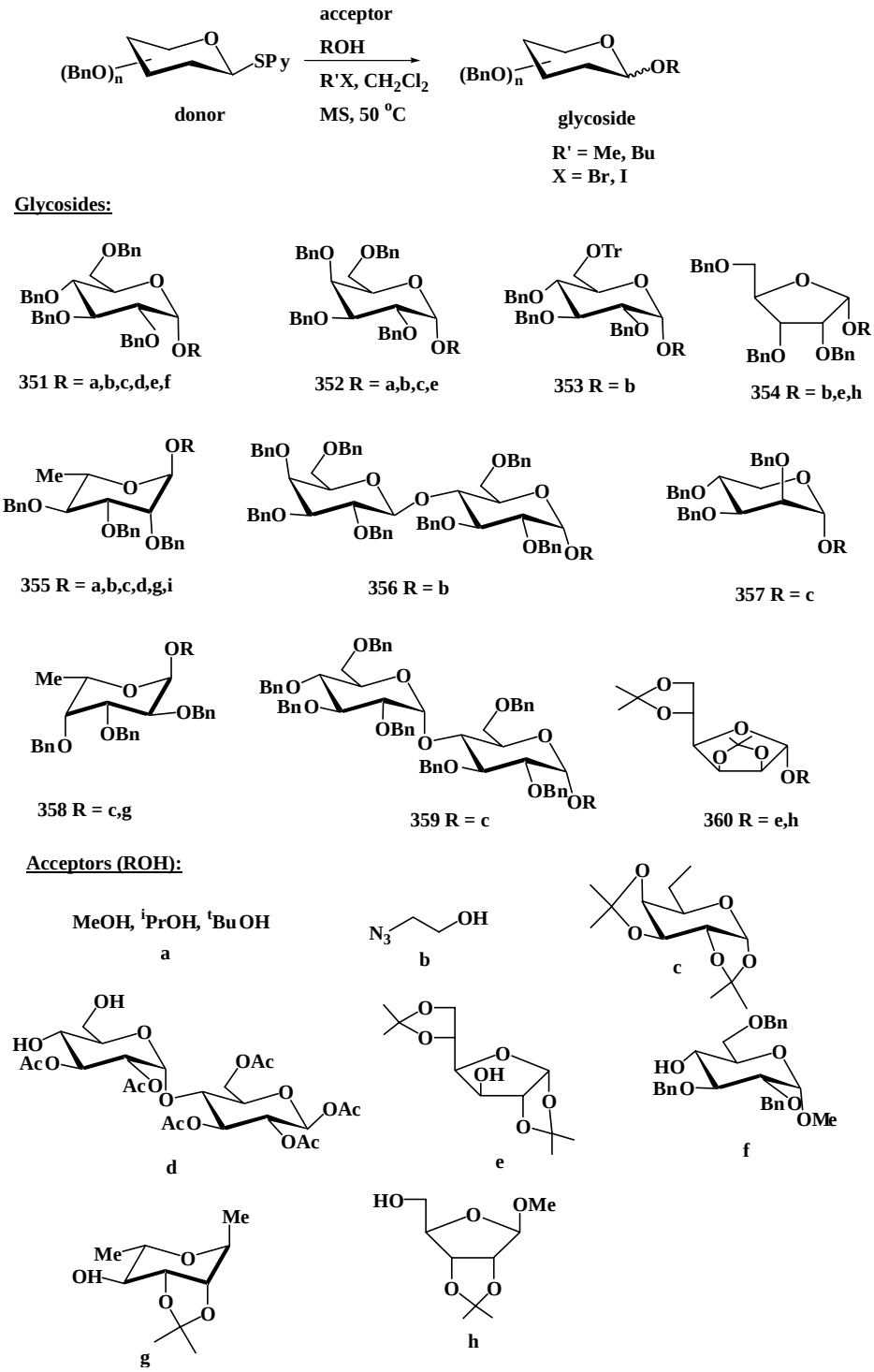
Scheme 43.

Table 1. Results of glycosidation of **269** and **270** with various alcohols in CH_2Cl_2 using MeI

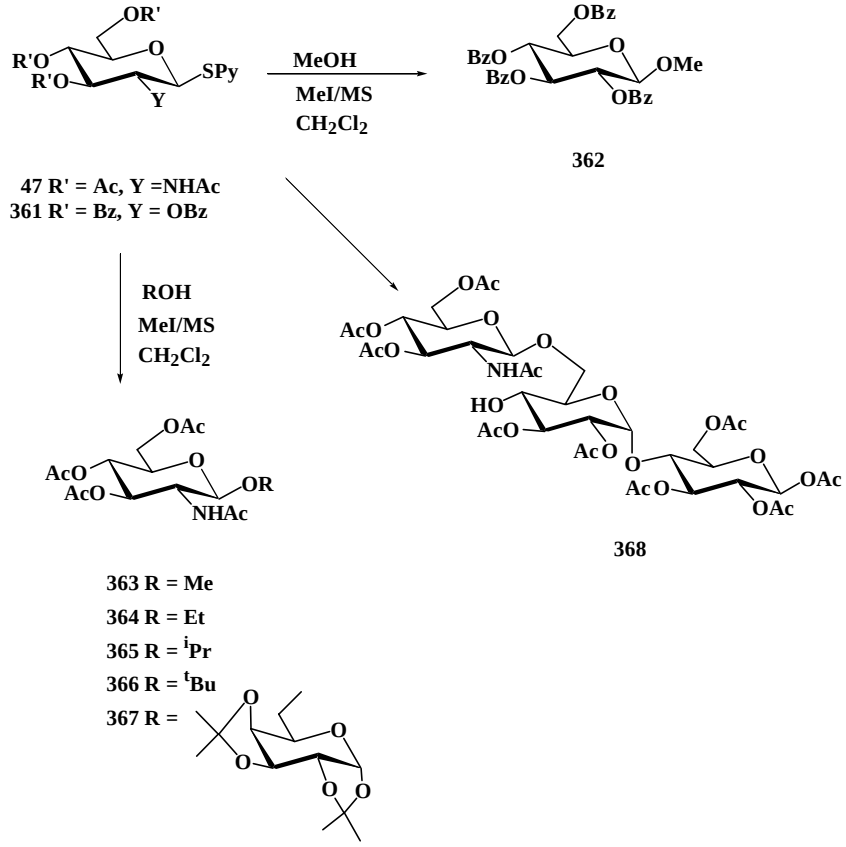
Acceptor	Glycosyl donor	Yield (%)	α:β
MeOH	**269**	95	65:35
^{i}PrOH	**269**	85	82:18
^{t}BuOH	**269**	82	89:11
MeOH	**270**	96	72:28
^{i}PrOH	**270**	87	87:13
^{t}BuOH	**270**	80	91:9

extended to the 2-deoxyrhamnopyranosides to give also the corresponding α-disaccharides **373** and **374**, whereas an α,β mixture of **373** (R=**a**, 86% yield, 85:15 α:β) and 1,2-elimination products were isolated.[42]

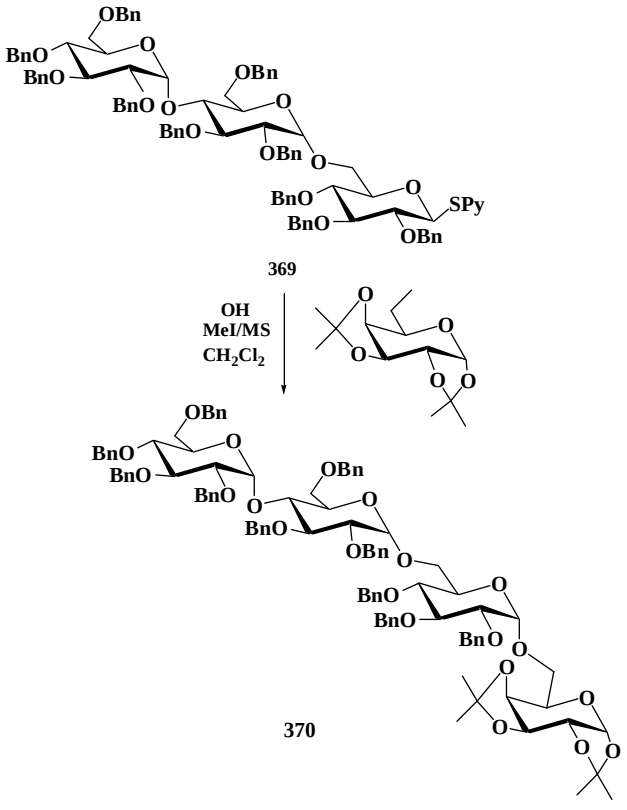
2-Pyridyl 3,5-di-*O*-benzoyl-2-deoxy-1-thio-α/β-D-ribofuranoside **263** was coupled with various acceptors to give only the α-2-deoxy disaccharides **375** (R=**a**,**b**,**c**,**i**) in 72–85% yield, along with 1,4-anhydro-2-deoxy-3,5-di-*O*-benzoyl-D-erythro-pent-1-enilol.[42]



Scheme 44.



Scheme 45.



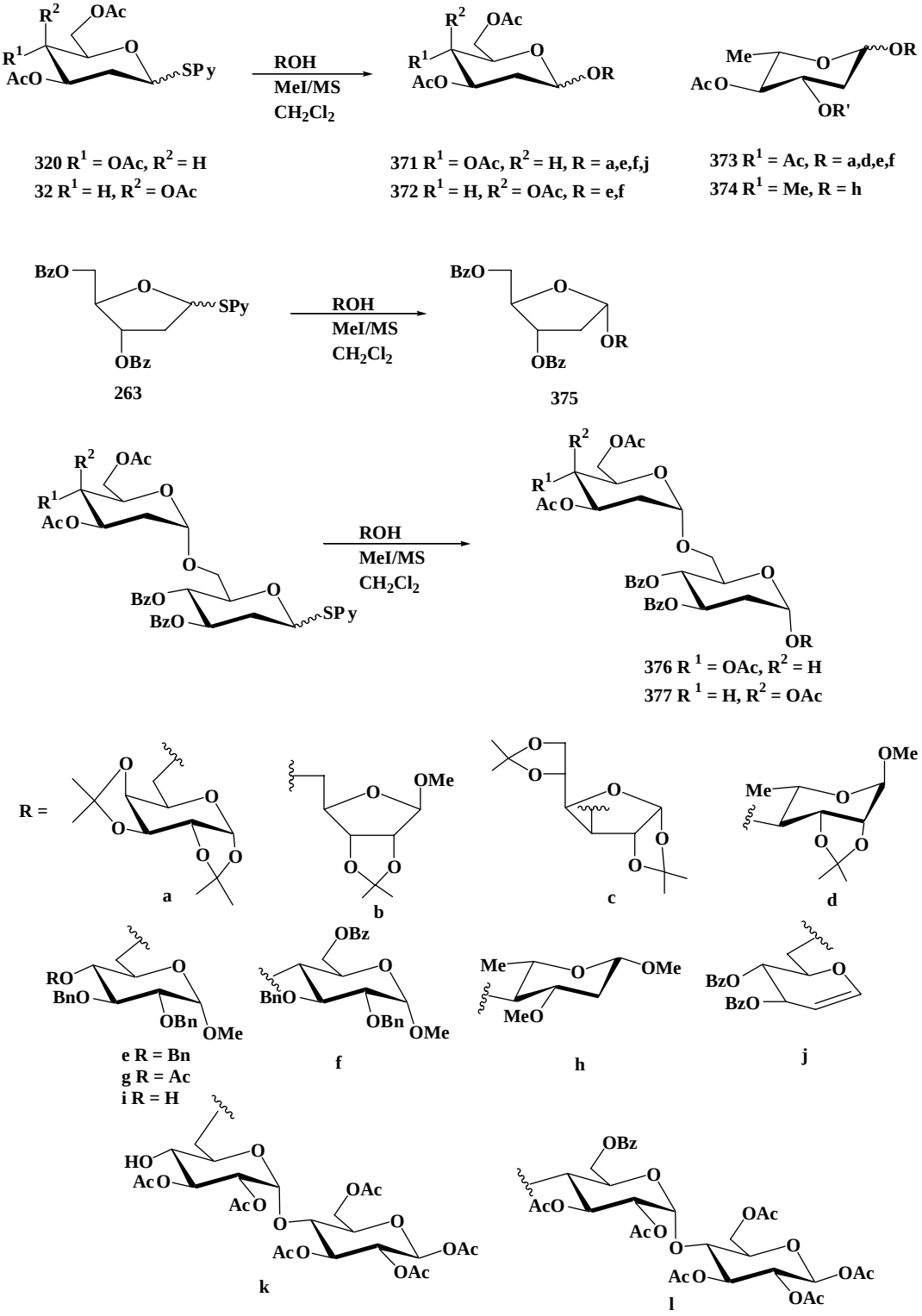
Scheme 46.

Similarly, the α-trisaccharides **372k**, **373k** and **373l** were obtained in 63, 71 and 66% yield, respectively,[42] and the α-anomer trisaccharides **376a**,**c** and **377a** in 73–81% yield[113] (Scheme 47).

The selectivity of coupling has been investigated using the acceptor, methyl 4,6-*O*-benzylidene-α-D-glucopyranoside α-**378** (R^1 = Me), which has two sites for reaction, the coupling of which with the donor **269** in the presence of methyl iodide in dichloromethane under reflux afforded the 1→2 disaccharide **379**, 1→3 disaccharide **380**, together with the trisaccharide **381**, in 20, 48 and 10% yield, respectively.[120] Under the same reaction conditions, an α-stereoselectivity was observed upon using the β-anomer **378** as acceptor, to give only the respective 1→2 and 1→3 disaccharides in 23.5 and 46% yield.[120] On the other hand, using long-chain alkyl groups such as *n*-octyl at the anomeric carbon of the glycosyl acceptor **378** (R = nC_8H_{17}) in the coupling reaction with **269** resulted in a high regioselectivity, with the formation of 2-*O*-β-glycosylated **379** (OR^1 = β-$nC_8H_{17}O$) in 77% yield and 3-*O*-α-**380** (OR^1 = α-$nC_8H_{17}O$, 58% yield).[120]

Glycosylation of (±)1-hydroxy-*trans*-2-(hydroxymethyl)cyclohexane **382** with 2-thiopyridyl glucoside **269**, in the presence of methyl iodide, gave four α-glucosides **383**, **384**, **385** and **386** in a ratio of 3:3:1:1 and a combined yield of 47% and, whereas **384** and **385** could be separated by chromatographic means, **383** and **386** were inseparable[121] (Scheme 48).

A high-pressure-assisted glycosylation reaction with the glycosyl donor, 2-benzothiazolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **102**, for the acceptors,



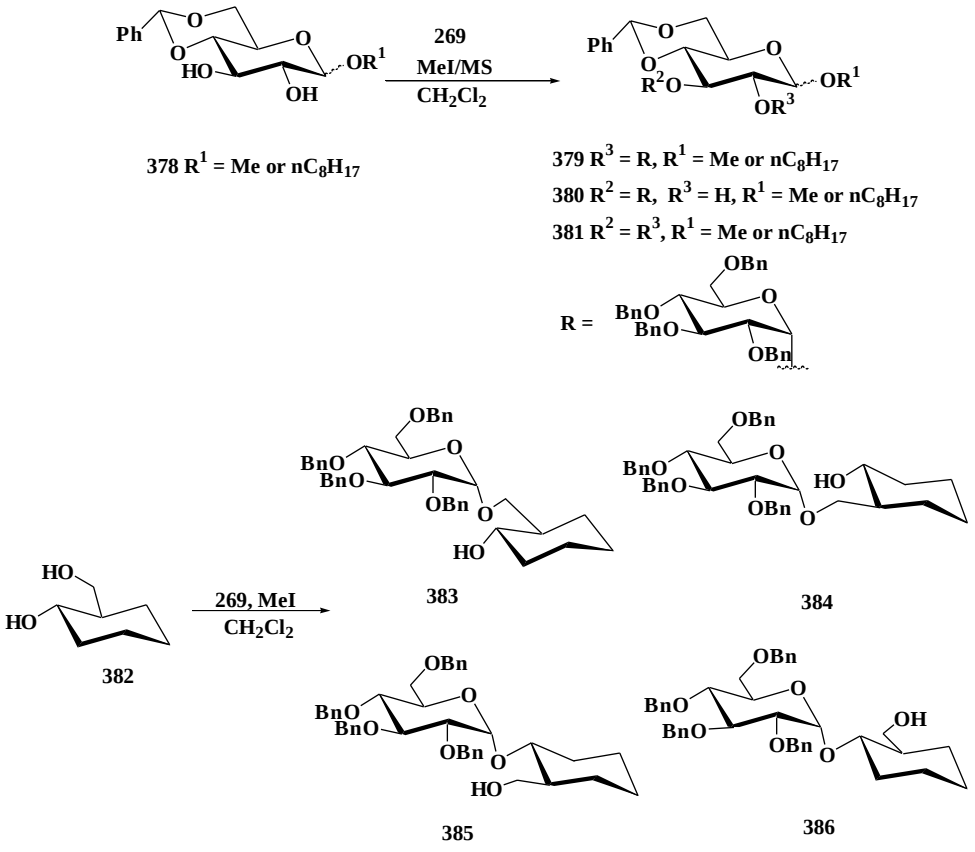
Scheme 47.

t-butanol, *n*-octanol, and cholesterol, using methyl iodide as an activator, gave the 1,2-*cis* glucosides **351** as the major products in good yield and high α-selectivity[122] (Table 2).

3.2. *N*-Halosuccinimides as promoters

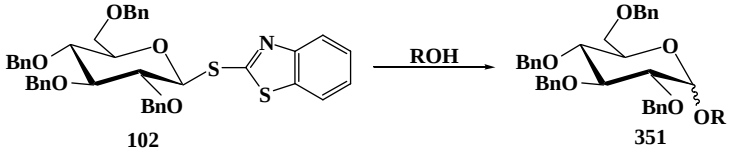
NBS in acetonitrile has been used for activating the thioglucosyl pyridine **387** towards glycosylation with methanol to give a 4:1 mixture of methyl α- and β-D-glucopyranosides[14] (Scheme 49).

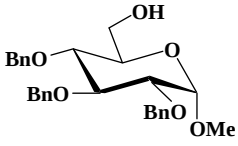
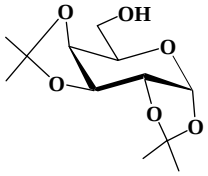
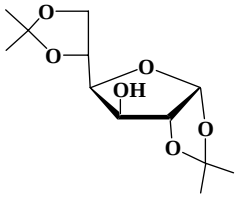
Glycosylation of pyrazol-3-yl per-*O*-acetyl-1-thio-β-D-glucopyranoside **305** with alcohol in the presence of NBS did not take place to give **390**. The per-*O*-benzylated derivative **388** could, however, be *O*-glycosylated[109] to give **389** (Scheme 49).

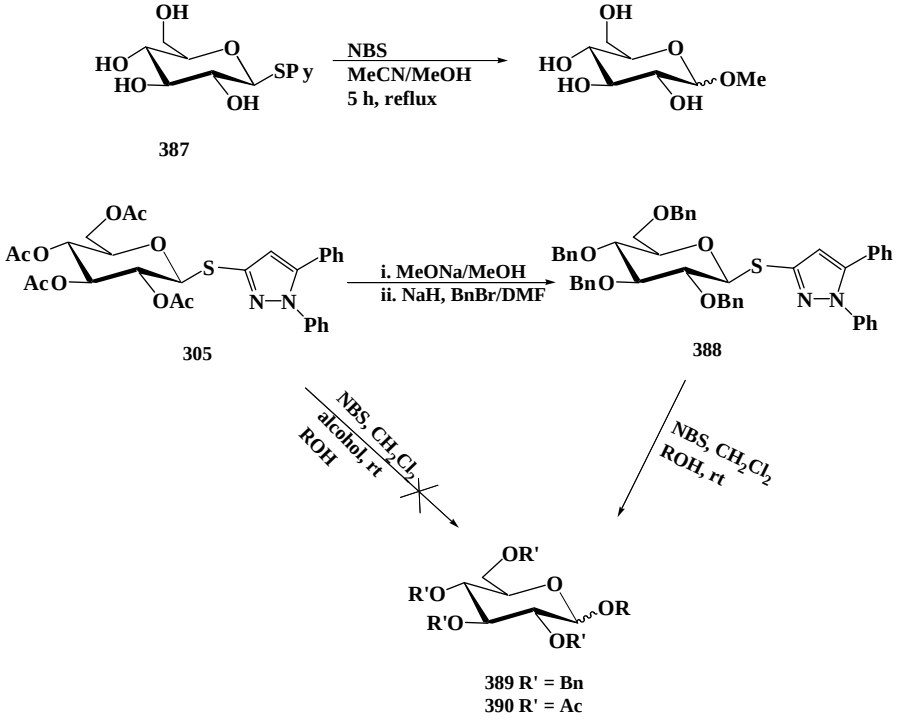


Scheme 48.

Table 2. Yields and anomeric ratios for coupling of **102** with different acceptors



Acceptor ROH	Yield (%)	α:β
$Me(CH_2)_6CH_2OH$	85	89:11
$(Me)_3COH$	65	89:11
	71	88:12
	71	90:10
	40	90:10
Cholesterol	80	90:10



Scheme 49.

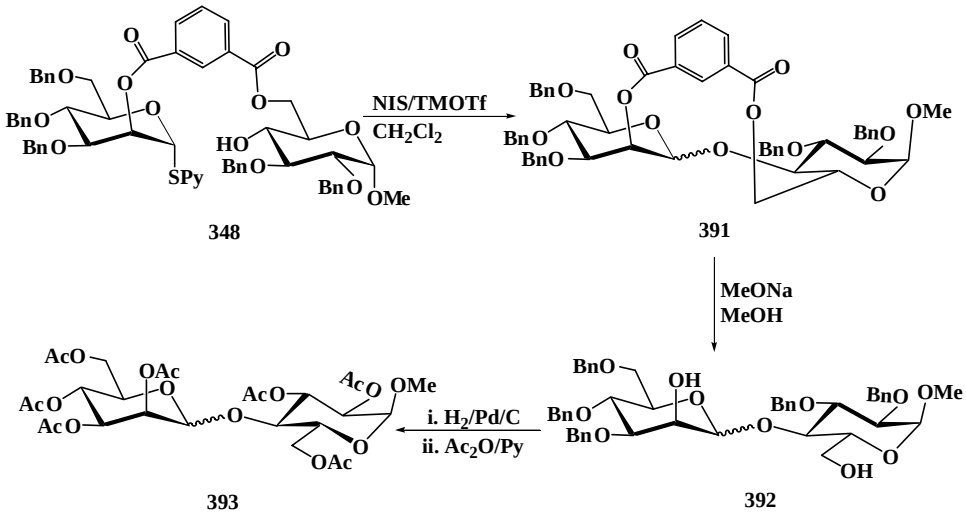
An efficient and highly region- and stereoselective protocol for intramolecular β-mannopyranoside synthesis was developed using 2-thio derivatives of nitrogen heterocycles as leaving groups at the anomeric position and isophthaloyl and *m*-xylenyl derivatives as rigid spacers linked to the 2-hydroxy group of the mannose residue.[117] Thus, *N*-iodosuccinimide (NIS, 1.3 equiv) and TMSOTf (0.1 equiv) in CH_2Cl_2 were used for the activation of intramolecular glycosylation in the isophthaloyl derivative **348** to give the 1→4 linked disaccharide **391** in an α:β ratio of 1:6 (70% yield).[117] Treatment of **391** with sodium methoxide in methanol afforded **392**, the debenzylation and subsequent acetylation of which gave **393** (Scheme 50).

Under the same reaction conditions, the *m*-xylenyl thiomannopyranosides **350a**,**c**,**d** were intramolecularly glycosylated to give the disaccharide **394** in an α,β ratio of 1:9–10, which, upon deprotection and subsequent acetylation, gave **393**, which was similarly obtained from **392**.[117] The disaccharide **394** was also obtained (72% yield, α:β 1:6) when the mannosyl donor **395** was activated with NIS–TMSOTf in CH_2Cl_2[117] (Scheme 51).

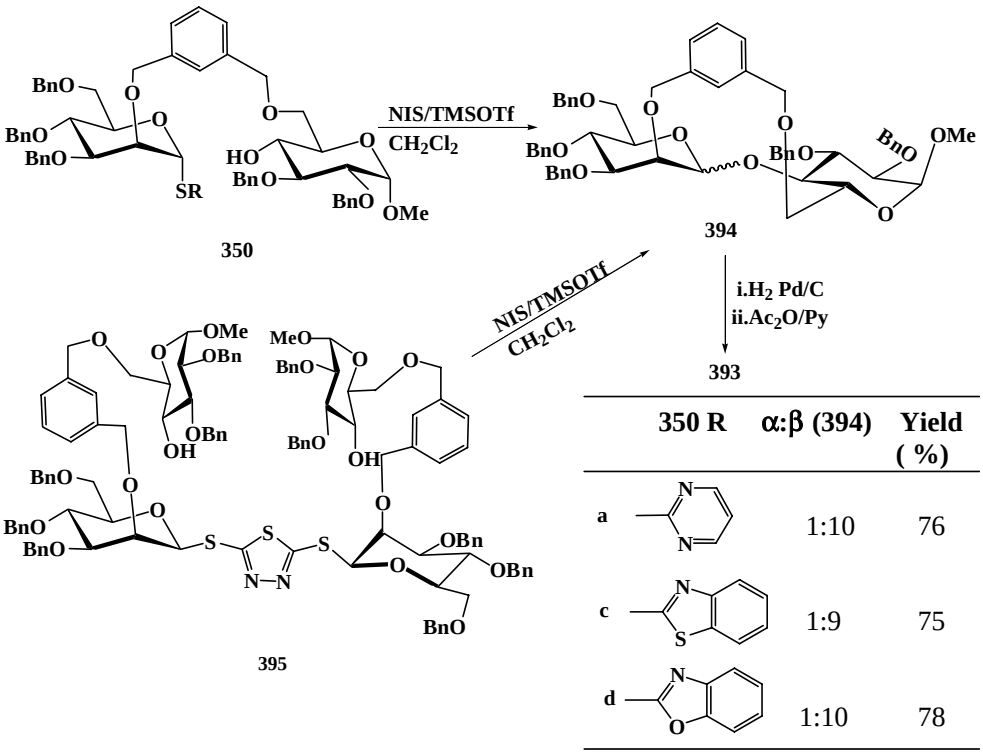
NIS has been used in combination with TfOH to activate the glycosylation of 2-benzoxazolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside,[35] (see Section 3.5).

3.3. Metal salts as promoters

Some salts of mercury, zinc and silver have been used for the activation of anomeric centers, and consequently, have promoted the glycosylation of glycosylthio heterocycles.



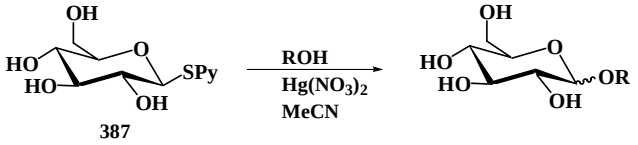
Scheme 50.



Scheme 51.

Thus, mercuric nitrate promoted the reaction of **387**, obtained by deacetylation of **15**, with various alcohols and monosaccharides in acetonitrile within a few minutes, to give the α-anomeric glucosides as the major products,[14] regardless of the structural complexity of the alcohol (Table 3). The 6-*O*-*tert*-butyldiphenylsilyl derivative of **387** glycosylated isopropanol in CH_2Cl_2 under the same reaction conditions, to give the same α:β ratio of isopropyl D-glucopyranoside. Similarly, using the 4,6-*O*-benzylidene derivative of **387** did not alter the α:β ratio of the resulting glucoside.[14] The low polarity of the solvent also did not alter the α:β ratio.

Table 3. Yields and anomeric ratios for glucosides resulting from **385** by activation with mercuric nitrate



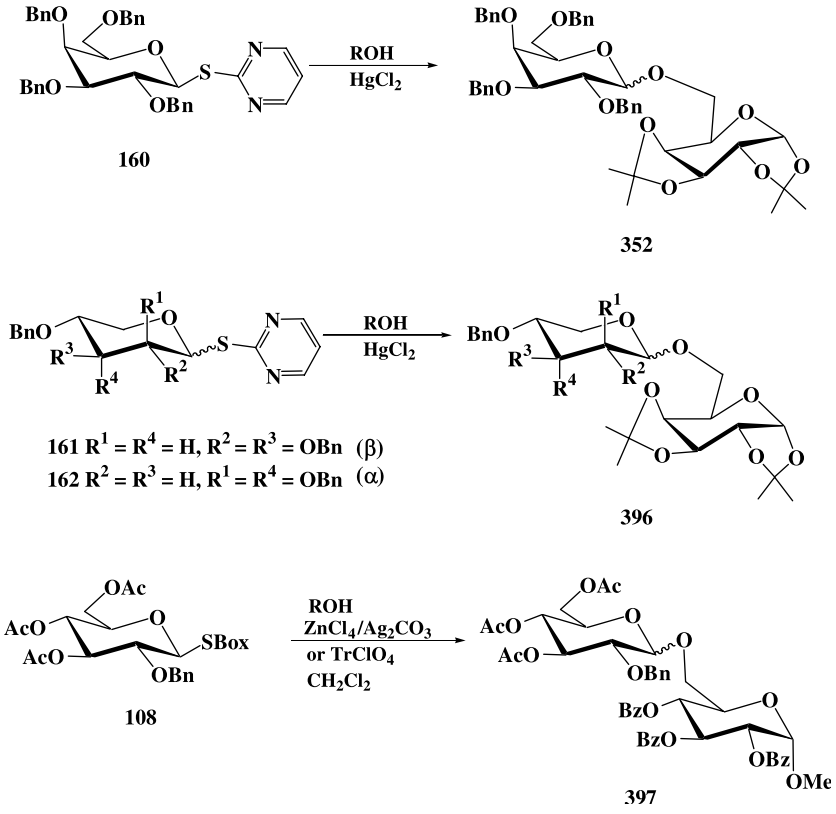
ROH	Solvent	Yield (%)	α:β
MeOH	MeCN	95	70:30
EtOH	MeCN	85	68:32
2-Propanol	MeCN	77	62:38
Cyclohexanol	MeCN	75	51:49
2,2-Dimethyl-1-propanol	MeCN	47	58:42
1,2:3,4-Di-*O*-isopropylidene-α-D-Galactopyranose	MeCN	35	55:45
2-Chloroethanol	-	80	α Only
2-Propanol	1-Chloro-pentane	70	1:1

The reaction of pyrimidinyl thioglycosides **160–162** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the presence of mercuric chloride as activator gave an α:β mixture of the disaccharides **352** and **396**, respectively, in 60% yield; the 1,2-*cis*(α)-glycosides were the major products.[13]

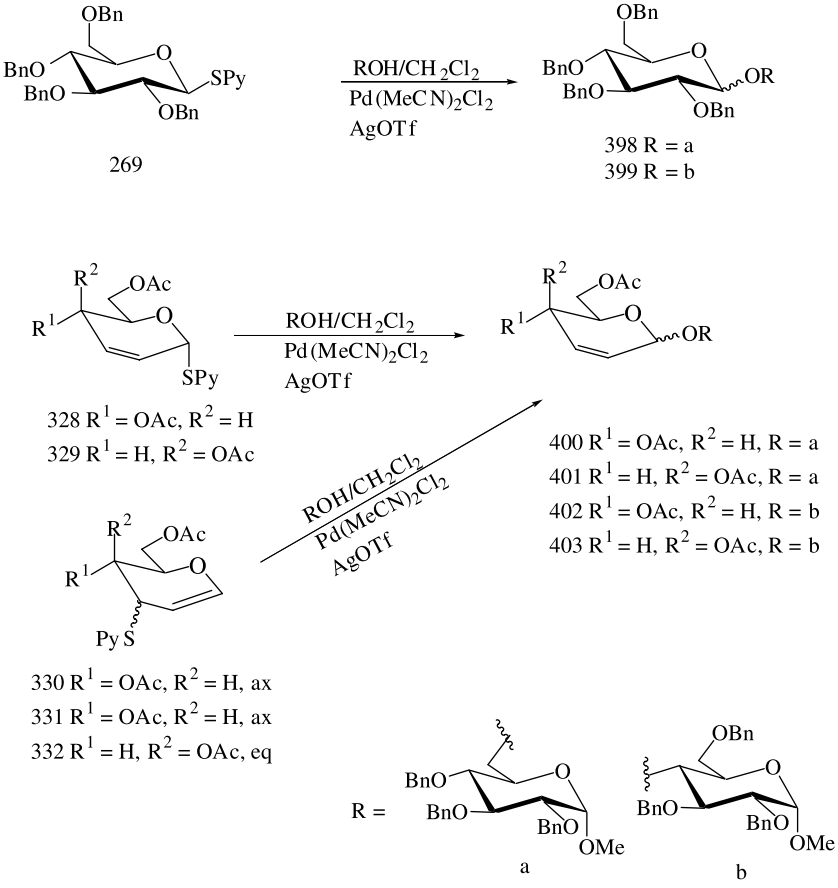
A high stereoselectivity was reported,[57] when the SBox-glucoside **108** was coupled with methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside in the presence of $ZnCl_4$/Ag_2CO_3, in CH_2Cl_2 to afford within 2 h the disaccharide **397** in 70% yield with high stereoselectivity (α:β 10:1). Moreover, compound **397** was obtained in 88% yield in higher α-stereoselectivity (α:β 15:1) upon using $TrClO_4$ as an activator[57] (Scheme 52).

A combination of silver triflate with bis(acetonitrile)dichloropalladium(II) activated the glycosidation reaction of β-**269** with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside in CH_2Cl_2; a molar ratio of **269**:ROH(**a**):$Pd(MeCN)_2Cl_2$:AgOTf of 2:1:2:2 gave an α:β (60:40) mixture of the disaccharide **398** in 80% yield. An increase in the molar ratio of AgOTf to 4 equiv increased the yield and α-ratio (93% yield, α:β 65:35) of **398**. On the other hand, coupling of **269** with the acceptors to give **398** and **399** was affected by the solvents; a mixture of acetonitrile and dichloromethane of molar equivalents 2:1:3:6 exhibited a marked β-favored solvent effect, compared to a dichloromethane solution.[114]

Glycosidation with 1-thio-2-enosides **328** and **329** or 3-thio-1-enosides **330**, **331** and **332** of the acceptors in the presence of $Pd(MeCN)_2Cl_2$-AgOTf as activator in CH_2Cl_2 in a molar ratio of donor:acceptor:Pd(II) and AgOTf of 2:1:2:2 afforded preferentially the α-2-enosides **400–403**, respectively, in 55–94% yield (Scheme 53). Increasing the molar ratio of **329** to 4 equiv or using an equivalent ratio of **332** and other reagents gave only the α-anomer **403**[114] (Table 4).



Scheme 52.



Scheme 53.

Table 4. Effect of molar ratio of reactants, promoters and solvents on stereoselectivity of disaccharides in Scheme 53

Donor	Acceptor ROH	Molar ratio	Solvent	Product	Yield (%)	α:β
269	a-OH	2:1:2:2	CH_2Cl_2	**398**	**80**	60:40
269	a-OH	2:1:2:4	CH_2Cl_2	**398**	**93**	65:35
269	a-OH	2:1:3:6	CH_2Cl_2–MeCN	**398**	**88**	13:87
269	b-OH	2:1:3:6	CH_2Cl_2–MeCN	**399**	**93**	42:58
328	a-OH	2:1:2:2	CH_2Cl_2	**400**	**94**	83:17
329	a-OH	2:1:2:2	CH_2Cl_2	**401**	**81**	94:6
329	b-OH	1:1:1:1	CH_2Cl_2	**403**	**68**	α Only
330	b-OH	2:1:2:2	CH_2Cl_2	**401**	**68**	96:4
330	b-OH	2:1:2:2	CH_2Cl_2	**403**	**72**	96:4
331	a-OH	2:1:2:2	CH_2Cl_2	**400**	**55**	α Only
331	b-OH	4:1:2:2	CH_2Cl_2	**402**	**87**	α Only
332	b-OH	2:1:2:2	CH_2Cl_2	**402**	**62**	90:10

3.4. Triflates as promoters

Glycosylation of 1-(1-phenyl-1*H*-tetrazol-5-yl)-2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **280** with a variety of glycosyl acceptors using silver triflate as a promoter afforded an α/β mixture of glucopyranosides **351**. The α:β anomeric ratio ratio was found to be dependent on the type of alcohol[102] (Table 5).

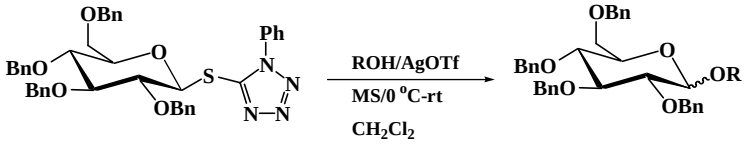
The S-Box-glycosides **110–112** were reacted with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**h**) in the presence of AgOTf or MeOTf and molecular sieves in 1,2-dichloroethane to give the 1,2-*trans* disaccharides **404–406** in 76–95% yield.[35] Similarly, the disaccharides **404a–g** were obtained when **110** was coupled with various acceptors using AgOTf or MeOTf.[35] NIS/TfOH promoted the glycosylation of **110** and **h**, in the absence of molecular sieves, to give **404**[35] (Scheme 54).

Coupling of the glycosyl donor **32** with cyclohexanol in CH_2Cl_2 at 0 °C in the presence of AgOTf gave cyclohexyl β-D-glucopyranoside **407**[41] in 68% yield. Similarly, nitrobenzimidazolyl **89** and pyridyl **15** thioglucosides gave **407** in 38 and 66% yields, respectively.[41]

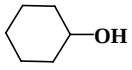
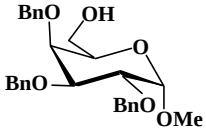
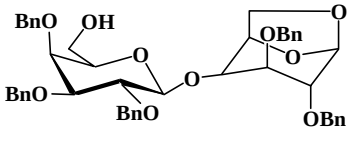
Under the same reaction conditions **32** coupled with thexyldimethylsilyl 3,6-di-*O*-benzyl-2-deoxy-2-*N*-dimethylmaleimido-β-D-glucopyranoside **408** to give the β-disaccharide **409** in 46% yield. On the other hand, the benzyl derivative **113**, under the same reaction conditions, gave the disaccharide **410** also in 46% yield, but in an α:β ratio of 1:3.[41] Similarly, **113** coupled with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside in the presence of AgOTf or TMSOTf to afford the disaccharide **398** in 44% yield and in an α:β ratio of 1:4[41] (Scheme 55).

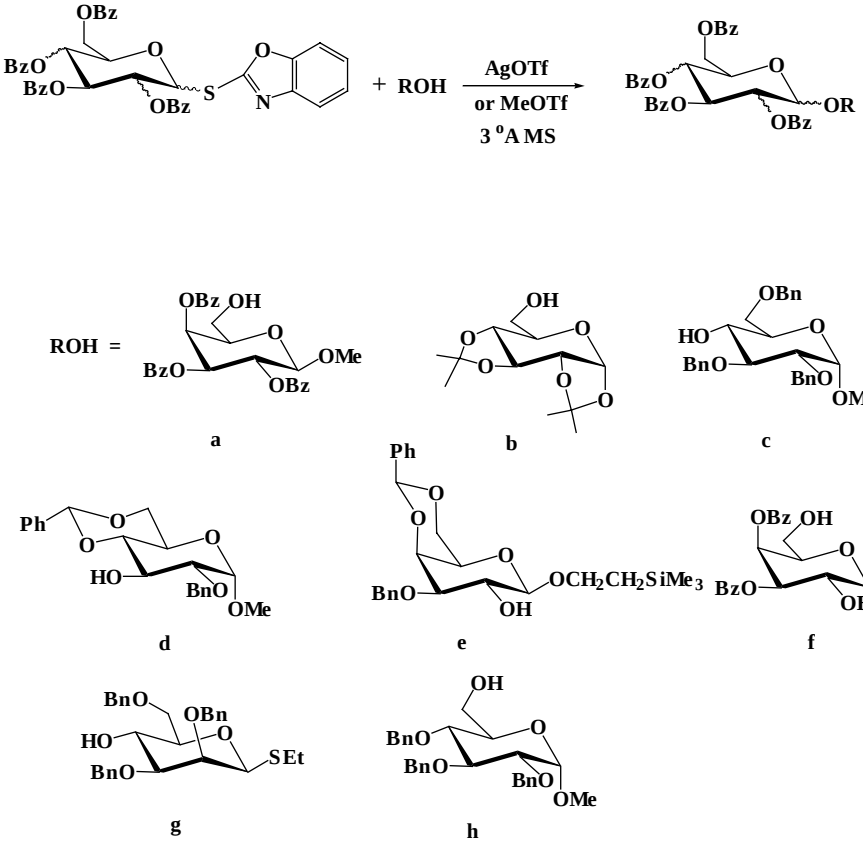
The presence of only one nonparticipating group on O-2 in the thioglycosides, 2-benzoxazolyl 3,4,6-tri-*O*-acetyl-2-*O*-benzyl-1-thio-β-D-glycopyranoside **108** and **109**, resulted in the formation of α-linked disaccharides **411** and **412**, respectively, in comparable yield when AgOTf/MS or MeOTf/MS were used as promoters for their coupling with **a**. In addition, **108** gave only the α-disaccharide **411** when coupled with **c** or **g** using AgOTf or MeOTf as a promoter. When TMSOTf was used as activator in the coupling of **108** with acceptor **a**, a sluggish reaction occurred (incomplete within 24–48 h) and, although a high or complete anomeric selectivity was found, a low isolated yield was obtained.[57] When NIS–TMSOTf was used as a promoter, however, an α:β mixture of **411** was obtained in a ratio of 15:1. On the

Table 5. Yields and α/β ratios of products from glycosylation of **280**

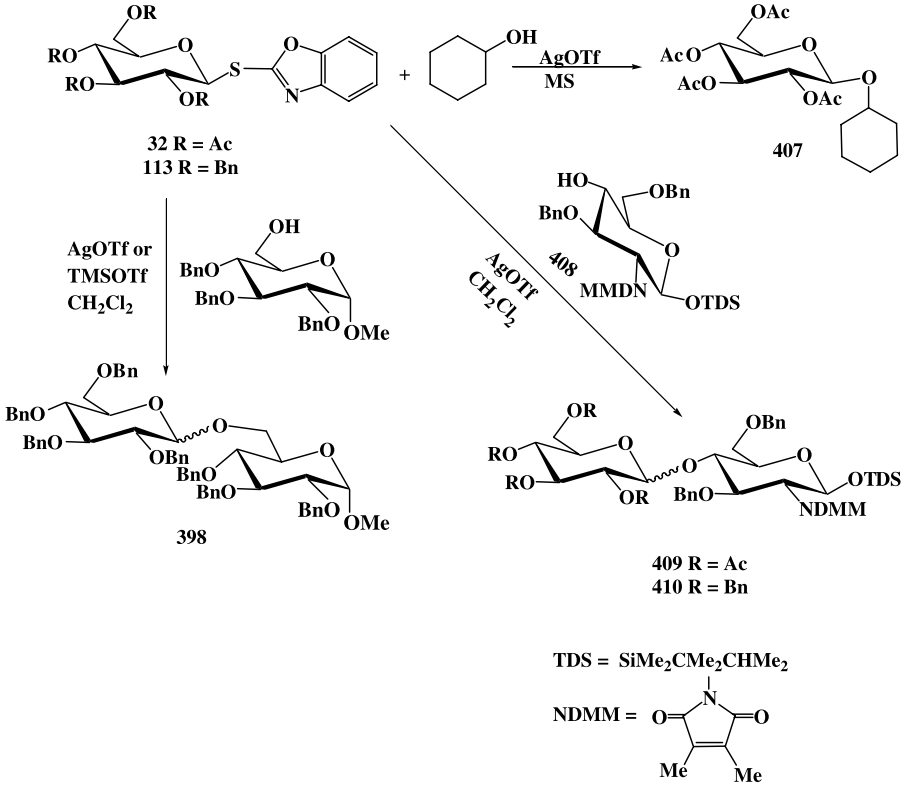


280 **351**

ROH	Yield (%)	α:β
MeOH	87	771:29
Cholesterol	95	50:50
	95	33:67
	48	66:34
	71	66:34

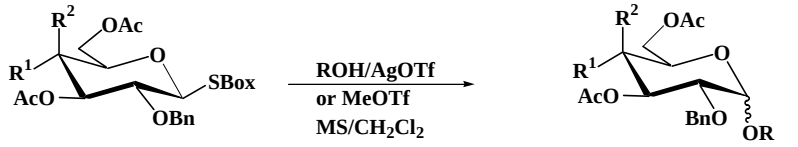


Scheme 54.



Scheme 55.

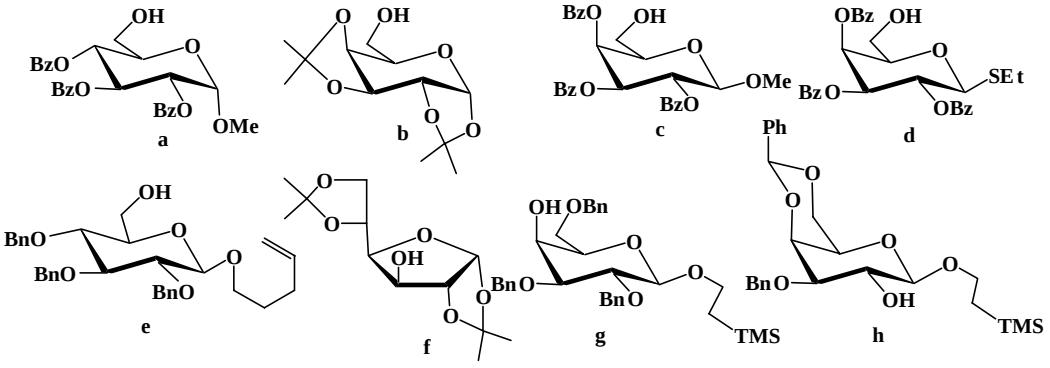
Table 6. Results of coupling of **108** or **109** with acceptors in presence of AgOTf or MeOTf



108 R^1 = OAc, R^2 = H
109 R^1 = H, R^2 = OAc

411 R^1 = OAc, R^2 = H
412 R^1 = H, R^2 = OAc

Donor	Acceptor	Promoter	Yield (%)	α:β
108	**a**	MeOTf/MS	**89**	α Only
108	**a**	AgOTf/MS	**92**	α Only
108	**b**	AgOTf	**99**	**11**:**1**
108	**c**	AgOTf/MS	**85**	**15**:**1**
108	**c**	AgOTf	**97**	α Only
108	**d**	AgOTf	**98**	α Only
108	**e**	AgOTf	**99**	**8**:**1**
108	**f**	MeOTf	**88**	**8**:**1**
108	**g**	MeOTf	**88**	**A** Only
108	**h**	MeOTf	**78**	**3**:**1**
109	**b**	AgOTf	**90**	**10**:**1**
109	**c**	AgOTf	**80**	α Only



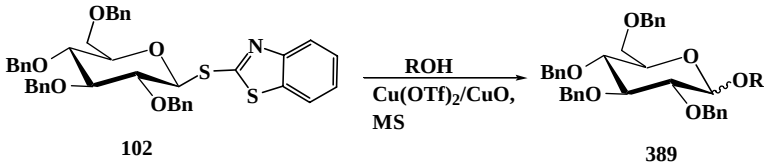
other hand, when an Ag_2CO_3/AgOTf promoter was used for the same reaction, the α-linked disaccharide **411** was obtained.[57] Glycosidation reactions of **108** and **109** with various acceptors in the presence of AgOTf or MeOTf are summarized in Table 6.

Cupric triflate activated the glycosidation of 2-benzothiazolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **102** with the acceptors in the presence of cupric oxide and 4 Å MS to give an α,β-mixture of glucosides **389**, with the α-glucoside as the major isomer[58] (Table 7).

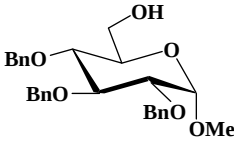
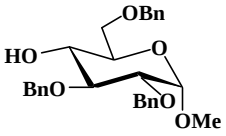
Pyrimidin-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-manno pyranoside **339a** and pyrimidin-2-yl 2,3,4-tri-*O*-benzyl- and 2-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyrano sides (**345a**,**345**) were coupled with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose using 2 mol equiv of AgOTf as activator to give only the respective 1,2-*trans* disaccharides **413** (R=**a**,**b**,**c**) in 93–95% yield.[116] Reducing the molar ratio of AgOTf in the coupling with **345a** lowered the yield (65%) of **411** (R=**c**), with the formation of benzyl 2-*O*-acetyl-3,4-di-*O*-benzyl-α-L-rahmnopyranoside,[116] which became the main product upon decreasing AgOTf to 0.4 equiv. The thioglycosides, pyrimidin-2-yl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside **160** and pyrimidin-2-yl 2,3,4-tri-*O*-benzyl-1-thio-β-D-xylo- and -β-D-arabino-pyranosides **161**,**162** were coupled with the same acceptor, in the presence of two equivalents of AgOTf, to give high yields of the 1→6 disaccharides **413**, where the 1,2-*cis* anomer was the major isomer; the α:β ratios were 1.6:1 for **413d**, 1.2:1 for **413i** and 1:2.3 for **413e**[13] (Scheme 56). The reaction was extended to the donors **339a**, and **340**, pyrimidin-2-yl 2,6-di-*O*-acetyl-3,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside **339b** with the acceptor **x** to give the α-linked disaccharides **414** (R=**a**,**f**,**g**).[116] The use of TMSOTf as a promoter gave similar results. Longer reaction times led to poorer selectivity, whereas a shorter reaction time did not change the selectivity, but decreased the yield.[13]

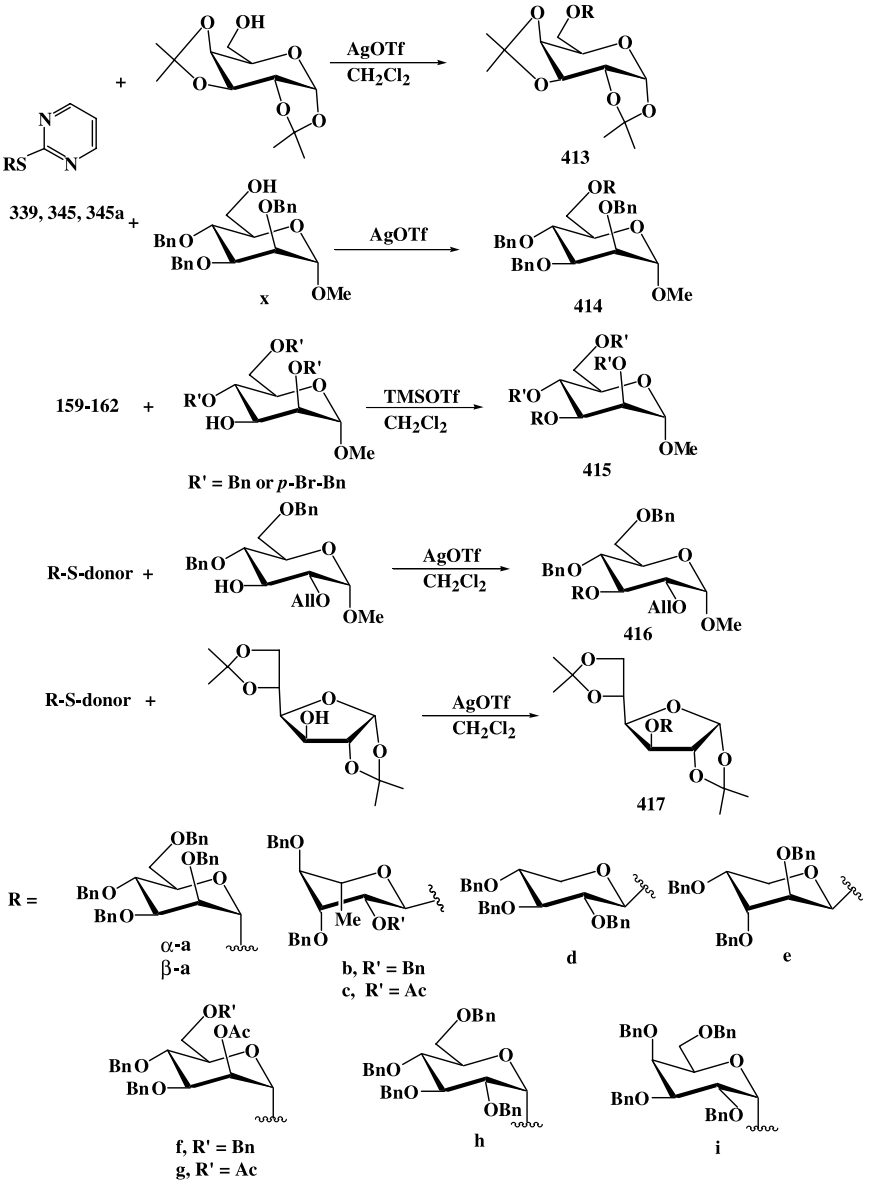
Reaction of fully benzylated pyrimidin-2-yl-1-thio-β-D-gluco- **159**, β-D-galacto- **160**, β-D-xylo- **161** and α-D-arabino-pyranosides **162** with methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside in CH_2Cl_2 at room temperature in the presence of TMSOTf as activator afforded the 1,2-*cis* disaccharides **415**, respectively, in good to excellent yields.[13] The use of AgOTf as a promoter also gave exclusive 1,2-*cis* selectivity, but in lower yield (no data).[13] If methyl 2,4,6-tri-*O*-*p*-bromobenzyl-α-D-mannopyranoside was, however, used as acceptor for coupling with **160** in the presence of TMSOTf, conversion took place into the respective α-linked disaccharide in 96% yield within 1 h.[13]

Table 7. Results of glycosylation with **102** in presence of $Cu(OTf)_2/CuO$ to give **389**

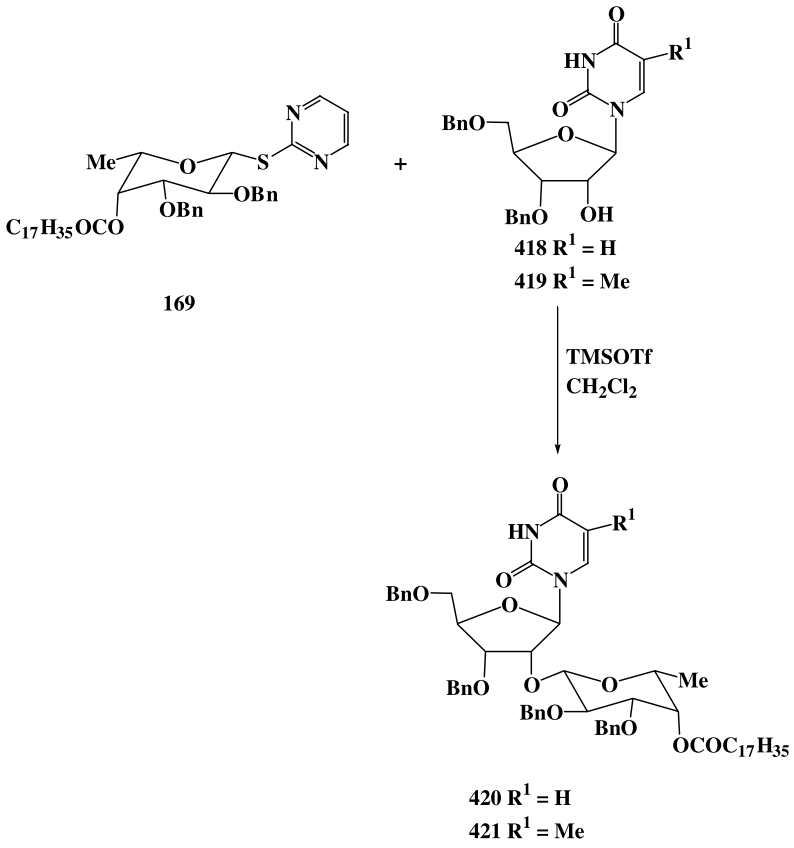


102 **389**

R	Yield (%)	α:β in **389**
MeOH	93	70:30
	92	80:12
	73	67:33
Cholesterol	79	83:17



Scheme 56.



Scheme 57.

Coupling of thiorhamnoside **345a** with methyl 2-*O*-allyl-4,6-di-*O*-benzyl-α-D-glucopyranoside afforded only the α-linked disaccharide **416** in high yield (87%). Under the same reaction conditions, however, the thioglycosides **339a** or **345a** were coupled with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, to give a nonseparable α,β anomeric mixture, 4:1 of **417** (R=**a**) and 1:1 of **417** (R=**b**) in 64–75% yield[116] (Scheme 56).

Pyrimidin-2-yl thiopyranoside **169** was coupled with the nucleoside acceptors **418** and **419** in the presence of TMSOTf (0.5 equiv) to give only the respective α-linked disaccharides **420** and **421** in 90–93% yield[72] (Scheme 57).

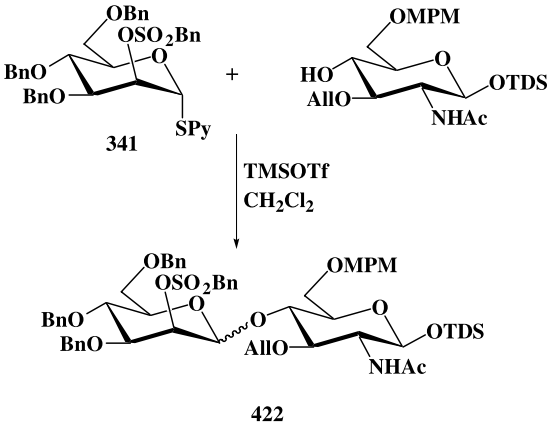
Stereoselective β-mannoside formation was achieved when 2-pyridyl 3,4,6-tri-*O*-benzyl-2-*O*-benzylsulfonyl-1-thio-α-D-mannopyranoside **341** was coupled with the acceptor, thexyldimethylsilyl-2-acetamido-3-*O*-allyl-6-*O*-(*p*-methoxybenzyl)-2-deoxy-β-D-glucopyranoside, in the presence of TMSOTf to give the respective disaccharide **422** in 82% yield with an α:β ratio of 1:7.4 (Scheme 58).[118]

Selective glycosylation of a hydroxyl group in the macrocyclic lactone **423** with D-desosaminide **424** in methylene chloride–toluene at room temperature in the presence of silver triflate afforded the β-glycoside **425**, the methanolysis of which gave **426** in 36% yield.[123] Further, glycosidation of **426** with L-cladinoside **427** in acetonitrile at room temperature in the presence of $Pd(ClO_4)_2$ gave, after methanolysis, the respective α-linked glycoside **428**[123] (Scheme 59).

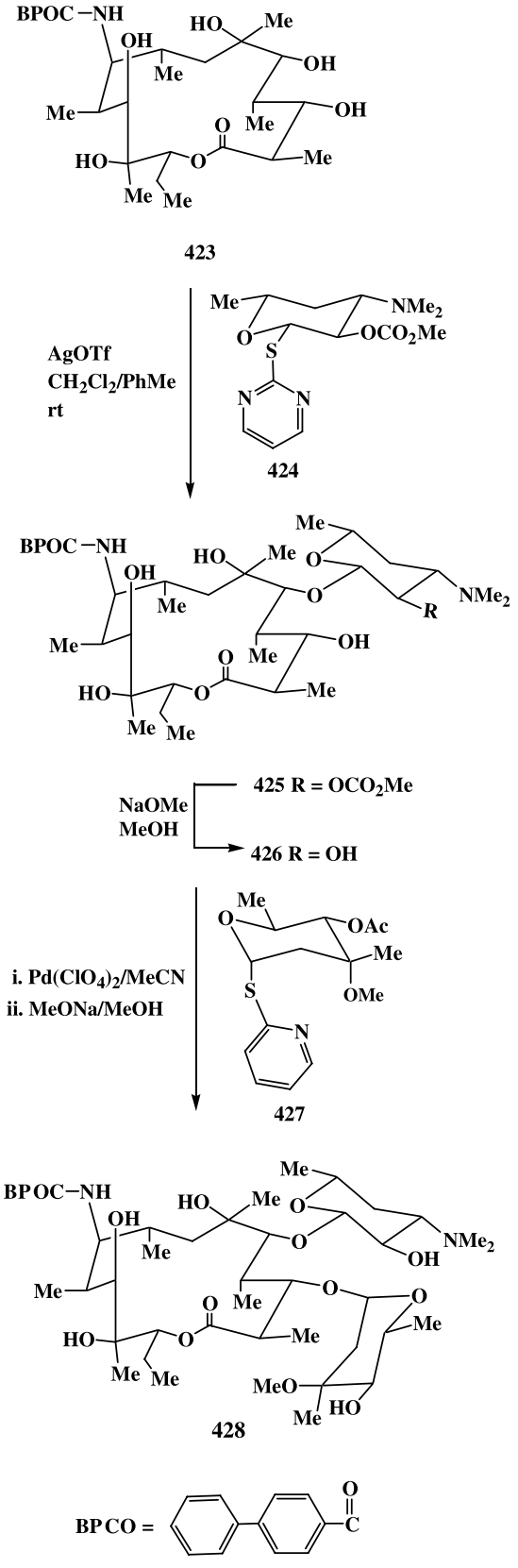
3.5. Sulphonic acids as promoters

Boiling of 2-pyridyl-1-thio-β-D-glucopyranoside **387** with methanol in the presence of one equivalent of methanesulfonic acid gave methyl α-D-glucopyranoside.[14] When isopropanol was the acceptor in acetonitrile containing *p*-toluenesulfonic acid (1.2 equiv) under reflux, however, it gave, after acetylation, a 3:2 α:β mixture of 2-propyl D-glucopyranoside.[14]

An NIS/TfOH-promoted glycosylation reaction of 2-benzoxazolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **110** with the acceptor, methyl 2,3,4-tri-



Scheme 58.



Scheme 59.

O-benzyl-α-D-glucopyranoside, afforded the β-disaccharide **404h** in 86% yield, within 30 min, which is a somewhat lower yield than those obtained from AgOTf or MeOTf (94–95%)[35] (Scheme 60).

4. Role of glycosylthio heterocycles in *C*-glycoside synthesis

The reaction of 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside **269** with trimethylsilyl enol ethers or electron-rich aromatics at room temperature in the presence of AgOTf afforded the respective *C*-glycosides **429** and **430**.[99] In this case an α-mode of attack was the general trend with moderately nucleophilic species.[99] The reaction presumably involved the rapid formation of an oxonium ion **A**, which could exist in CH_2Cl_2 as a solvent separated ion pair of α/β-triflates **B** and **C**, in which the β-triflate **C** would be the reactive species and, consequently, gave the α selectivity. With 1,3,5-trimethoxybenezene in CH_2Cl_2, however, the β-anomer only was obtained, which could be due to the high reactivity of the nucleophile that intercepts the oxonium ion **A** from the less hindered β face before the equilibrium between the triflates can be established, as was found to have occurred with the less nucleophilic species[99] (Scheme 61).

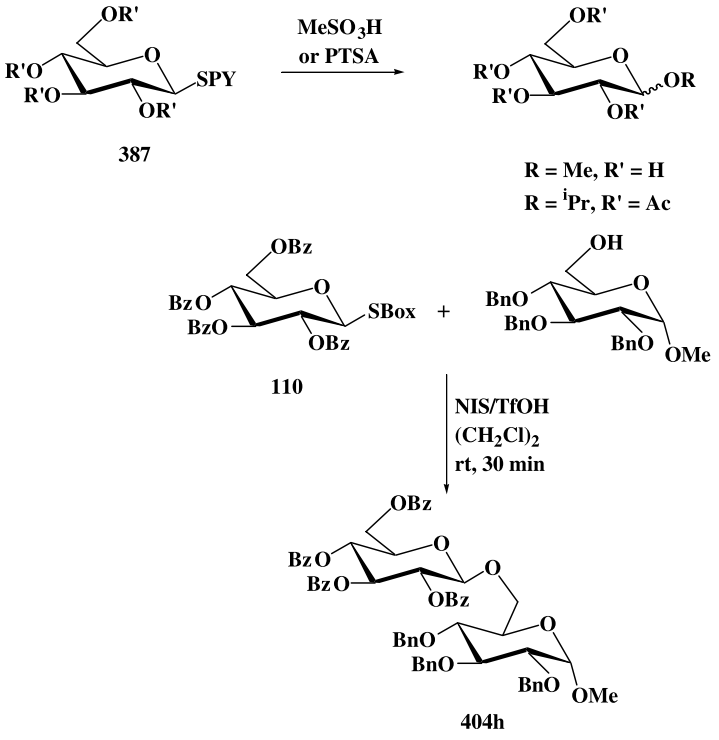
In more polar solvents such as diethyl ether, the α selectivity was observed exclusively.[99] Highly polar solvents such as acetonitrile or tetrahydrofuran were unsuccessful for C-glycosidation. Ribose substrates **259** and **261** exhibited high degrees of α/β stereocontrol,[99] to favor the formation of **431** and **432**. Glycosidation with **259** and **261** of 1,3,5-trimethoxybenzene, however, afforded the respective β-*C*-glycosides[99] (Table 8) (Scheme 62).

Treatment of the thiopyridyl derivative of L-arabino-pyranoside **273** with TBDMSOTf in the presence of triethylamine in ether at room temperature gave the silylated derivative **433**, which, upon treatment with AgOTf, underwent intramolecular cyclization to give **434**[100] (Scheme 63).

5. Role of glycosylthio heterocycles as acceptors

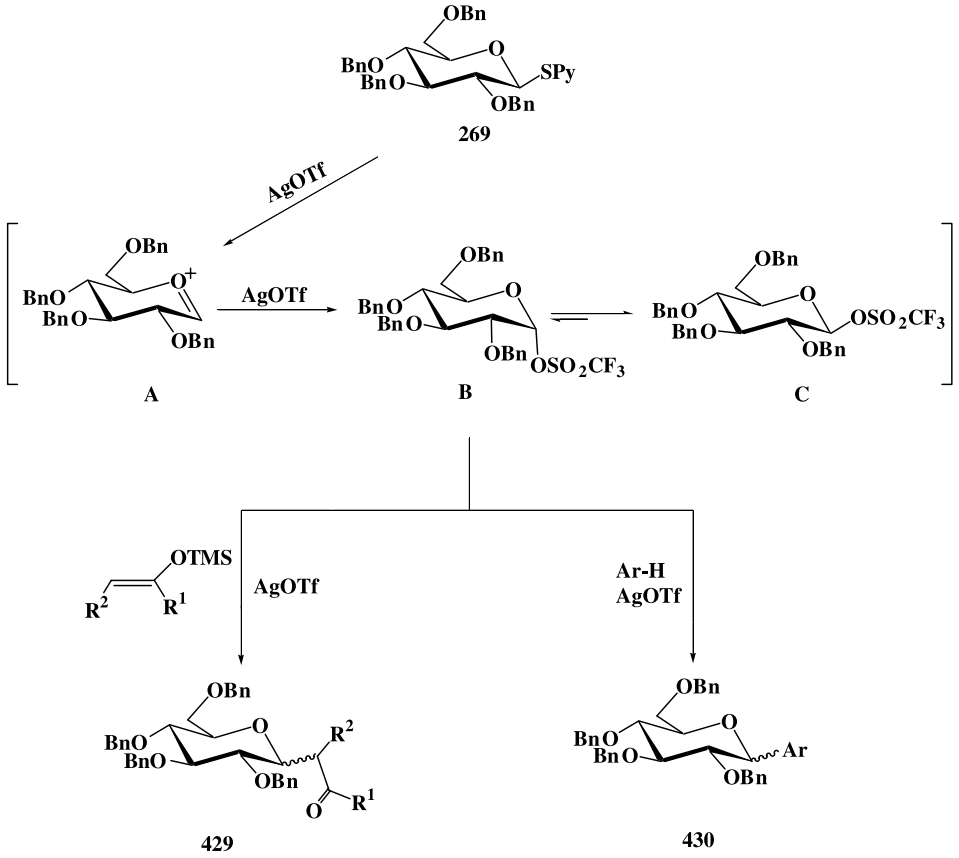
Heteroaryl thioglycosides with electron-withdrawing groups in the ring are very stable donors under most glycosylation conditions.[124] 5-Nitro-2-pyridyl β-D-thio-glucoside **435** was found to be an inert donor towards methanol and di-isopropylidene α-D-galactopyranose as glycosyl acceptors by using different promoters.[124] Coupling of **435** with several glycosyl donors **436** using a variety of promoters, however, took place smoothly to afford the disaccharides **437** in good yields with moderate to high stereoselectivity[124] (Scheme 64) (Table 9).

Glycosidation of *N*,*N*-diethyl *S*-(2,3,5-tri-*O*-benzyl-D-ribo-furanosyl) dithiocarbamate **436g** with the glycosyl acceptor **435** using NIS/TfOH as an activator in toluene afforded the 1→6 disaccharide **437g** with high α selectivity.[124,125] Under the same reaction conditions, D-xylo- **436f** and L-arabino-furanoside **436h** coupled with **435** to afford the disaccharides **437f** and **437h** in high yield, but in moderate 1,2-*cis* seteroselectivity.[124] The use of AgOTf and TMSOTf as catalysts was less successful. In the presence of $BF_3 \cdot Et_2O$, however, the coupling of **435** with **436g** took place within 48 h, with the formation of the respective α:β mixture of **437** in a ratio of 1:5[124,125] (Scheme 64).



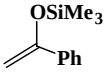
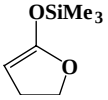
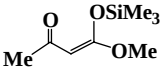
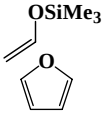
Scheme 60.

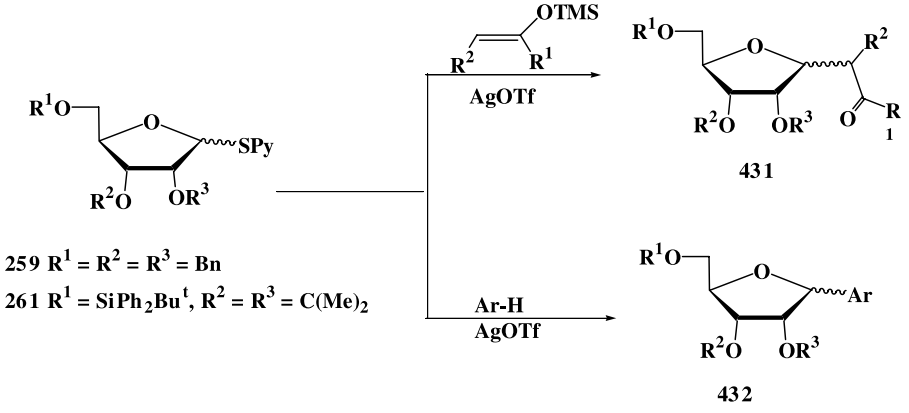
Thioglycosyl pyridines have been used for making more complex sequences of oligosaccharides by utilization of them as acceptors and donors, based on selecting the activation conditions and the more reactive thioglycosyl heterocycle to be the donor in the first sequence of the scheme protocol. Thus, the glycosyl acceptor, 2-pyridyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranoside, required for the glycosidation reaction, was synthesized from **15** by



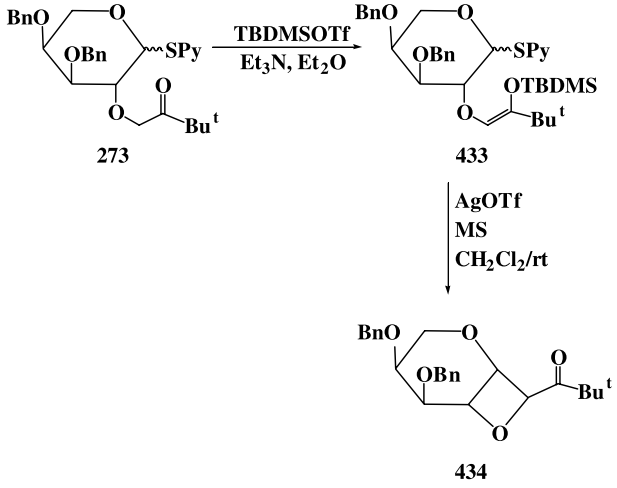
Scheme 61.

Table 8. Results of C-glycosidation of **259**, **261** and **269**

Nucleophile	Substrate	Solvent	Product α:β	Yield (%)
1,3,5-Trimethoxybenzene	**269**	CH_2Cl_2	β Only	63
1,3,5-Trimethoxybenzene	**259**	CH_2Cl_2	β	49
1,3,5-Trimethoxybenzene	**261**	CH_2Cl_2	β	61
1,3-Dimethoxybenzene	**261**	CH_2Cl_2	α	48
	**269**	CH_2Cl_2	α	81
	269	CH_2Cl_2	4:1	60
	**259**	CH_2Cl_2	α	70
	261	CH_2Cl_2	α	56
	**269**	CH_2Cl_2	α	43
	259	CH_2Cl_2	β	72
	**269**	CH_2Cl_2	α	35
	269	Furan, CH_2Cl_2	5:1	65



Scheme 62.

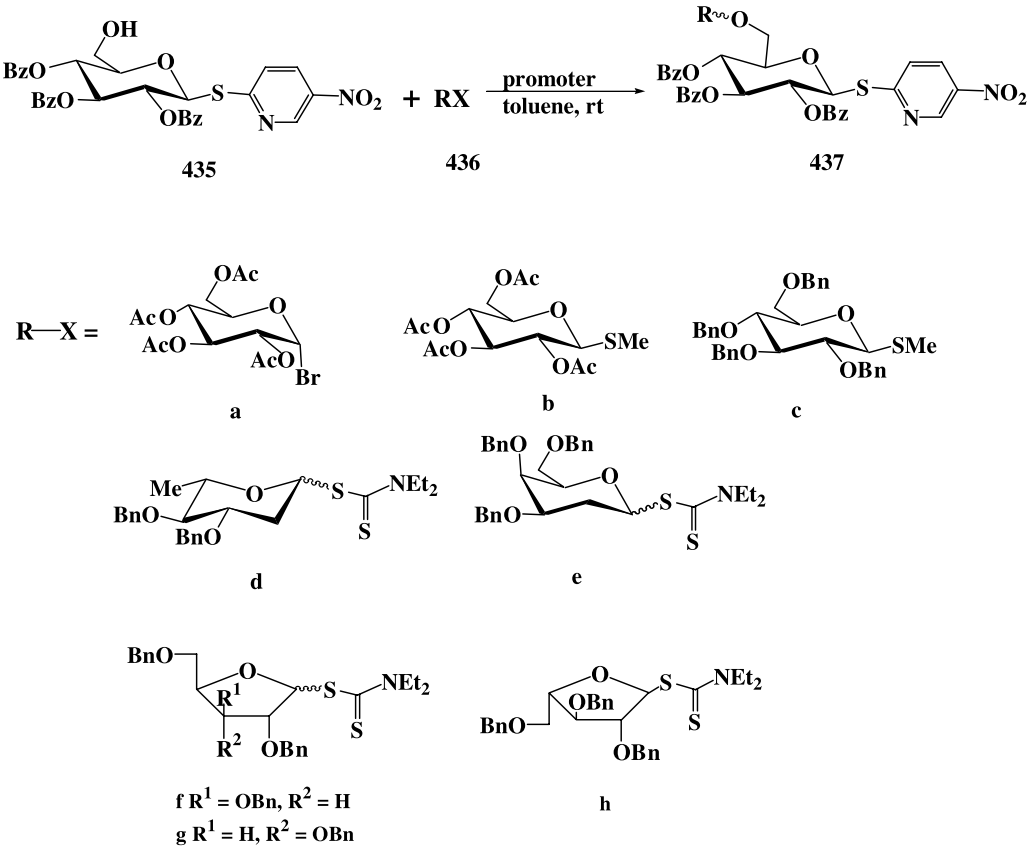


Scheme 63.

deacetylation to give **387** with subsequent selective 6-*O*-silylation to give **438**, that upon acetylation, gave **439** and desilylation gave **440**.[119] Coupling of **440** with **269** in CH_2Cl_2 in the presence of MeI/MS as a promoter afforded the α-disaccharide **441** in 66% yield. Replacement of the acetyl groups with benzyl groups gave **442**, which, upon coupling with 1,2:3,4-di-*O*-isopropylidine-D-galacto-pyranose, gave the α-1,6-linked trisaccharide **443** in 64% yield[119] (Scheme 64). Similarly, the glycosyl donor, 2-pyridyl-1-thio-β-maltoside **53**, was coupled with **440** to give the trisaccharide glycosyl donor **444**, which, on deacetylation and subsequent benzylation, gave **445** that, upon reaction with the acceptor **a**, gave the tetrasaccharide[119] **446** (Scheme 65).

6. Biological activity of glycosylthio heterocycles

The 5,6-dichlorobenzimidazol-2-yl β-D-thioribofuranoside derivative **28** was tested for its in vitro inhibitory effects on the replication of a number of DNA viruses, that is, human cytomegalovirus (CMV), herpes simplex virus types 1 and 2, vaccinia virus and RNA viruses (parainfluenza virus type

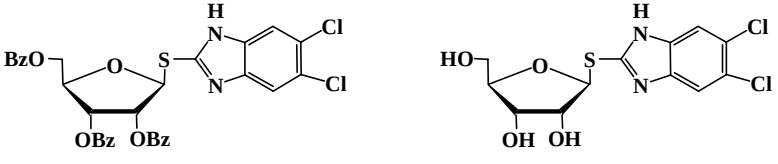


Scheme 64.

Table 9. Reaction of **435** as acceptor with different donors in Scheme 64

Donor	Reaction time	Promoter	α:β	Yield (%)
436a	24 h	Ag_2O	β Only	62
436b	24 h	NIS/TfOH	β Only	82
436c	1 h	NIS/TfOH	2:1	85
436d	5 min	AgOTf	4:1	67
436d	15 min	AgOTf	9:2	81
436d	15 min	TMSOTf	5:1	78
436d	1 h	$BF_3.Et_2O$	6:1	94
436d	25 min	NIS/TfOH	9:2	93
436d	50 min	IDCP	3:2	92
436e	25 min	AgOTf	15:1	71
436e	25 min	TMSOTf	15:1	95
436e	45 min	$BF_3.Et_2O$	16.5:1	92

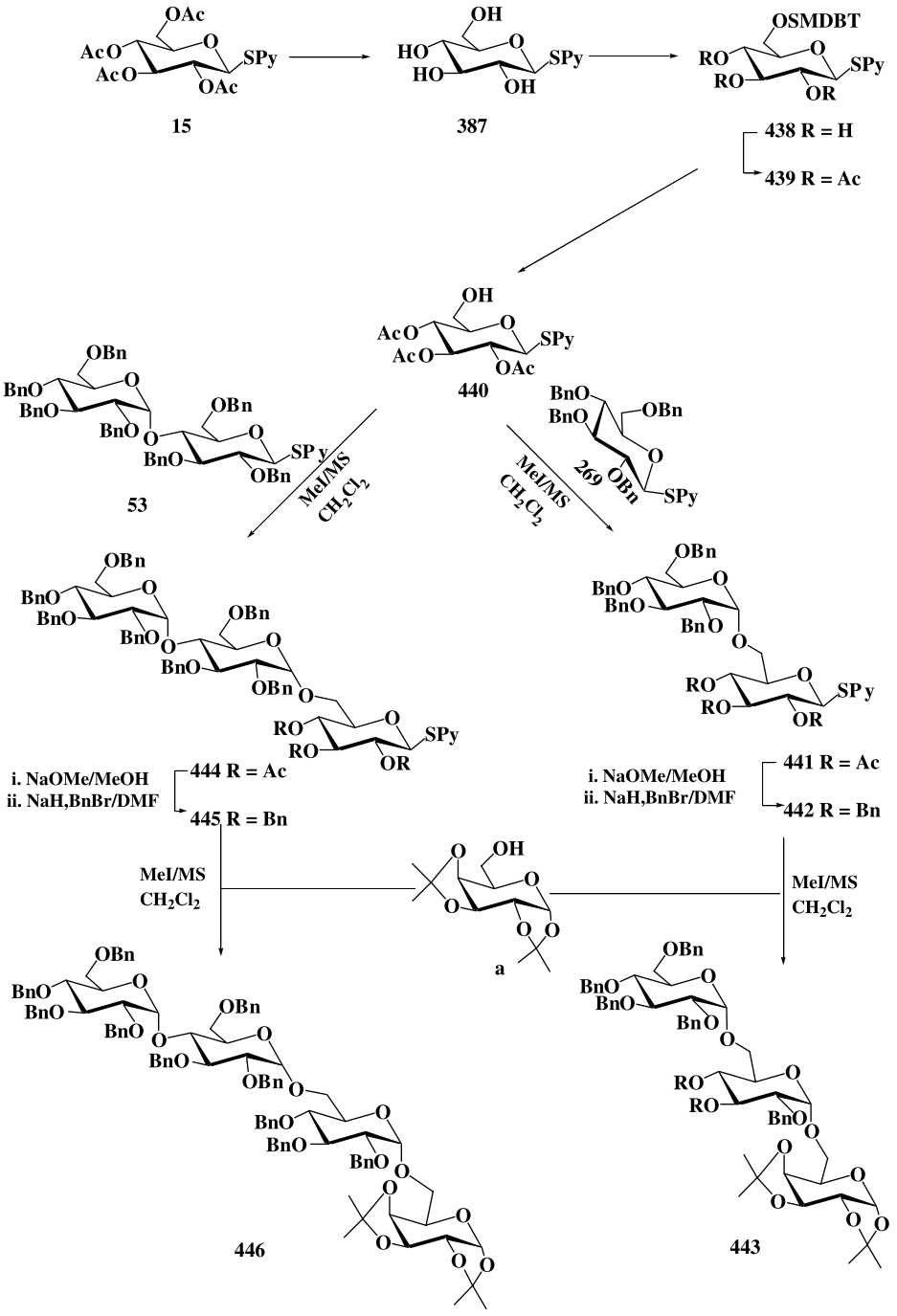
III, respiratory syncytial virus-1) in three cell systems (MRC-5, Vero and KB cells). Only the unprotected S-riboside **28a** showed an antiviral effect against CMV in MRC-5 cells without toxicity at 10^{-4} or 10^{-3} M with an ED_{50} value of 10^{-4} M.[34]



28 **28a**

The enzyme, β-glucuronidase, exists in human cancer tissues at a higher concentration than the normal level, which may be used in devising prodrugs. The activity of the β-glucuronidase was enhanced when the cell become more acidic. The cancer cells are already known to be more acidic than the normal cells and can specifically be increased by glucose.[126,127] Therefore, glucuronides of known anticancer compounds can selectively deliver these drugs to cancer tissues. Thus, ammonium 7*H*-purin-6-yl 1-thio-β-glucopyranosiduronate **447** and 7*H*-purin-6-yl 1-thio-β-glucopyranosiduronamide **448** were tested as substrates for the β-glucuronidase enzyme.[89] It was believed that the substrate behavior of **448** is not due to a nonspecific protein effect and that hydrolysis of **448** occurs at the enzyme active site.[128]

Glucopyranosiduronamide **448** has no effect on the growth of either the Chinese hamster lung fibroblast V79 line (a cell line not of tumor origin) or L1210 cells (a line of tumor origin).[89] In addition, **447** (10^{-5}–10^{-3} M) has no effect on the growth of the V79 line.[89] Compound **447**, however, at a concentration 10^{-4} M, showed 22% inhibition of the L1210 cells in 48 h, whereas, at lower concentrations (10^{-7}–10^{-5} M), no inhibition of cell growth was observed within 48 h.[89]

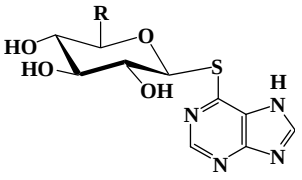


Scheme 65.

These results showed that **447** and **448** possess selectivity and that β-glucuronidase is most likely an obligate partner in the drug delivery.[89] Consequently, **448** is not cytotoxic, probably because it is too a poor substrate of glucuronidase to release an adequate amount of 6-mercaptopurine to inhibit L1210 cell growth.[89] On the other hand, **447** was virtually inactive towards the L1210 mouse screen employed by National Cancer Institute (NCI). The more lipophilic methyl ester **450** was, however, scarcely more active,[88] but not as active as 6-mercaptopurine.[88] No information is available concerning whether **450** penetrates cancer cells or is hydrolyzed in situ, either chemically or enzymatically, and it may be active in its own right.[88] Compound **447** was found to be of moderate selectivity for leukemic cells,[129] and both **447** and **450** appear to be less toxic than 6-mercaptopurine.[88]

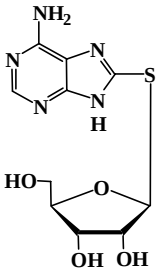
Purin-6-yl 6′-deoxy-1′-thio-β-D-glucopyranoside **450**, a substrate for almond β-glucosidase, was found to be a weak competitive inhibitor of bovine liver

β-D-glucuronidase ($K_i \sim 20$ mM). Purin-6-yl 1′-thio-β-D-glucopyranoside **449** was found to be active against sarcoma 180 and adenocarcinoma 755 and had relatively little toxicity, compared to 6-mercaptopurine.[88]

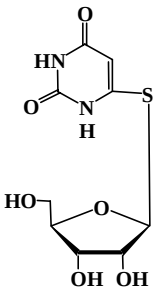


447 R = CO_2NH_4
448 R = $CONH_2$
449 R = CH_2OH
450 R = Me

6-Amino-8-(β-D-ribofuranosyl)thiopurine **451** and 6-(β-D-ribofuranosyl)thiouracil **452** were tested for the inhibition of cell growth of *Escherichia coli*, leukemia K1210 and Ehrlich ascites. The thioriboside **451** showed quite effective inhibition of 50% of *Escherichia coli* and *Ehrlich ascites* at concentrations of 5×10^{-6} and 3×10^{-4} M, respectively, whereas **452** was essentially inactive. In the tumor systems, **451** was moderately active, whereas **452** was inhibitory only at relatively high concentrations of $1\text{–}2\times10^{-3}$ M.[74]

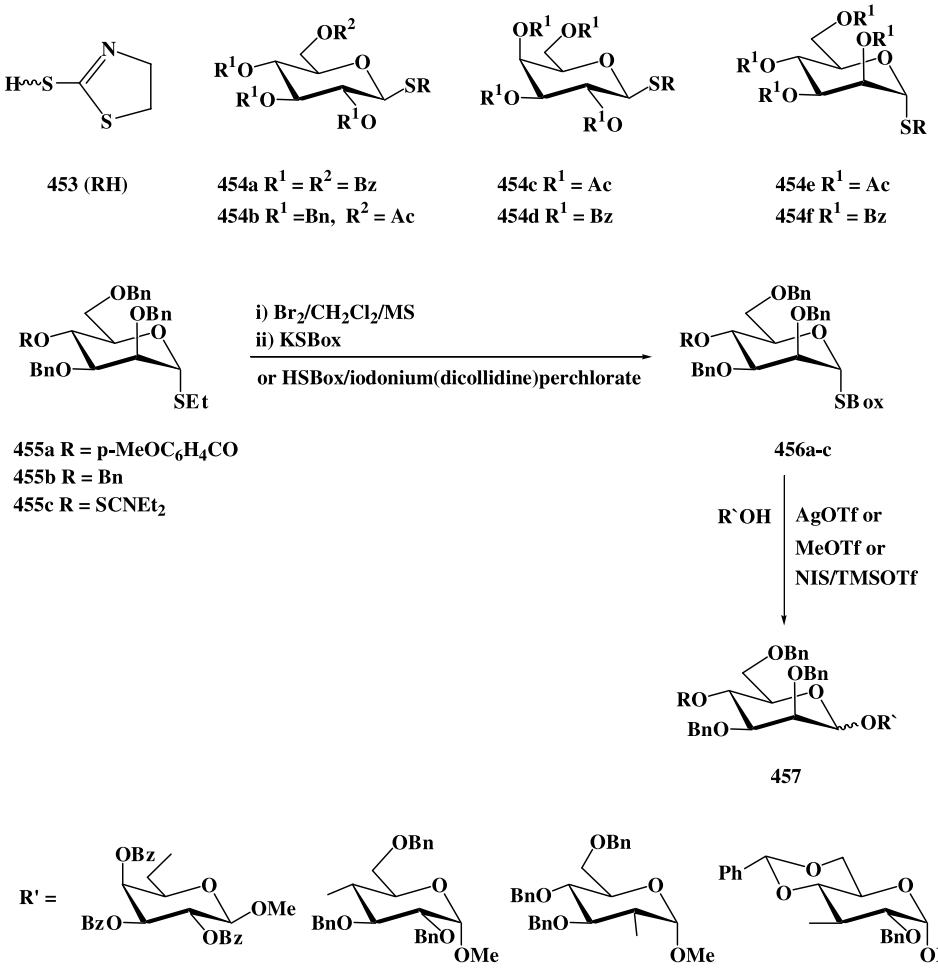


451



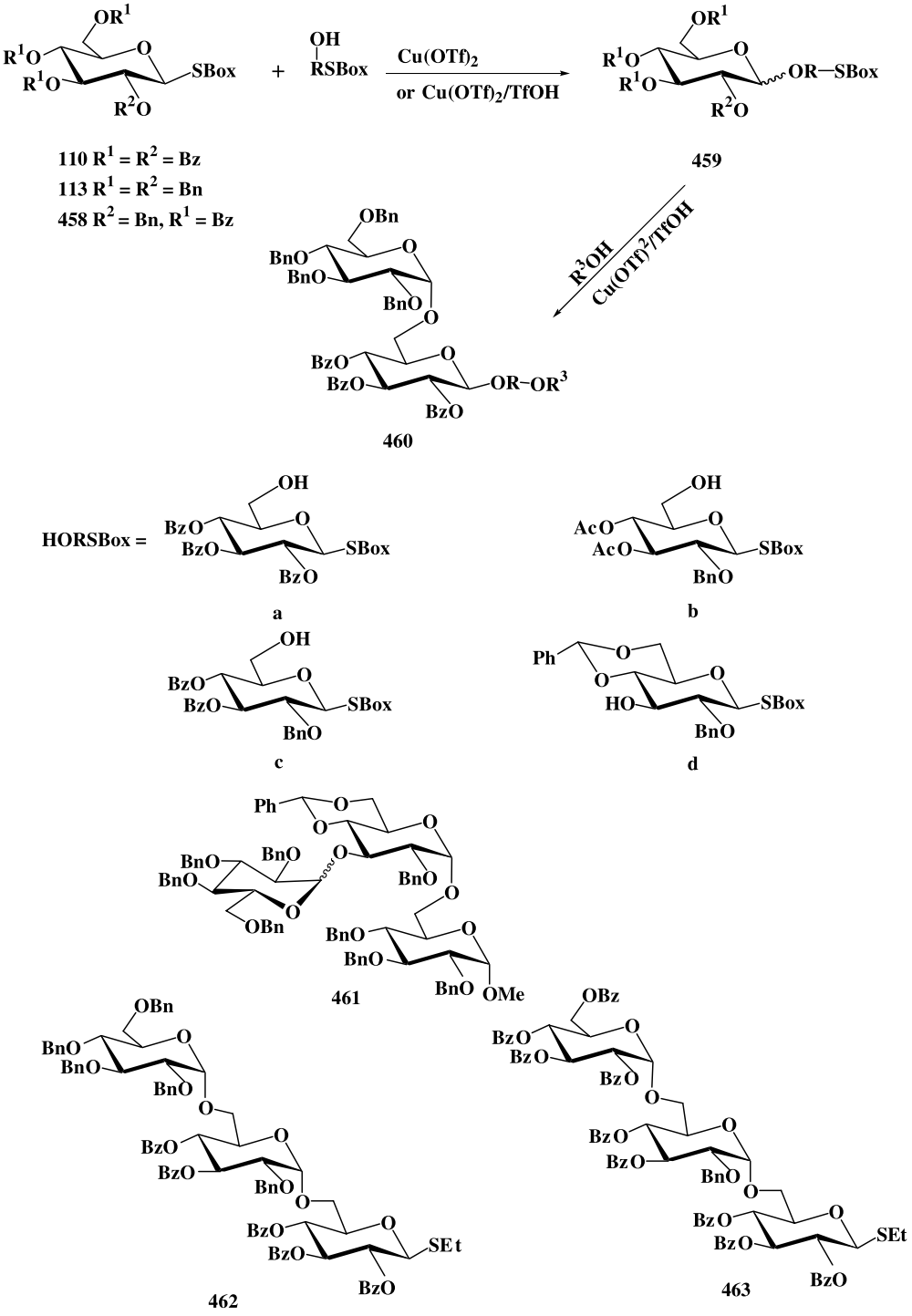
452

A low concentration of the thioglucoside **139** had no significant effect in vitro on the activity of α-glucosidase in liver homogenates of mice and the SBox **32** caused no detectable change in the activity of the enzyme.[130] The kinetics of inhibition of the lysosomal α-glucosidase fraction in vitro by compound **139** showed 23.2% competitive inhibition, with K_i 9×10^{-3} M, whereas **32** showed no detectable change in the enzyme activity.[130] Using *p*-nitrophenyl β-D-glucopyranoside as the substrate, compound **139** showed competitive inhibition of liver homogenate β-glucosidase in vitro.



Scheme 66.

The relative specific inhibition of β-glucosidase in vivo by compound **139** was found to be 60%.[130] The effect of compound **139** on blood sugar levels was studied to determine the relation between its inhibitory actions on the glucosidases and the antihyperglycemic behavior. Compound **139**, in low doses, did not cause a change in the blood sugar levels, whereas higher doses (0.74 mg/gm body weight) reduced the level to 56.6%, but a complete depression of the animal took place as a side effect.[130]



Scheme 67.

Acknowledgements

The partial support from AvH and BFG in Germany are highly appreciated. Thanks are due to N. Rezki and M.R. Aouad for their valuable help in preparing this manuscript.

Appendix A

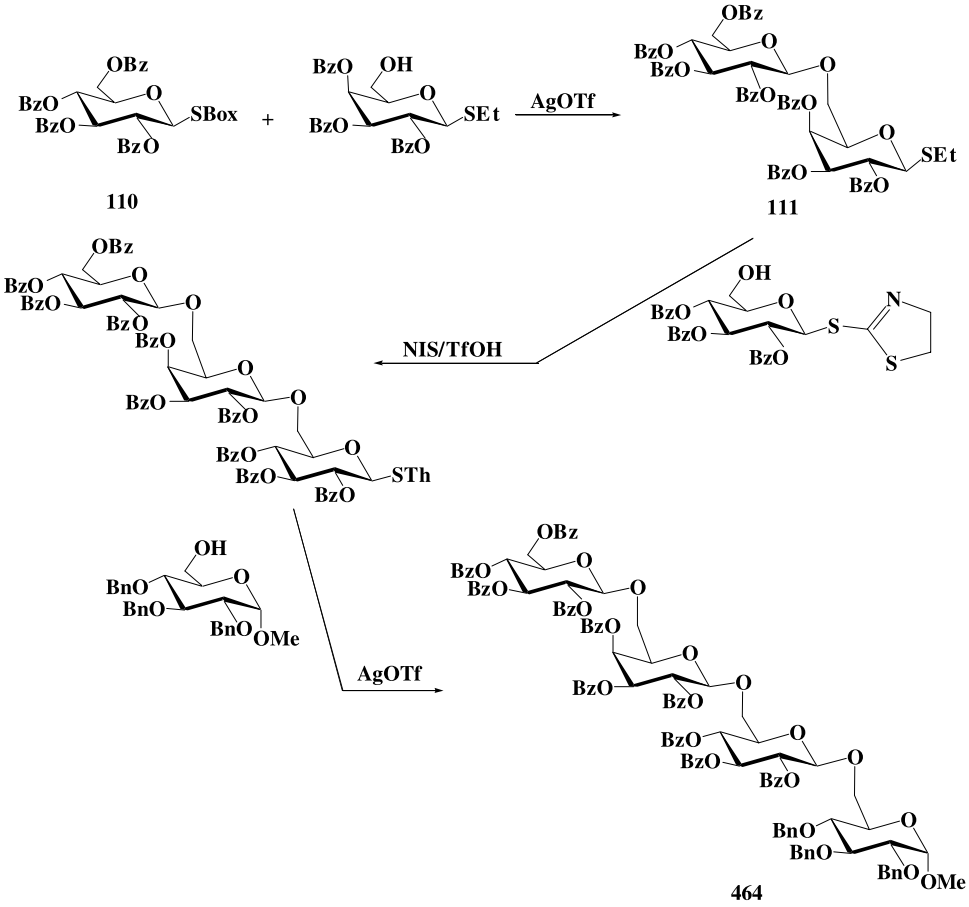
After this review was written, we found interesting and recent publications related to the topic which is worth being introduced under this appendix.

Thiothiazolin-2-yl thioglycosides **93** and **454** have been synthesized in complete stereoselectivity (1,2-*trans*) and in high yield from the reaction of per-*O*-acetylated D-glycopyranose and thiazoline-2-thiol **453** in the presence of $BF_3 \cdot Et_2O$ and 3 Å molecular sieves in methylene chloride.[131] Reaction of 3,4,6-tri-*O*-acetyl-1,2-anhydro-D-glucopyranose with **453** gave thiazolin-2-yl 3,4,6-tri-*O*-acetyl-1-thio-β-D-glucopyranoside by using $ZnCl_2$ as catalyst.[131] On the other hand, when **453** or its potassium or sodium salts were reacted with glycosyl halides in the presence of sodium hydride or crown ether, the 1,2-*trans* thioglycosides **94**, **454** in addition to the isomeric *N*-thiazolinylglycosides were obtained.[131]

Bromination of ethyl-1-thio-α-D-mannopyranosides **455a**,**b** with bromine followed by treatment with KSBox in presence of 18-crown-6 afforded 2-benzoxazolyl-1-thio-α-D-mannopyranosides **456a**,**b** in 58 and 79% yields, respectively. The 4-*O*-(*N*,*N*-diethylthiocarbamoyl)-derivative **456c** was obtained in 49% yield when **455c** was reacted with HSBox in CH_2Cl_2 followed by iodonium(dicollidine) perchlorate.[132] (Scheme 66)

Stereoselective β-mannosylation was improved by the use of electron-withdrawing substituent at C-4 and a bulky SBox leaving group at the anomeric center of the glycosyl donor. Thus, 2-benzoxazolyl 1-thio-α-D-mannopyranosides **456a**,**c** were coupled with the acceptor methyl 2,3,4-tri-*O*-benzoyl- β-D-galactopyranoside using AgOTf, MeOTf or NIS/TMSOTf to give the disaccharide **457** with α:β 1:3–5. The presence of 4-*O*-nonparticipating benzyl substituent as in **456b** resulted in a lower β-selectivity using AgOTf or MeOTf as promoters.[132] A slightly more β-selectivity was observed when a secondary glycosyl acceptors were coupled with **456a** rather than **456b**, although such selectivity was dependent on the position of the hydroxyl group (α:β 1:2.3–7.0) (Scheme 66).

Activation of fully benzylated 2-benzoxazolyl 1-thio-β-D-glucopyranoside **113** with $Cu(OTf)_2$ then coupling with 1,2,3,4-diisopropylidene galacose afforded the disaccharide **351c** in an α:β ratio 5.4:1 (89% yield).[133] On the other hand, no reaction has taken place when **108** or 2-benzoxazolyl 2-*O*-benzyl-3,4,6-tri-*O*-benzoyl-1-thio-β-D-glucopyranosides **458** were used as donors. This can be due to the electronically activated, armed benzyl groups in the



Scheme 68.

glycosyl donors. Chemoselective activation of armed **113** or moderately disarmed **110** glycosyl donors over the partially protected SBox glycoside acceptors (HORSBox) was achieved using $Cu(OTf)_2$ or $Cu(OTf)_2$/TfOH to give the disaccharides **459** together with the corresponding NBox disaccharides and the isomerized NBox glycosides.[133] (Scheme 67). Furthermore, reaction of the disaccharide **459** with R′OH gave the respective glycoside **460**.

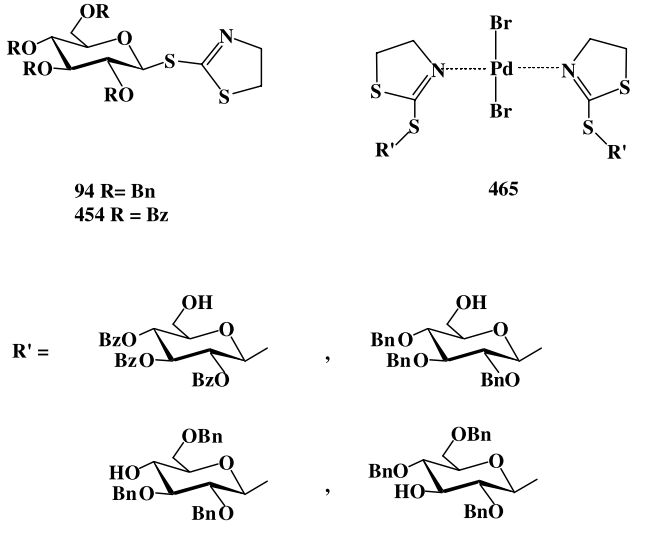
Coupling of fully benzoylated thiazolin-2-yl thioglycosides **454a**,**d**,**f** with various glycosyl acceptors using AgOTf, MeOTf, NIS/TfOH or $Cu(OTf)_2$ as promoters took place with complete stereoselectivity forming the 1,2-*trans* disaccharides in high yield (84–99%). On the other hand, 1,2-*cis* disaccharides were obtained when the thiazolinyl thioglycosides **94** or **454b** having 2-*O*-benzyl group were coupled with various acceptors using AgOTf as promoter. The α:β ratio of the disaccharide formed was dependent on the solvent used.[131]

Selective activation by using AgOTf of the thiazolinyl thioglycosides donors **454a**,**d** over partially protected ethyl 1-thio-β-D-glycopyranosides led to use the latter as acceptors.

Similarly, Silvertriflate activated the 2-benzoxazolyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside **110** over ethylthioglycosides to give β-disaccharides in high yields. The α-disaccharide were obtained when a non participating 2-*O*-benzylglycosyl donors were used.

On the other hand, when NIS/TfOH was used as a promoter, the ethyl or phenyl thioglycosides have been activated over the thiazolin-2-yl thioglycosides.[134] Thus allowed the synthesis disaccharides and tri-saccharides such as **461–463**[131,133] (Scheme 68). Also, the tetra-saccharide **464** was synthesized with complete 1,2-*trans* stereoselectivity[134] following the activation sequence as shown in Scheme 68.

Partially protected thiazolinyl thioglucoside acceptors can be deactivated by forming stable palladium II complexes by their reaction with $PdBr_2$ in 1,2-dichloroethane in the presence of 3 Å molecular sieve to give **465**. The coupling of which with thiazolinyl glycosyl donors such **94** and **454** using MeOTf, Cu(OTf) or NIS/TfOH gave the corresponding disaccharide (Scheme 69). Thus, this strategy provides a novel approach for oligosaccharides synthesis.[135]



Scheme 69.

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A facile two-step chemoenzymatic access to natural germination inhibitor (+)-erigeronic acid A☆

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Abstract—A facile two-step synthesis of natural germination inhibitor 5-butyl-3-oxo-2,3-dihydrofuran-2-yl-acetic acid [(+)-erigeronic acid A, **1**] has been described via highly regioselective ring opening of (*R*)-acetoxysuccinic anhydride with the primary enolate of butyl methyl ketone, followed by an enzymatic hydrolysis and an in situ dehydrative cyclization pathway with 77% overall yield. On the basis of the present chemoenzymatic approach, (*R*)-configuration has been assigned to the C-2 chiral centre of the natural erigeronic acid.

1. Introduction

Plants are known to produce secondary metabolites, which affect the germination and growth of other plants and allelopathy is the term used to describe such interactions.[1] 5-Butyl-3-oxo-2,3-dihydrofuran-2-yl-acetic acid [erigeronic acid A, **1** (Fig. 1)] was isolated by Kwon et al.[2] from the flowers of *Erigeron annuus* and it possesses strong lettuce seed germination inhibitory activity [IC_{50} (mM) 2.13]. The structure of acid **1** was unambiguously deduced by analysis of 2D NMR spectroscopic data (COSY, HMQC and HMBC) but the configuration at the C-2 centre was not determined.[2] The structure of compound **1** represents a unique natural alkyl furanone possessing carboxylic acid and *n*-butyl substituents and it can be a agriculturally useful product. During the past several years, we have been using cyclic anhydrides as potential precursors for the synthesis of structurally interesting bioactive natural and unnatural products[3] and we could reason and foresee (*S*)/(*R*)-acetoxysuccinic anhydride as a suitable building block for the synthesis and stereochemical assignment of acid **1**. Acetoxysuccinic anhydride is known to react regioselectively at the hindered, more electron deficient carbonyl with oxygen and nitrogen nucleophiles[3f,4] and the stable carbanion from ethyl acetoacetate.[5] Now we herein report a highly regioselective ring opening of (*S*)- and (*R*)-acetoxysuccinic anhydrides with the kinetic enolate from alkyl methyl ketones, to design natural/unnatural **1** and its congeners (Schemes 1 and 2).

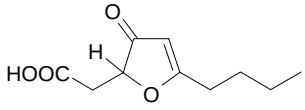

Figure 1. 5-Butyl-3-oxo-2,3-dihydrofuran-2-yl-acetic acid (erigeronic acid A, **1**).

2. Results and discussion

(*S*)/(*R*)-Malic acids on treatment with acetyl chloride furnished the corresponding (*S*)/(*R*)-acetoxysuccinic anhydrides (**2**) in 98% yield.[6] As desired, the (*S*)-acetoxysuccinic anhydride underwent a highly regioselective ring opening at the more reactive hindered carbonyl at −78 °C with the kinetic enolate generated from butyl methyl ketone using LDA as a base to exclusively provide the intermediate diketo compound in 93% yield, which was transformed in situ to a mixture of enantiomerically pure enols **3** and **4** in the ratio 80:20 (by ^{1}H NMR) (Scheme 1). The structural assignment of **3** and **4** was done on the basis of the presence of vinylic and enolic protons in the ^{1}H NMR spectrum. As expected the allylic methine proton in **3** was more deshielded than the corresponding methine proton in **4**, whereas the allylic methylene protons in **4** were more deshielded in comparison with the corresponding methylene protons in **3**. We feel that, due to the electron withdrawing influence of the acetoxy group, the enolization of an adjacent carbonyl occurs to a larger extent, forming **3** as

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Keywords: Natural germination inhibitor; (+)-Erigeronic acid; (*R*)-Acetoxysuccinic anhydride; Primary enolate of butyl methyl ketone; Synthesis.
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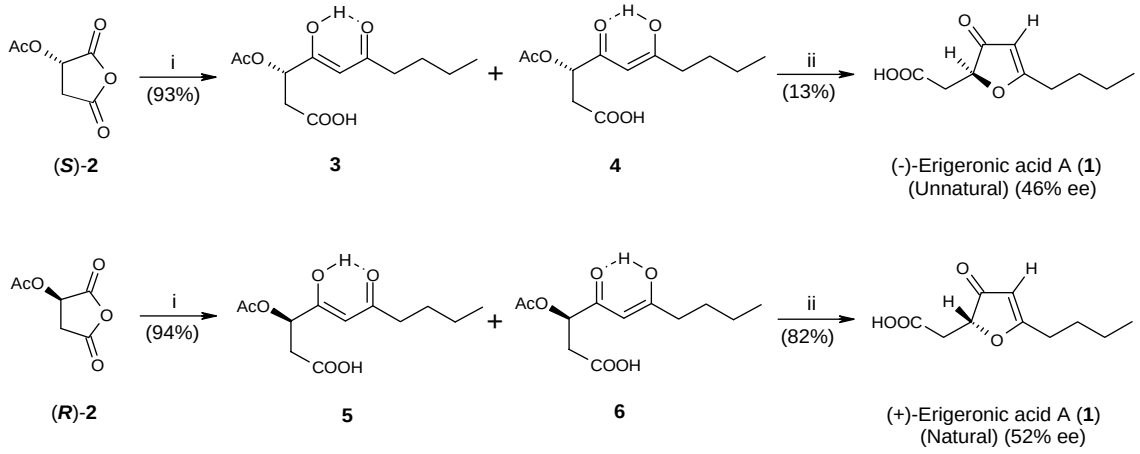
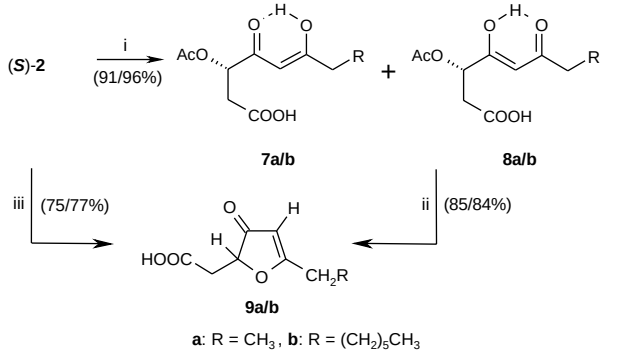


Scheme 1. Reagents, conditions and yields: (i) (a) $CH_3COCH_2(CH_2)_2CH_3$, LDA, THF, −78 °C, 90 min, (b) H^+/HCl (**3**:**4**/**5**:**6**=8:2); (ii) Amano PS, petroleum ether–benzene (2/1), rt, 40 h, phosphate buffer pH 7.0.



Scheme 2. Reagents, conditions and yields: (i) (a) $CH_3COCH_2CH_3$/$CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, −78 °C, 90 min, (b) H^+/HCl (a: 91%, b: 96%; **7a/b**:**8a/b**=8:2); (ii) (a) K_2CO_3, MeOH, 6 h, (b) H^+/HCl (a: 85%, b: 84%); (iii) (a) $CH_3COCH_2CH_3$/$CH_3COCH_2(CH_2)_5CH_3$, LDA, THF, −78 °C, 90 min, (b) 10% aq LiOH, rt, 8 h, (c) H^+/HCl (a: 75%, b: 77%).

a major isomer. The potassium carbonate catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture directly furnished the desired erigeronic acid in 89% yield via the intramolecular dehydrative cyclization pathway, but in a racemic form. The triethylamine/(−)-quinine catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture also directly furnished the erigeronic acid in 62–65% yield but with only 10–15% ee (by rotation). The acid catalyzed alcoholysis of the acetoxy group in **3** plus **4** mixture in methanol directly furnished the methyl ester of desired natural product in 95% yield, following the same pathway but again in racemic form. Under both acidic and basic conditions, we could isolate the erigeronic acid/ester in racemic form only and hence we planned for an enzymatic hydrolysis of **3** plus **4** mixture under neutral conditions at pH 7. The Amano PS catalyzed hydrolysis of **3** plus **4** mixture was very slow and gave the unnatural (−)-erigeronic acid only in 13% yield (46% ee, from the comparison with reported rotation value of the natural product). With the hope that the enzyme Amano PS will better recognize opposite isomer, we similarly obtained the mixture of **5** plus **6** from the corresponding (*R*)-acetoxysuccinic anhydride with 94% yield. The Amano PS catalyzed hydrolysis of **5** plus **6** mixture directly furnished the desired natural (+)-erigeronic acid A in 82% yield (52% ee, from the comparison with reported rotation value of the natural product). The analytical and spectral data obtained for (+)-erigeronic acid A was in agreement with the reported data[2] (Table 1) and thus we could assign the (*R*)-configuration to C-2 chiral centre in the natural acid using the present chiral pool strategy and chemoenzymetic pathway. During these studies we noticed that the (+)-erigeronic acid A in its neat form at room temperature undergoes a continuous racemization process and becomes completely racemic in 96 h time. The present racemization of (+)-**1** could be attributed to the high acidity of the C-2 proton and the higher propensity for keto-enol tautomerism. We feel that alike the preparation of enantiomerically pure α-hydroxycyclopentanone,[7] herein too, after the enzymatic hydrolysis of **5** plus **6** mixture, the formed product (+)-**1** undergoes a partial racemization process during the course of reaction and isolation procedures and hence, we could get only the 52% ee for (+)-**1**.

The present approach to 5-alkyl-3-oxo-dihydrofuranyl-2-acetic acids is general in nature and starting from **2** and ethyl methyl ketone/heptyl methyl ketone, we could synthesize **9a/b** in very good yields both in one pot and a stepwise fashion, with or without isolation of the intermediates **7a/b**+**8a/b** (Scheme 2). In the one pot synthesis, we quenched the anhydride **2** and ketone condensation reactions with 10% aqueous lithium hydroxide and then acidified the reaction mixture with 2 M hydrochloric acid to obtain **9a/b** in 75–77% yield.

3. Conclusions

In summary, starting from (*R*)-acetoxysuccinic anhydride, an elegant first synthesis of natural germination inhibitor (+)-erigeronic acid has been demonstrated using chiral pool strategy and an enzymatic hydrolysis pathway, which helped us to assign (*R*)-configuration to the C-2 chiral centre in acid (+)-**1**. In the present synthesis of (+)-**1**, the highly regioselective ring opening of anhydride (+)-**2** with the primary enolate of butyl methyl ketone and an enzymatic hydrolysis of **5** plus **6** mixture and subsequent in situ dehydrative cyclization to form (+)-**1** are noteworthy.

Table 1. ^{1}H and ^{13}C NMR data of natural and synthetic erigeronic acid (**1**)

Position[2]	^{1}H NMR data of erigeronic acid (**1**)		^{13}C NMR data of erigeronic acid (**1**)	
	Natural (Ref. 2)[a]	Synthetic[b]	Natural (Ref. 2)[c]	Synthetic[d]
1	2.90 (dd, J=16.9, 3.2 Hz, 1H) and 2.61 (dd, J=16.9, 8.3 Hz, 1H)	2.91 (d, J=18 Hz, 1H) and 2.61 (d, J=18 Hz, 1H)	36.9	36.4
2	4.83 (m, 1H)	4.83 (m, 1H)	82.4	83.3
3	—	—	206.4	206.4
4	5.54 (s, 1H)	5.54 (s, 1H)	102.7	104.1
5	—	—	195.8	197.3
6	2.56 (t, J=8.3 Hz, 2H)	2.57 (t, J=8 Hz, 2H)	31.3	31.4
7	1.65 (quintet, J=7.4 Hz, 2H)	1.65 (quintet, J=8 Hz, 2H)	29.2	29.3
8	1.42 (sextet, J=7.4 Hz, 2H)	1.41 (sextet, J=8 Hz, 2H)	23.2	23.3
9	0.95 (t, J=7.4 Hz, 3H)	0.95 (t, J=8 Hz, 3H)	14.0	14.1
10	—	—	171.6	172.8

[a] CD_3OD, 500 MHz.
[b] CD_3OD, 200 MHz.
[c] CD_3OD, 125 MHz.
[d] CD_3OD, 50 MHz.

The present approach is general in nature and can be used to design the analogs of **1**.

4. Experimental

4.1. General

Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Commercially available (*S*)-malic acid (97% ee), (*R*)-malic acid (98% ee), ethyl methyl ketone, butyl methyl ketone, heptyl methyl ketone, acetyl chloride and *n*-butyllithium were used. Amano PS-1360 U from Amano Pharmaceuticals, Japan was used. The activity of the lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder.[8]

4.1.1. (*R*)-3-Acetoxy-4-hydroxy-6-oxo-dec-4-enoic acid (5) plus (*R*)-3-acetoxy-6-hydroxy-4-oxo-dec-5-enoic acid (6). To a stirred solution of butyl methyl ketone (253 mg, 2.53 mmol) in THF (8 mL) at −78 °C was added freshly prepared LDA (271 mg, 2.53 mmol) in THF (5 mL) in a drop wise fashion under argon atmosphere. The reaction mixture was stirred at −78 °C temperature for 30 min and the above reaction mixture was added to a stirred solution of the anhydride (*R*)-**2** (400 mg, 2.53 mmol) in THF (10 mL) at −78 °C under argon atmosphere in a drop wise fashion. Further stirring was continued for 90 min at the same temperature. The reaction was then quenched with water and acidified with 2 M HCl. The reaction mixture was then immediately extracted with ethyl acetate (30 mL×4) and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate–petroleum ether (2/8) as an eluent gave **5** plus **6** as a thick oil.

Compound **5**+**6** (8:2): 614 mg (94% yield); $[\alpha]_D^{20}$ +40 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J=8 Hz, 0.6H), 0.91 (t, J=8 Hz, 2.4H), 1.15–1.45 (m, 2H), 1.45–1.70 (m, 2H), 2.13 (s, 0.6H), 2.15 (s, 2.4H), 2.30 (t, J=8 Hz, 1.6H), 2.51 (t, J=8 Hz, 0.4H), 2.75–3.00 (m, 2H), 5.25–5.40 (m, 0.2H), 5.53 (dd, J=8, 6 Hz, 0.8H), 5.63 (s, 1H), 9.00 (br s, 1H), 15.02 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) (major enol isomer **5**) δ 13.7, 20.7, 22.2, 27.8, 36.2, 37.2, 71.1, 96.1, 169.8, 174.9, 191.7, 192.8; MS (*m*/*e*) 297, 281, 276, 259, 199, 144; IR ($CHCl_3$) ν_{max} 3207, 2700–2500, 1747, 1733, 1719, 1603 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.73; H, 6.99.

The compounds **3**+**4**, **7a**+**8a** and **7b**+**8b** were similarly prepared using the above procedure.

4.1.2. (*S*)-3-Acetoxy-4-hydroxy-6-oxo-dec-4-enoic acid (3) plus (*S*)-3-acetoxy-6-hydroxy-4-oxo-dec-5-enoic acid (4). Starting from (*S*)-**2** (400 mg, 2.53 mmol), the title compounds mixture was obtained as a thick oil.

Compound **3**+**4** (8:2): 607 mg (93% yield); $[\alpha]_D^{20}$ −41 (*c* 1.4, CH_3OH); IR and ^{1}H NMR spectral data was identical with **5**+**6**.

4.1.3. (*S*)-3-Acetoxy-6-hydroxy-4-oxo-oct-5-enoic acid (7a) plus (*S*)-3-acetoxy-4-hydroxy-6-oxo-oct-4-enoic acid (8a). Starting from (*S*)-**2** (400 mg, 2.53 mmol) and ethyl methyl ketone (183 mg, 2.53 mmol) the title compounds mixture was obtained as a thick oil.

Compound **7a**+**8a** (8:2): 530 mg (91% yield); $[\alpha]_D^{20}$ −42 (*c* 1.7, CH_3OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (t, J=8 Hz, 0.6H), 1.15 (t, J=8 Hz, 2.4H), 2.14 (s, 0.6H), 2.15 (s, 2.4H), 2.36 (q, J=8 Hz, 1.6H), 2.55 (q, J=8 Hz, 0.4H), 2.75–3.02 (m, 2H), 5.25–5.40 (m, 0.2H), 5.54 (dd, J=8, 6 Hz, 0.8H), 5.64 (s, 1H), 7.80 (br s, 1H), 15.04 (br s, 1H); MS (*m*/*e*) 269, 253, 248, 231, 193, 171, 153; IR (neat) ν_{max} 3225, 2700–2500, 1744, 1735, 1720, 1605 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.31; H, 6.22.

4.1.4. (*S*)-3-Acetoxy-6-hydroxy-4-oxo-tridec-5-enoic acid (7b) plus (*S*)-3-acetoxy-4-hydroxy-6-oxo-tridec-4-enoic acid (8b). Starting from (*S*)-**2** (400 mg, 2.53 mmol) and heptyl methyl ketone (360 mg, 2.53 mmol) the title compounds mixture was obtained as a thick oil.

Compound **7b**+**8b** (8:2): 729 mg (96% yield); $[\alpha]_D^{20}$ −35 (*c* 1.4, CH_3OH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J= 6 Hz, 3H), 1.28 (br s, 8H), 1.50–1.70 (m, 2H), 2.14 (s, 0.6H), 2.16 (s, 2.4H), 2.31 (t, J=6 Hz, 1.6H), 2.51 (t, J=6 Hz, 0.4H), 2.75–3.05 (m, 2H), 5.30–5.45 (m, 0.2H), 5.54 (dd, J= 8, 4 Hz, 0.8H), 5.63 (s, 1H), 9.00 (br s, 1H), 15.03 (br s, 1H); MS (*m*/*e*) 339, 323, 318, 301, 255, 241; IR (neat) ν_{max} 3220, 2700–2500, 1751, 1730, 1720, 1597 cm^{-1}. Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 60.11; H, 7.86.

4.1.5. (±)-Erigeronic acid A [(±)-1]. To a stirred solution of enols **5** and **6** (60 mg, 0.23 mmol) in methanol (3 mL) was added K_2CO_3 (42 mg, 0.30 mmol) and the reaction mixture was stirred at room temperature for 4 h. Methanol was removed in vacuo at room temperature and water (10 mL) was added to the reaction mixture, then acidified to pH 2 using 2 N HCl and extracted with ethyl acetate (15 mL×4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate–petroleum ether (2/8) as an eluent gave (±)-**1** as a thick oil.

Compound (±)-**1**: 41 mg (89% yield); ^1H NMR (CD_3OD, 200 MHz) δ 0.95 (t, J=8 Hz, 3H), 1.41 (sextet, J=8 Hz, 2H), 1.65 (quintet, J=8 Hz, 2H), 2.57 (t, J=8 Hz, 2H), 2.61 (d, J=18 Hz, 1H), 2.91 (d, J=18 Hz, 1H), 4.83 (m, 1H), 5.54 (s, 1H); ^{13}C NMR (CD_3OD, 50 MHz) δ 14.1, 23.3, 29.3, 31.4, 36.4, 83.3, 104.1, 172.8, 197.3, 206.4; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.94 (t, J=8 Hz, 3H), 1.40 (sextet, J=8 Hz, 2H), 1.65 (quintet, J=8 Hz, 2H), 2.52 (t, J=8 Hz, 2H), 2.65 (dd, J=17, 8 Hz, 1H), 3.04 (dd, J=17, 4 Hz, 1H), 4.84 (dd, J=9, 4 Hz, 1H), 5.51 (s, 1H), 7.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 22.2, 28.0, 30.5, 35.7, 81.5, 103.2, 174.5, 195.3, 203.6; IR (neat) ν_{max} 2700–2500, 1732, 1713, 1585 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.60; H, 7.19.

The compounds **9a** and **9b** were similarly prepared using the above procedure.

4.1.6. (5-Ethyl-3-oxo-2,3-dihydro-furan-2-yl)-acetic acid (9a). Starting from acids **7a** and **8a** (60 mg, 0.26 mmol), and K_2CO_3 (42 mg, 0.30 mmol) the title compound was obtained as a thick oil.

Compound **9a**: 38 mg (85% yield); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J=8 Hz, 3H), 2.55 (q, J=6 Hz, 2H), 2.65 (dd, J=18, 8 Hz, 1H), 3.04 (dd, J=18, 4 Hz, 1H), 4.85 (dd, J=10, 4 Hz, 1H), 5.53 (s, 1H), 8.77 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.1, 24.2, 35.7, 81.5, 102.6, 174.6, 196.2, 203.5; IR (neat) ν_{max} 2700–2500, 1722, 1684, 1585 cm^{-1}. Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.33; H, 6.06.

4.1.7. (5-Heptyl-3-oxo-2,3-dihydro-furan-2-yl)-acetic acid (9b). Starting from acids **7b** and **8b** (60 mg, 0.20 mmol), and K_2CO_3 (42 mg, 0.30 mmol) the title compound was obtained as a thick oil.

Compound **9b**: 40 mg (84% yield); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J=8 Hz, 3H), 1.15–1.45 (br m, 8H), 1.64 (quintet, J=8 Hz, 2H), 2.51 (t, J=8 Hz, 2H), 2.63 (dd, J=16, 8 Hz, 1H), 3.04 (dd, J=17, 4 Hz, 1H), 4.85 (dd, J=9, 4 Hz, 1H), 5.52 (s, 1H), 9.78 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.0, 22.5, 25.9, 28.8, 29.0, 30.8, 31.5, 35.7, 81.5, 103.2, 174.5, 195.3, 203.7; IR (neat) ν_{max} 2700–2500, 1734, 1707, 1584 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.11; H, 8.23.

4.1.8. Methyl (5-butyl-3-oxo-2,3-dihydro-furan-2-yl)acetate. To a stirred solution of **5** plus **6** (60 mg, 0.23 mmol) in methanol was added concd HCl (0.1 mL) and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was concentrated in vacuo and diluted with water (10 mL). The aqueous layer was extracted with ethyl actetate (15 mL×4) and the combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo gave the corresponding methyl ester as a thick oil.

Methyl ester of (±)-**1**: 47 mg (95% yield); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.93 (t, J=8 Hz, 3H), 1.39 (sextet, J=8 Hz, 2H), 1.63 (quintet, J=8 Hz, 2H), 2.50 (t, J=8 Hz, 2H), 2.59 (dd, J=17, 8 Hz, 1H), 2.97 (dd, J=16, 4 Hz, 1H), 3.74 (s, 3H), 4.81 (dd, J=10, 4 Hz, 1H), 5.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.6, 22.2, 28.0, 30.4, 35.7, 52.2, 81.6, 103.2, 170.0, 194.5, 203.1; IR (neat) ν_{max} 1744, 1703, 1593 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.37; H, 7.49.

4.1.9. (+)-Erigeronic acid A (1). A solution of acids **5** and **6** (74 mg, 0.29 mmol) in petroleum ether–benzene (2/1) mixture (6 mL) was added to a suspension of Amano PS lipase (20 mg) in aqueous sodium phosphate (0.01 M, 2 mL) at pH 7. The reaction mixture was stirred at room temperature for 40 h. The reaction mixture was filtered through Celite and the aqueous layer was extracted with ethyl acetate (15 mL×4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic separation using a mixture of ethyl acetate–petroleum ether (2/8) as an eluent gave (+)-**1** as a thick oil.

Compound (+)-**1**: 47 mg (82% yield); $[\alpha]_D^{20}$ +15.1 (*c* 1.0, CH_3OH), [lit.[2] +29 (*c* 0.07, CH_3OH)]; IR and ^1H NMR spectral data was identical with (±)-**1**.

Similarly starting from **3** and **4** (100 mg, 0.39 mmol) the title compound (−)-**1** was obtained as a thick oil.

Compound (−)-**1**: 10 mg (13% yield); $[\alpha]_D^{20}$ − 13.3 (*c* 0.3, CH_3OH); IR and ^1H NMR spectral data was identical with (±)-**1**.

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Atom transfer radical cyclization reactions (ATRC): synthetic applications

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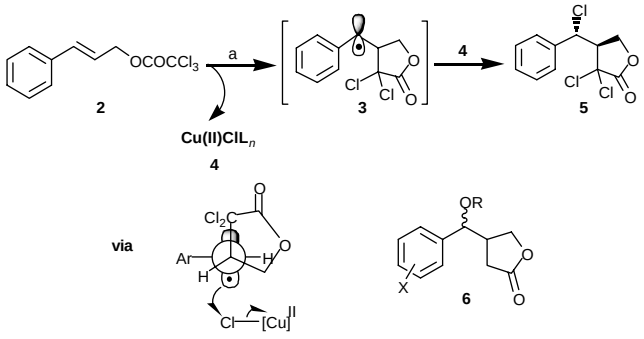
Abstract—Atom transfer cyclization reactions (ATRC) provide rapid access to functionalized γ-butyrolactones.

1. Introduction

Transition metal catalyzed atom transfer radical cyclization reactions[1] (ATRC) provide a useful alternative to the more widely adopted[2] 'tin hydride' variants of this process. ATRC reactions are of interest in that they generate intermediates, which possess a potentially useful carbon–halogen bond for manipulation after cyclization has taken place. Although a number of groups[1] have reported on the ATRC of polyhaloacetates and amides, leading to γ-butyrolactones and γ-butyrolactams, there are scant reports concerning their use in target-oriented synthesis.[3] In this paper, we detail our preliminary results in this area.

2. Results and discussion

In previous reports,[4] we demonstrated that a range of catalysts including the 1st generation Grubbs catalyst promotes cyclization of the ester **2** affording the lactone **5** in high yield. Of note was the observation that the reaction proceeds with very high levels of diastereoselectivity affording the *threo*-isomer **5** as the sole product. Subsequent studies established that the stereochemical outcome of this radical reaction is essentially independent of the catalyst used, the same result being obtained with, for example, copper catalysts. This stereochemical result may be rationalized[5] in terms of an 'allylic strain model' depicted below (Scheme 1). Cyclization of **2** initially generates **3** in which the (planar) benzylic radical adopts a conformation in which the bulky aromatic residue takes up an 'outside-' orientation with respect to the lactone ring, thereby minimizing unfavorable steric interactions. Halogen abstraction from the copper (II) complex **4**, generated in the first step of the reaction, proceeds in a direction *anti*- to the bulky geminal dichloromethylene residue[6] (steric approach control). Given that structurally related γ-butyrolactones, for example, **6** have found application[7] in the synthesis of a variety of lignans we wondered whether an ATRC approach[8] could be employed in the preparation of these synthetically useful intermediates.



Scheme 1. Reagents and conditions: (a) CuCl (5 mol%), dHbipy (5 mol%), DCE, 80 °C, 89% (dr > 95:5).

Initial studies were concerned with the synthesis of the trichloroacetate **8**, which was readily accomplished[9] in three steps from piperonal (Scheme 2). Purely fortuitously we also observed that attempted trichloroacetylation of 1′-hydroxysafrole **7** also resulted in the isolation of

Keywords: Atom; Transfer; Cyclization; Radical; ATRC; Copper.
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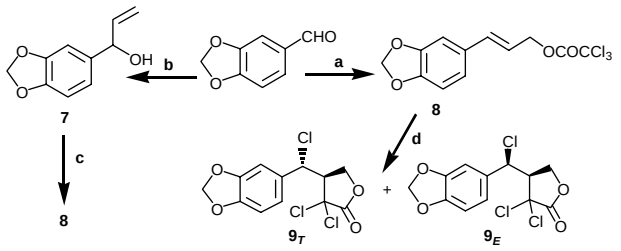


Scheme 2. Reagents and conditions: (a) i. $Ph_3P{=}CHCO_2Et$ (1 equiv), THF, 20 °C, 89%, ii. Dibal-H (2.2 equiv), THF, −78 °C, 88% (cf. Ref. 9), iii. $ClCOCCl_3$ (1 equiv), Et_3N (1 equiv), Et_2O, 0 °C, 85%; (b) $H_2CCHMgBr$, THF, −78 °C, (c) $ClCOCCl_3$ (1 equiv), Et_3N (1 equiv), Et_2O, 0 °C, 91% (over two steps); (d) CuCl (5 mol%); dHbipy (5 mol%); DCE, 80 °C; 90%.

the rearranged ester **8**. This facile high-yielding reaction (>90% over two steps) sequence could be conducted very simply on a preparative scale and became the route of choice to this particular substrate. Surprisingly exposure of the ester **8** (3 mmol) to a preformed solution of a Cu(I)–dHbipy catalyst[10] (5 mol%) in degassed 1,2-dichloroethane for 3.5 h at reflux was almost stereo-random and afforded the diastereoisomeric chlorolactones $\mathbf{9}_T$ and $\mathbf{9}_E$ ($\mathbf{9}_T$:$\mathbf{9}_E$=3:2) in 90% isolated yield. Stereochemical assignments in this series were secured on the basis of a single crystal X-ray structure[11] carried out on the major diastereisomer $\mathbf{9}_T$ (Fig. 1). On scaling-up this reaction (46 mmol) we observed that the initial product of the reaction was indeed the *threo*-isomer $\mathbf{9}_T$, as predicted ($\mathbf{9}_T$:$\mathbf{9}_E$=19:1), suggesting that equilibration had taken place after cyclization in our initial experiments. That this was the case was confirmed when it was found that subjecting either of the isomers $\mathbf{9}_T$ or $\mathbf{9}_E$ separately to mild thermolysis in DCE again afforded $\mathbf{9}_T$ and $\mathbf{9}_E$ as a 3:2 mixture at equilibrium. This isomerisation is apparently thermally driven and does not necessitate the addition of a copper catalyst, Scheme 2.

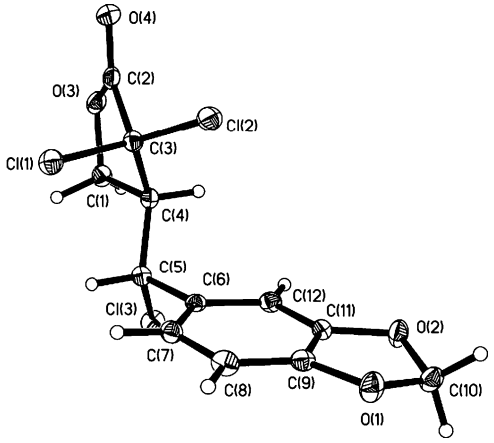


Figure 1. X-ray structure of $\mathbf{9}_T$ (crystallographic numbering).

With the chlorolactones $\mathbf{9}_T$ and $\mathbf{9}_E$ in hand their solvolysis[12] was next attempted. After some experimentation it was discovered that dissolution of a diastereoisomeric mixture of lactones $\mathbf{9}_T$,$\mathbf{9}_E$ ($\mathbf{9}_T$:$\mathbf{9}_E$=3:2) in CH_2Cl_2 containing benzyl alcohol (2 equiv of a 1.7 M soln) at 50 °C resulted in a clean conversion into a single crystalline *threo*-ether **11a** in 85% yield. Again stereochemical assignments were based upon single crystal X-ray analysis (Fig. 2). We presume that these reactions proceed via heterolysis of the C–Cl bond,

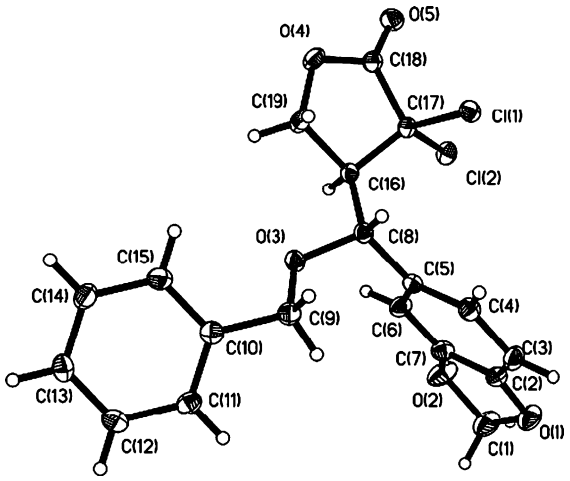
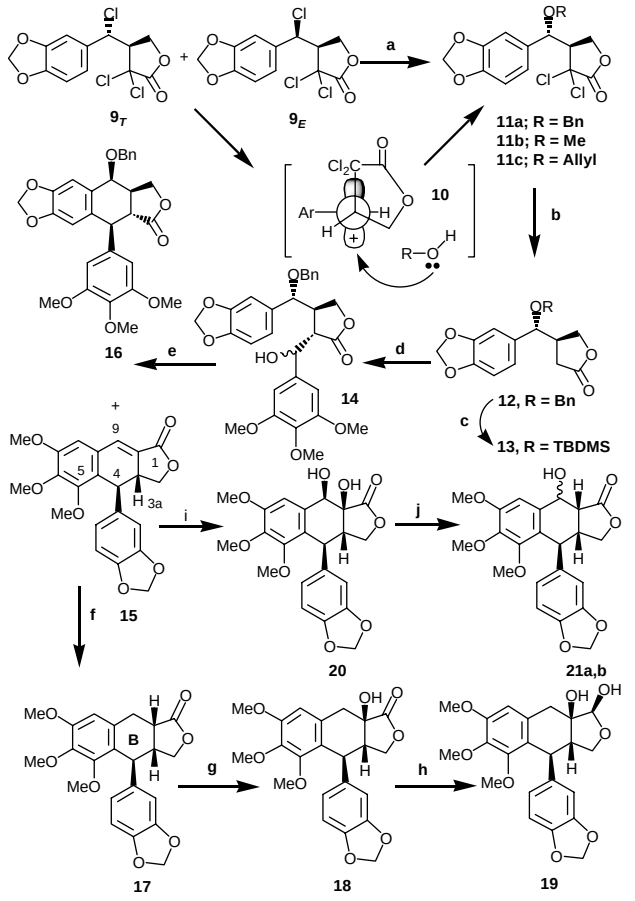


Figure 2. X-ray structure of **11a** (crystallographic numbering).

generating a planar benzylic cation **10** whose interception by benzyl alcohol would, as in the case of the radical chemistry, affords the *threo*-product $\mathbf{11a}_T$ (dr>95:5). Replacing benzyl alcohol with allyl alcohol or methanol in this reaction also resulted in the isolation of the ethers **11b** (91%) and **11c** (75%), both with reasonable levels of diastereoselectivity (dr ca. 9:1; stereochemistry by analogy, vide supra). Dechlorination of **11a** (Bu_3SnH, AIBN, PhH, 80 °C) proved uneventful and afford the known[13] lactone **12** in 83% isolated yield. Regioselective catalytic hydrogenolysis (10% Pd–C, H_2, EtOAc, of **12** followed by in situ protection (TBDMSCl, imidazole, DMAP, TBAB, CH_2Cl_2) led directly to the known[14] TBS ether **13** in 72% overall yield from **12**. The spectral data for **13** were identical to that reported by Coelho[14] thereby providing additional support for our stereochemical assignments (Scheme 3).

With a practical synthesis of the intermediate **12** to hand we have briefly investigated its chemistry. In keeping with Brown's[13] earlier work, enolate generation (LDA, 1.2 equiv, THF; −78 °C; 1 h) followed by reaction with 3,4,5-trimethoxybenzaldehyde afforded the aldol products **14** as a 1:1 mixture of diastereoisomers at the newly created benzylic centre (76% yield). Exposure of the diastereoisomeric mixture **14** to a Lewis acid ($BF_3{\cdot}OEt_2$, 1.0 equiv; CH_2Cl_2; −78 °C, 30 min) resulted in the isolation[15a] of the retro-lignan **15** (71%) together with the bis-epipodophyllotoxin[15b] derivative **16** as a minor component (12%). Molecular models indicate that the cyclohexene ring of **15** adopts a half-boat conformation in which the aromatic substituent at C-4 is pseudo-equatorially disposed ($^3J_{H3a–H4}$ 15 Hz), Figure 3.

This conformational bias places the aromatic ring of the C-1 substituent over the C-5 methoxy group, a situation which results in a large upfield shift[16] of this substituent in its ^1H NMR spectrum compared to **14** ($\Delta\delta\approx0.5$ ppm). Catalytic hydrogenation of **15** (10% Pd–C; EtOAc; H_2) proved to be highly stereoselective[17] (dr>95:5), as depicted in Figure 3, and afforded the tetrahydronaphthalene **17** possessing a cis-fused lactone in high yield (86%). Reduction of the $\Delta^{9,9a}$-double bond of **15** results in a conformational change in ring **B** of **17**. Detailed NOE experiments led us to conclude that whilst the cyclohexane ring of **17** still



Scheme 3. Reagents and conditions: (a) ROH (2.0 equiv), CH_2Cl_2, 50 °C, 85% (R=Bn) or ROH (excess), 20 °C, 82% (R=Allyl); 78% (R=Me); (b) TBTH (2.0 equiv), AIBN (20 mol%), PhH, 80 °C, 83%; (c) i. 10% Pd–C, H_2, EtOAc, ii. TBDMSCl (1.0 equiv), imidazole (1 equiv), DMAP (cat.), CH_2Cl_2, RT, 72% overall; (d) i. LDA (1.2 equiv), THF, −78 °C, ii. ArCHO (1.2 equiv), THF, −78 °C, 76% (1:1 mixture of isomers), (e) $BF_3.Et_2O$ (1.0 equiv), CH_2Cl_2, RT, **15** (71%) and **16** (12%), (f) 10% Pd–C; H_2, EtOAc, 86%; (g) i. KHMDS (1.0 equiv), THF, −78 °C, ii. (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (2.2 equiv), −78 °C; 67%; (h) $LiAlH_4$ (2.4 equiv), THF, 0 °C; 87%; (i) i. OsO_4 (1.2 equiv), pyridine, 20 °C, 12 h, ii. Na_2SO_3, 65%; (j) SmI_2: 3 equiv, THF:H_2O (98:2), 20 °C, 15 min, 86%.

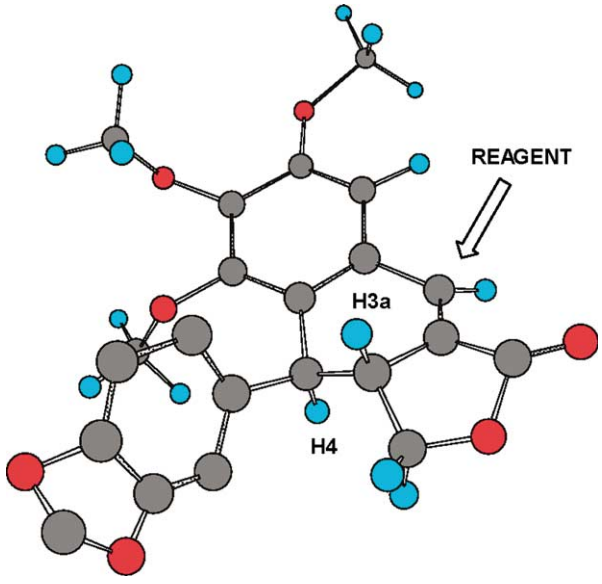


Figure 3. Chem 3D representation of **15**.

adopts a half-boat conformation[18a] the aryl residue at the C-1 substituent is now pseudo axially disposed ($^3J_{H3a–H4} \approx 1$ Hz). Presumably this conformational change occurs in order to minimize a potentially destabilizing *peri*-interaction between the bulky substituent at C-4 and the C-5 methoxy group (Fig. 4). Reaction of the enolate derived from **17** was highly stereoselective[19a] resulting in attack from the *exo*-face of the cup-shaped enolate. Hence, enolate generation (KHMDS, 1 equiv; THF, −78 °C) followed by reaction with (1*R*)-camphorsulfonyloxaziridine (2.2 equiv; THF; −78 °C) afforded the diastereoisomerically pure hydroxylated lactone **18**[19b] in good yield (67%).

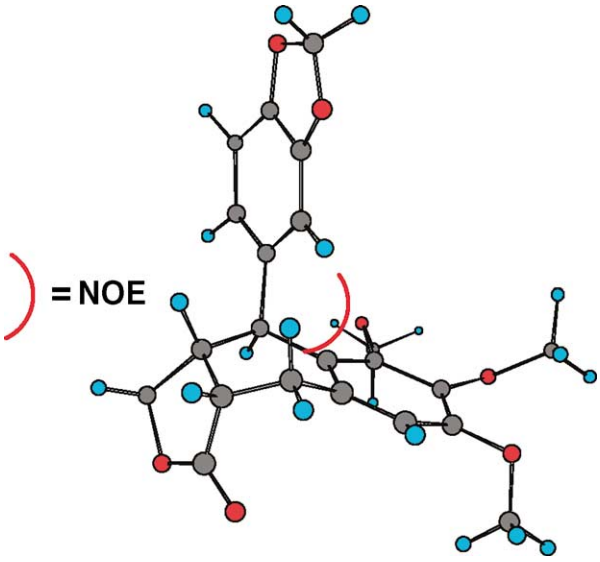


Figure 4. Chem 3D representation of **17**.

Again, NOE studies infer that ring **B** of **18** exists in a half-boat conformation in which the aryl substituent at C-4 is pseudo-axially disposed ($^3J_{H3a–H4}$ 1.5 Hz). Reduction[20] of the lactone **18** ($LiAlH_4$, 2.4 equiv; THF; 0 °C; 5 min) afforded the lactol **19** as a single diastereoisomer in 87% yield, which we have tentatively assigned as the β-epimer on the basis of NOE measurements. The lactol **19** is related to other oxygenated lignans such as the africanal[21] and the triol cycloovitol[22] which, notwithstanding their interesting biological activity, have received scant attention from synthetic chemists.[22] In addition, dihydroxylation of the electron deficient $\Delta^{9,9a}$-bond of **15** proved sluggish but proceeded cleanly following the procedure adopted by Criegee,[23a] which is stoichiometric in osmium tetroxide.

This reaction also proved to be highly stereoselective, affording the diol **20** in 65% yield, again as a result of the reagent approaching from the *β*-face of **15** as depicted in Figure 3. In passing it is also noteworthy that the intermediate osmate ester, **20′** (Fig. 5), formed during this reaction, proved to be quite stable towards hydrolysis and survived chromatography although its demetallation could be readily achieved using Sarrett's procedure.[23b] Analysis of the coupling constant data derived from the ^{1}H NMR spectrum of **20′** suggests that this molecule rapidly interchanges[18b] between two boat conformations on the NMR time scale and that the resulting coupling pattern differs from that which would be expected for the conformationally constrained isomer **20″**,

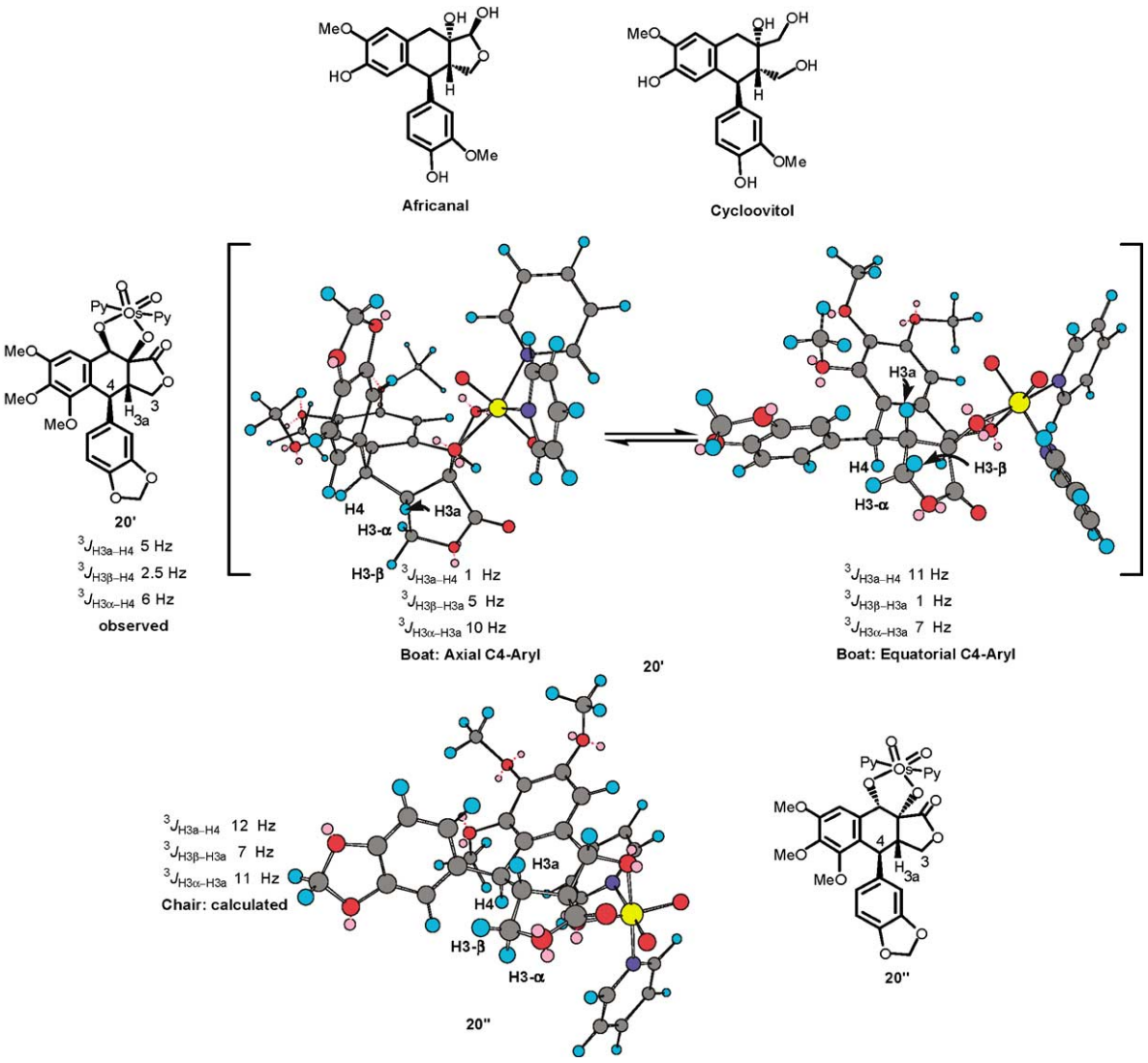
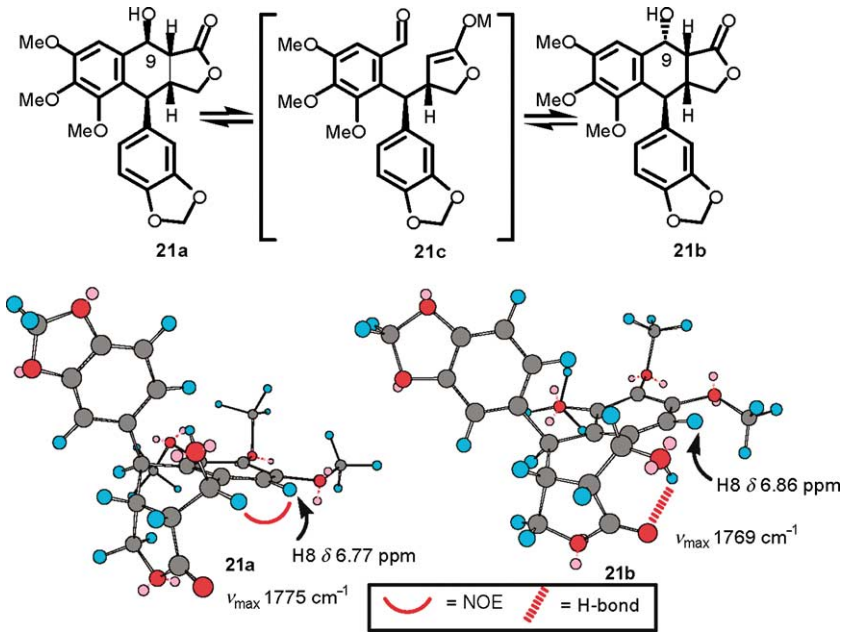


Figure 5. Conformational analysis of **20**′ and **20**″.



Scheme 4. Interconversion of **21a**,**b**.

the product of α-attack by the oxidizing agent on lactone **15**, Figure 5.

Whilst the deoxygenation of the diastereoisomerically pure diol **20** was readily achieved, in high isolated yield, using the conditions reported by Hanessian[24] (SmI_2 in wet THF; 86%) we were surprised to find that this reaction afforded an inseparable mixture of isomeric alcohols, tentatively assigned as **21a**,**b**[25] (dr=3:1). Specifically, NOE measurements support the assertion that both isomers possess a cis-lactone moiety, with the β-isomer, **21a**, exhibiting an additional mutual enhancement between C8–H and C9–Hα. Molecular models suggest these substituents in **21a** are almost co-planar, whilst in **21b**, the C9–OH group is coplanar with the C8–H resulting in a down-field shift of C8–H ($\Delta\delta \approx 0.1$ ppm) in this isomer. We presume that the formation of **21b** during this reaction proceeds via an aldol–retroaldol reaction[26] involving the intermediacy of an enolate anion **21c** or its equivalent, Scheme 4.

The synthesis of steganone and related lignans has been a popular target[27] in recent years and we mused whether a direct approach to the steganacin system could be accomplished via a bi-aryl coupling reaction[28] of the lactone **22**. In order to investigate this strategy we therefore embarked upon the synthesis of the model substrate **23**. Unfortunately, attempts to alkylate the enolate derived from **12** were fraught with problems and resulted in the preferential formation of the di-alkylated lactone **24**. Nevertheless enough of **24** could be prepared in order to investigate the pivotal oxidative coupling reaction. Waldvogel[29] has recently advocated the use of $MoCl_5$ for the promotion of such reactions, demonstrating it to be superior to other oxidizing agents more commonly employed in intramolecular oxidative coupling of aromatics. However, exposure of the lactone **24** to $MoCl_5$ (2 equiv; CH_2Cl_2; 0 °C) resulted not in oxidative coupling of the aromatic rings but rather in the isolation of the cyclolignan **25**, as a single diatereosisomer, in 50% yield. Again stereochemical assignments were established on the basis of NOE experiments, Figure 6. It would appear that the intended bi-aryl coupling reaction is again dogged by the proclivity of the benzylic substituents to undergo ionization and subsequent intramolecular Friedel–Crafts alkylation, a process presumably aided by the Lewis acidity of the oxidizing agent.[30]

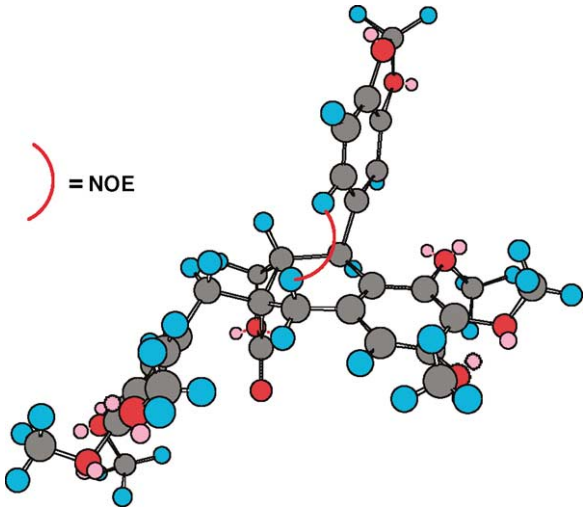
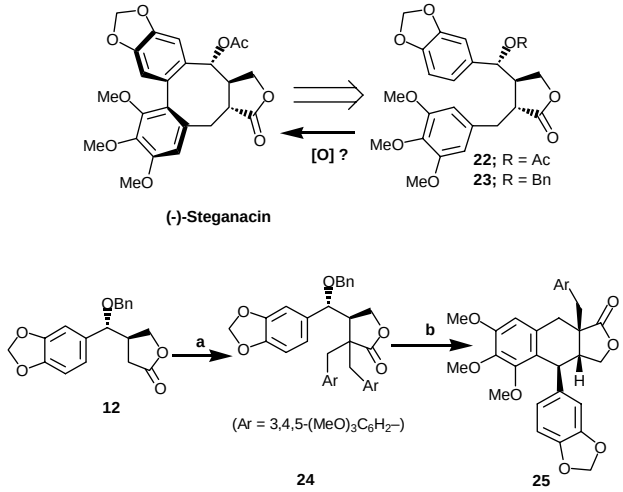


Figure 6. Chem 3D representation of **25**.

3. Conclusion

This work demonstrates that ATRC reactions can be utilized in the rapid, stereoselective synthesis of functionalized γ-butyrolactones (Scheme 5).



Scheme 5. Reagents and conditions: (a) i. KHMDS (2 equiv); THF; 2 h; −78 °C, ii. $ArCH_2Br$ (2.0 equiv); THF; −78 °C; 55%; (b) $MoCl_5$ (2.0 equiv); CH_2Cl_2; 0 °C; 50%.

4. Experimental

4.1. General

All non-aqueous reactions were performed under an atmosphere of dry nitrogen at temperatures, which were those of the external bath. Proton nuclear magnetic resonance (^1H) spectra were recorded on Varian INOVA 400 (400 MHz) or Varian INOVA Unity 300 (300 MHz) spectrometers, with residual non-deuterated solvent as internal standard. All chemical shifts are quoted in parts per million downfield from tetramethylsilane. *J* values are given in Hz. Splitting patterns were abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Carbon NMR spectra (^{13}C NMR) were recorded on a Varian INOVA unity 300 spectrometer at 75 MHz. Infrared spectra were recorded on a Perkin-Elmer 1710 FT spectrometer as evaporated films unless otherwise stated. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Mass spectra were recorded on a Micromass Trio 200 spectrometer (low resolution). High-resolution mass spectra were recorded on a Kratos Concept IS spectrometer using electron impact (EI), chemical ionization (CI; ammonia) or electrospray in positive mode (ES^+) modes of ionization. Microanalysis was performed at the University of Manchester. Melting points were recorded on a Kofler heated stage microscope, and are uncorrected. Hexanes refers to that fraction of light petroleum ether, which distills between 40 and 60 °C, and was redistilled

prior to use. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and distilled under an atmosphere of dry nitrogen. Dichloromethane was dried over phosphorus pentoxide and distilled. Triethylamine and pyridine were dried over potassium hydroxide pellets and redistilled under nitrogen. Where ether is mentioned it refers to diethyl ether. *n*-Butyllithium was supplied as solution in hexanes. Trichloroacetyl chloride and tri-*n*-butyltin hydride were distilled prior to use. Chromatography refers to flash column chromatography and was carried out using Merck silica gel 60H (40–63 μm, 230–400 mesh) as stationary phase. Thin-layer chromatography was carried out on plates pre-coated with Kieselgel 60 F_{254} silica. Visualization was achieved by ultraviolet absorption or treatment with an ethanolic solution of dodecamolybdophosphoric acid followed by heating. 4,4′-Di-*n*-heptyl-2,2′-bipyridine (dHbipy) was prepared according to the literature[31] procedure.

4.1.1. (2*E*)-3-(1′,3′-Benzodioxol-5-yl)prop-2-enyl trichloroacetate, 8. a. To a solution of (2*E*)-3-(1′,3′-benzodioxol-5-yl)prop-2-en-1-ol[9] 4.63 g, 26 mmol) and triethylamine (3.61 mL, 26 mmol) in dry ether (90 mL) was slowly added, at 0 °C, freshly redistilled trichloroacetyl chloride (2.89 mL, 26 mmol) and the mixture was allowed to stir at 0 °C for 3 h. After stirring for 3 h, the reaction was quenched with water (100 mL) and the organic phase was extracted with ether (2×100 mL). The combined organic phases were washed with saturated sodium hydrogencarbonate solution (10%, 50 mL), brine (200 mL), dried ($MgSO_4$) and the solvent removed in vacuo to afford the title compound as a pale yellow, chromatographically unstable oil which solidified on standing, which was used without further purification. Yield 7.15 g, (85%). δ_H (300 MHz, $CDCl_3$) 6.95 (1H, s), 6.70–6.90 (2H, m, ArH), 6.66 (1H, br d, $J=16$ Hz, alkene), 6.20 (1H, dt, $J=16$, 7 Hz, alkene), 6.0 (2H, s, O–CH_2–O), 5.00 (2H, dd, $J=7$, 1 Hz, CH_2–$OCOCCl_3$) ppm; δ_C (75 MHz, $CDCl_3$) 162.1, 148.4, 148.3, 136.8, 130.3, 122.3, 118.8, 108.6, 106.2, 101.7, 90.2, 70.2 ppm; ν_{max} (evaporated film) 2896, 1763 (s), 1607, 1503, 1491, 1447, 1250 cm^{-1}; *m/z* (ES) 323, 325, 329.

b. To a solution of piperonal (2.0 g, 1.3 mmol) in anhydrous THF (50 mL) at −78 °C was added, under an atmosphere of nitrogen, vinylmagnesium bromide (14.6 mL of a 1 M solution in THF *ex* Aldrich; 14.7 mmol) and the reaction mixture allowed to warm up to room temperature. On re-cooling to 0 °C the reaction was quenched by the addition of saturated aqueous ammonium chloride (20 mL), the organic phase was extracted with ether (3×30 mL), the combined extracts dried ($MgSO_4$) and concentrated in vacuo to afford 1′-hydroxysafrole **7** [δ_H (300 MHz, $CDCl_3$) 3.00 (1H, br s, OH), 5.07 (1H, br d, $J=6$ Hz, CH_2O), 5.18 (1H, dt, $J=10$, 1.5 Hz, alkene), 5.32 (1H, dt, $J=16$, 1.5 Hz, alkene), 5.94 (2H, s, OCH_2O), 5.96–6.06 (1H, m, alkene), 6.76–6.88 (3H, m, ArH) ppm] in an essentially pure state (yield 2.27 g, 95%), which was used in the next step without further purification. The crude product, **7**, was redissolved in dry ether (100 mL), to which was added, at 0 °C, triethylamine (1.8 mL, 12.8 mmol) followed by trichloroacetyl chloride (1.4 mL, 12.8 mmol). The reaction mixture was left to stir at 0 °C for 1 h after which time it was quenched by the addition of water (30 mL). The aqueous layer was extracted (ether, 3×20 mL), the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo to afford the title compound **8** as a low-melting solid, which was used in subsequent ATRC reactions without further purification. Crude overall yield 4.04 g (91%).

4.1.2. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(chloro)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one and 9_T and (4*R**)-4-[(*S**)-1,3-benzodioxol-5-yl(chloro)methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 9_E.** A dry Schlenck tube was charged with CuCl (0.014 g, 5 mol%), dHbipy (0.046 g; 5 mol%) and anhydrous 1,2-DCE (3 mL) and the resulting brown solution was allowed to stir for 10 min at room temperature. The contents of the flask were then degassed (three times using freeze–thaw cycle). To this solution was added, by syringe, a solution of trichloroacetate **8** (0.91 g, 2.8 mmol) in 1,2-DCE (1 mL). After degassing (three times freeze–thaw cycle), the Schlenck tube was placed in a pre-heated oil bath (90 °C) and was allowed to stir for 3.5 h under an atmosphere of argon. Upon cooling, the solvent was removed in vacuo and the residue chromatographed (silica; 1:19 EtOAc/hexanes) to give the diastereoisomeric lactones 9_T and 9_E. The major product 9_T (R_f 0.2; silica; 1:19 EtOAc/hexanes) was isolated as a white solid. Yield 0.30 g (31%), mp 165–166 °C (from DCE–hexanes). δ_H (300 MHz, $CDCl_3$) 3.59 (1H, td, $J=10$, 8 Hz, C4–H), 3.75 (1H, apparent t, $J=10$ Hz, C5–H), 3.90 (1H, dd, $J=9$, 8 Hz, C5–H), 5.12 (1H, d, $J=10$ Hz, CHCl), 5.95 (2H, s, OCH_2O), 6.82 (1H, d, $J=8$ Hz, ArH), 6.88 (1H, dd, $J=8$, 1.5 Hz, ArH), 6.93 (1H, d, $J=1.5$ Hz, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 167.9, 149.1, 149.0, 130.6, 121.4, 108.8, 107.4, 102.0, 79.3, 67.5, 58.4, 57.8 ppm; ν_{max} (Nujol) 2906, 1803 (s), 1609, 1503, 1447, 1374, 1250 cm^{-1}; *m/z* (EI) 323 (M^+10%), 287 (20%), 169 (100%), 135 (40%), 122 (40%); *m/z* (CI) 341 ($[M+NH_4]^+$10%), 287 (50%), 236 (70%), 168 (100%). HRMS (EI) $C_{12}H_9^{35}Cl_3O$ (M^+) requires: 321.9561; found: 321.9569. The minor isomer 9_E (R_f 0.35; silica; 1:19 EtOAc/hexanes), was isolated as a white solid. Yield 0.192 g (21%), mp 159–160 °C (from DCE–hexanes). δ_H (300 MHz, $CDCl_3$) 3.50–3.64 (1H, m, C4–H), 4.20 (1H, apparent t, $J=7$ Hz, C5–H), 4.75–4.85 (1H, m, C5–H), 5.20 (1H, d, $J=10$ Hz, CHCl), 5.95 (2H, s, OCH_2O), 6.72 (1H, dd, $J=8$, 2 Hz, ArH), 6.95–7.05 (2H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 167.8, 149.1, 148.4, 130.6, 122.5, 108.4, 108.2, 101.8, 78.8, 69.1, 60.5, 57.7 ppm; ν_{max} (Nujol) 2925, 1810 (s), 1613, 1528 cm^{-1}; *m/z* (EI) 323 (M^+10%), 287 (20%), 169 (100%), 135 (40%), 122 (40%); *m/z* (CI) 341 ($[M+NH_4]^+$10%), 287 (50%), 236 (70%), 168 (100%). HRMS (EI) $C_{12}H_9^{35}Cl_3O_4$ (M^+) requires: 321.9561; found: 321.9563.

4.1.3. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 11a.** The trichlorolactone $9_{E,T}$ (0.56 g, 1.73 mmol) and benzyl alcohol (0.374 g, 3.46 mmol, 2.0 equiv) were dissolved in a minimum volume of anhydrous dichloromethane (2 mL). The resulting solution was placed in a preheated oil-bath (50 °C), which was maintained at this temperature until TLC analysis indicated that all of the starting material had been consumed. The solvent was removed in vacuo and the residue was purified by chromatography (silica, 1:17 EtOAc/hexanes) affording the title compound as a white solid. Yield 0.622 g (91%), 152–154 °C (from DCM–hexanes). δ_H (300 MHz, $CDCl_3$) 3.20 (1H, q, $J=7$ Hz,

C4–H), 4.28 (1H, d, $J=11$ Hz, CH_2Ph), 4.34 (1H, dd, $J=9$, 7 Hz, C5–H), 4.48 (1H, d, $J=11$ Hz, CH_2Ph), 4.62 (1H, dd, $J=9$, 7 Hz, C5–H), 4.80 (1H, d, $J=7$ Hz, $CHOCH_2Ph$), 6.05 (2H, s, OCH_2O), 6.85–6.95 (3H, m, ArH), 7.22–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 168.3, 148.6, 148.4, 142.2, 137.2, 131.0, 128.8, 128.2, 128.0, 121.6, 108.7, 107.5, 101.6, 79.3, 79.1, 70.5, 68.1, 60.6, 57.1 ppm; ν_{max} (evaporated film) 2900, 1803, 1502, 1489, 1241, 1182, 1038 cm^{-1}; *m/z* (EI); 394 (M^+, 5%), 324 (5%), 287 (10%), 241 (10%), 169 (20%), 149 (30%), 91 (100%); *m/z* (CI); 412 ($[M+NH_4]^+$, 25%), 340 (20%), 246 (30%), 230 (60%), 126 (100%). HRMS (EI) $C_{19}H_{16}^{35}Cl_2O_5$ (M^+) requires: 394.0369; found: 394.0360.

4.1.4. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-dihydrofuran-2(3*H*)-one, 12.**[13] To a stirred solution of the lactone **11a** (1.04 g, 2.65 mmol) and AIBN (88 mg, 0.53 mmol, 20 mol%) in benzene (35 mL) was added tri-*n*-butyltin hydride (1.42 mL, 5.30 mmol). The resulting mixture was placed in an oil bath at 80 °C and heated for 6 h. The solvent was removed in vacuo and the residue was chromatographed (silica, 1:9 EtOAc/hexanes) to afford the title compound as a white solid. Yield 0.717 g (83%), mp 126–128 °C (from DCM–hexanes; lit.[13] mp 120–123). δ_H (300 MHz, $CDCl_3$) 2.28 (1H, dd, $J=18$, 8 Hz, C3–H), 2.32 (1H, dd, $J=18$, 8 Hz, C3–H), 2.85–2.95 (1H, m, C4–H), 4.15 (1H, d, $J=8$ Hz, ArCHO), 4.20 (1H, d, $J=11$ Hz, CH_2Ph), 4.34 (1H, dd, $J=10$, 6 Hz, C5–H), 4.42 (1H, dd, $J=10$, 6 Hz, C5–H), 4.48 (1H, d, $J=11$ Hz, CH_2Ph), 6.0 (2H, s, OCH_2O), 6.75–6.85 (3H, m, ArH), 7.22–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 176.4, 148.4, 147.8, 137.4, 132.8, 128.5, 127.9, 120.9, 108.3, 106.7, 101.2, 81.7, 70.9, 70.3, 42.3, 31.3 ppm; ν_{max} (evaporated film) 1778, 1505, 1487, 1253 cm^{-1}; *m/z* (EI); 326 (M^+, 20%), 219 (40%); *m/z* (CI) 344 ($[M+NH_4]^+$, 25%) 246 (30%), 230 (60%), 126 (100%). HRMS (CI) $C_{19}H_{18}O_5$ (M^+) requires: 326.1145; found: 326.1149.

Treatment of $\mathbf{9}_{E,T}$ with methanol or allyl alcohol similarly afforded the ethers **11b** and **11c**, respectively.

4.1.5. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(methoxy)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 11b.** Dissolution of $\mathbf{9}_{E,T}$ (50 mg) in methanol (2 mL) for 12 h at ambient temperature, followed by removal of the solvent in vacuo and column chromatography afforded the title compound as a colourless oil. Yield 38 mg (78%). δ_H (300 MHz, $CDCl_3$) 3.09–3.13 (1H, m, C4–H), 3.25 (3H, s, OMe), 4.40 (1H, dd, $J=9$, 6 Hz, C5–H), 4.56 (1H, dd, $J=10$, 7 Hz, C5–H), 4.63 (1H, d, $J=6$ Hz, ArCH), 6.05 (2H, s, OCH_2O), 6.88–6.90 (3H, m, ArH); δ_C (75 MHz, $CDCl_3$) 168.4, 148.6, 148.3, 131.0, 121.3, 108.7, 107.3, 101.6, 81.4, 79.5, 67.8, 57.0, 56.8 ppm; ν_{max} (evaporated film) 2904, 1802 (s), 1505, 1489, 1242 cm^{-1}; *m/z* (ES) 341, 343, 345 ($[M+Na]^+$). HRMS (ES) $C_{13}H_{12}^{35}Cl_2NaO_5$ ($[M+Na]^+$) requires: 340.9954; found: 340.9956. The presence of a minor amount of an isomeric compound, presumably (4*R**)-4-[(*S**)-1,3-benzodioxol-5-yl(methoxy)methyl]-3,3-dichlorodihydrofuran-2-(3*H*)-one, was also apparent from the ^1H NMR spectrum of **11b**: δ_H (300 MHz, $CDCl_3$) 3.30 (3H, s, OMe), 3.75–3.85 (2H, m, C5–H), 4.49 (1H, d, $J=9$ Hz, ArCH).

4.1.6. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(allyloxy)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 11c.** Dissolution of $\mathbf{9}_{E,T}$ (100 mg) in allyl alcohol (2 mL) for 12 h at ambient temperature followed by removal of the solvent in vacuo and column chromatography afforded the title compound as a colourless oil. Yield 88 mg (82%). δ_H (300 MHz, $CDCl_3$) 3.75 (1H, ddt, $J=13$, 6, 1.5 Hz, CH_2O), 3.15 (1H, q, $J=7$ Hz, C4–H), 3.95 (1H, ddt, $J=13$, 6, 1.5 Hz, CH_2O), 4.38 (1H, dd, $J=9$, 7 Hz, C5–H), 4.58 (1H, dd, $J=9$, 7 Hz, C5–H), 4.77 (1H, d, $J=7$ Hz, ArCH), 5.16–5.25 (2H, m, alkene), 5.76–5.84 (1H, m, alkene), 6.00 (2H, s), 6.78–6.90 (3H, m, ArH); δ_C (75 MHz, $CDCl_3$) 168.4, 148.6, 148.3, 133.8, 131.1, 131.0, 121.4, 117.8, 107.0, 101.7, 79.5, 78.7, 69.5, 68.0, 57.0 ppm; ν_{max} (evaporated film) 2901, 1803 (s), 1504, 1489, 1445, 1242, 1182, 1039 cm^{-1}; *m/z* (ES) 367 ($[M+Na]^+$, 100%). HRMS (ES) $C_{15}H_{14}^{35}Cl_2NaO_5$ ($[M+Na]^+$) requires: 367.0111; found: 367.0109.

4.1.7. (4*R)-4-{(*R**)-Benzo[1,3]dioxol-5-yl(*tert*-butyldimethy-lsilyloxy)methyl}-dihydrofuran-2(3*H*)-one, 13.** A solution of **12** (0.102 g, 0.312 mmol) in ethyl acetate (5 mL) was hydrogenolysed over 5% Pd–C (0.051 g, 50 wt%) at 20 °C under atmospheric pressure for 5 h. The reaction mixture was filtered through a pad of Celite®, the cake was washed (EtOAc, 2×20 mL), and the combined filtrates concentrated in vacuo to afford the crude product, (4*R**)-4-[(*R**)-benzo-1,3-dioxol-5yl)hydroxymethyl]dihyd-rofuran-2-one,[32] as a viscous oil, which was used in the next step without further purification. Yield 0.065 g (82%). δ_H (300 MHz, $CDCl_3$) 2.25 (1H, dd, $J=18$, 7 Hz, C3–H), 2.38 (1H, dd, $J=18$, 9 Hz, C3–H), 2.42–2.52 (1H, br s, OH), 2.78–2.90 (1H, m, C4–H), 4.38 (2H, apparent d, $J=7$ Hz, C5–H), 4.55 (1H, d, $J=8$ Hz, CHO), 5.98 (2H, s, OCH_2O), 6.75–6.85 (3H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 177.2, 148.4, 147.9, 136.0, 119.9, 108.6, 106.5, 101.5, 75.4, 70.8, 42.8, 31.6 ppm; ν_{max} (evaporated film) 3600–3200, 1771 (s), 1457, 144, 1243 cm^{-1}; *m/z* (ES) 235 (100%). HRMS (ES) $C_{12}H_{12}NaO_5$ ($[M+Na]^+$) requires: 259.0577; found: 259.0575.

To a suspension of imidazole (0.018 g, 0.26 mmol) in DCM (3 mL) was added *tert*-butyldimethylsilylchloride (0.038 g, 0.26 mmol) before cooling to 0 °C. A solution of crude (4*R**)-4-[(*R**)-benzo-1,3-dioxol-5-yl)hydroxyme-thyl]dihydrofuran-2-one (0.051 g, 0.22 mmol) in DCM (2 mL) was added by syringe and the resulting mixture was allowed to warm to room temperature. DMAP (cat.) and TBAI (cat.) were added before stirring for 14 h, dilution with DCM (20 mL), and filtration. The filtrate was partitioned with water (10 mL), the organic layer separated and the aqueous layer re-extracted (DCM; 3×10 mL). The combined organic extracts were washed (brine; 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (1:9 EtOAc/hexanes) affording the title compound **13**, as a colourless oil. Yield 0.079 g (88%). δ_H (300 MHz, $CDCl_3$) −0.21 (3H, s, $SiMe_2$), 0.04 (3H, s, $SiMe_2$), 0.92 (9H, s, SiC $(CH_3)_3$), 2.28 (1H, dd, $J=18$, 8 Hz, C3–H), 2.36 (1H, dd, $J=18$, 8 Hz, C3–H), 2.71–2.84 (1H, m, C4–H), 4.24–4.36 (2H, m, OCH_2), 4.49 (1H, d, $J=7$ Hz, CHOSi), 5.96–5.98 (2H, m, OCH_2O), 6.70 (1H, dd, $J=8$, 1.5 Hz, ArH), 6.76 (1H, d, $J=8$ Hz, ArH), 6.77 (1H, br s, ArH) ppm; δ_C (75 MHz, $CDCl_3$)

176.9, 148.1, 147.4, 136.3, 119.7, 108.2, 106.4, 101.3, 75.8, 70.2, 44.3, 31.5, 25.9, 18.2, −4.2, −5.0 ppm; ν_{max} (evaporated film) 1769, 1515, 1468 cm^{-1}; *m/z* (CI) 368 ($[M+NH_4]^+$, 100%) 351 ($[M+H]^+$, 20%), 219 (60%), 91 (20%). HRMS $C_{18}H_{26}O_5Si$ (M^+) requires: 350.1544; found: 350.1539

4.1.8. (3*S,4*R**)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-3-[(*R***S**)-hydroxy(3,4,5-trimethoxyphenyl)-methyl]dihydrofuran-2(3*H*)-one, 14a,b.** To a solution of di-isopropylamine (0.31 mL, 2.21 mmol, 1.20 equiv) in anhydrous tetrahydrofuran (2 mL) was added, at −78 °C, *n*-butyllithium (1.26 mL, 2.02 mmol, 1.1 equiv, 1.6 M in hexanes) and the resulting mixture was stirred at −78 °C for 5 . After this time the solution was allowed to warm to 0 °C and was stirred for 30 min then re-cooled to −78 °C. The resulting solution of lithium di-isoproplyamide was then added by cannula to a solution of the benzylether **12** (0.60 g, 1.84 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (5 mL). The resulting solution was stirred for 1 h, at −78 °C, and a solution of 3,4,5-trimethoxybenzaldehyde (0.433 g, 2.21 mmol, 1.20 equiv) in anhydrous tetrahydrofuran (1 mL) was added dropwise over 10 min by syringe. The solution was stirred for 2 h at −78 °C and allowed to warm to 20 °C over 2 h after which time the reaction was quenched by addition of saturated aqueous ammonium chloride solution (2 mL). The aqueous layer was extracted (DCM, 3×10 mL) and the combined organic extracts were washed (brine, 2×10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica, 7:13 EtOAc/hexanes) affording the diastereomeric products **14a**,**b**. The less polar isomer, R_f 0.43 (silica, 7:13 EtOAc/hexanes) was isolated as a white foam, yield 0.394 g (41%): δ_H (300 MHz, $CDCl_3$) 2.50 (1H, br s, OH), 2.62 (1H, dd, *J*=8, 3 Hz, C3–H), 2.77–2.87 (1H, m, C4–H), 3.80 (6H, 2×overlapping s, 2×OCH_3), 3.85 (3H, s, OCH_3), 3.90 (1H, dd, *J*=9, 4 Hz, OCH_2), 4.0 (1H, d, *J*=12 Hz, OCH_2Ph), 4.30 (1H, d, *J*=12 Hz, OCH_2Ph), 4.39 (1H, apparent triplet, *J*=9 Hz, $CHOCH_2Ph$), 4.52 (1H, dd, *J*=9, 4 Hz, OCH_2), 5.20 (1H, d, *J*=2 Hz, C*H*OH), 5.98 (1H, d, *J*=1 Hz, OCH_2O), 6.08 (1H, d, *J*=1 Hz, OCH_2O), 6.32–6.36 (3H, m, ArH), 6.44 (1H, dd, *J*=8, 2 Hz, ArH), 6.63 (1H, d, *J*=8 Hz, ArH), 7.20–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 178.7, 153.5, 148.6, 147.9, 137.7, 137.3, 136.6, 132.2, 128.8, 128.2, 121.2, 107.5, 106.1, 101.9, 81.4, 72.7, 70.9, 70.6, 61.1, 56.2, 50.7, 42.0, 28.1, 27.1 ppm; *m/z* (EI); 522 (M^+, 5%), 405 (10%) 209 (20%); *m/z* (CI) 540 ($M+NH_4^+$, 20%). HRMS $C_{29}H_{34}O_9N$ ($[M+NH_4]^+$) requires: 540.2228; found: 540.2215. The more polar isomer, R_f 0.38 (silica, 7:13 EtOAc/hexanes) was isolated as a white foam, yield 0.336 g (35%): δ_H (300 MHz, $CDCl_3$) 2.58 (1H, ddd, *J*=13, 8, 5 Hz, C4–H), 2.92 (1H, t, *J*=8 Hz, C3–H), 3.58 (1H, d, *J*=5 Hz, OCHAr), 3.82 (6H, 2×overlapping s, 2×OCH_3), 3.84 (3H, s, OCH_3), 3.88 (1H, d, *J*=12 Hz, OCH_2Ph), 4.00–4.18 (1H, m, C5–H), 4.32 (1H, d, *J*=12 Hz, OCH_2Ph), 4.45 (1H, dd, *J*=9, 8 Hz, C5–H), 4.76 (1H, d, *J*=9 Hz, C*H*OH), 6.0 (2H, dd, *J*=8, 1 Hz, OCH_2O), 6.44–6.50 (2H, m, ArH), 6.56 (2H, s, ArH), 6.75 (1H, d, *J*=8 Hz, ArH), 7.20–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 178.9, 153.7, 148.6, 147.9, 137.6, 136.0, 132.4, 128.8, 128.2, 127.7, 120.2, 108.4, 106.2, 103.7, 101.6, 79.0, 74.6, 71.2, 68.0, 61.1, 60.6, 56.3, 48.6, 45.2, 21.3 ppm; *m/z* (EI); 522 (M^+, 10%), 405 (15%) 209 (15%); *m/z* (CI) 540 ($[M+NH_4]^+$, 10%). HRMS (CI) $C_{29}H_{34}NO_9$ ($[M+NH_4]^+$) requires: 540.2228; found: 540.2221.

4.1.9. (3a*R,4*S**)-4-{(1,3-Benzodioxol-5-yl)-5,6,7-trimethoxy-3a,4-dihydronaphtho[2,3-*c*]}furan-1(3*H*)-one, 15 and *O*-benzyl-isoepipodophyllotoxin, 16.**[15a] To a solution of the aldol adducts **14a**,**b** (0.10 g, 0.19 mmol) in anhydrous dichloromethane (5 mL) was added, at 20 °C, boron trifluoride diethyl ether complex (0.023 mL, 0.19 mmol, 1.0 equiv) and the resulting solution was stirred for 30 . The reaction was quenched by the addition of saturated sodium hydrogencarbonate solution (1 mL) and the aqueous phase was extracted with dichloromethane (3× 5 mL). The combined organic extracts were washed (brine; 2×10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (silica, 1:4 EtOAc/hexanes) afforded two products, the less polar of which was identified as the olefin **15**, a white crystalline solid. Yield 0.051 g (71%), mp 171–173 °C (from DCM–hexanes), (lit. mp[15a] 170–172 °C), R_f 0.19 (silica, 1:4 EtOAc–hexanes). δ_H (300 MHz, $CDCl_3$) 3.25 (3H, s, OCH_3), 3.30–3.41 (1H, m, C3a–H), 3.94 (1H, d, *J*= 15 Hz, C4–H), 3.82 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.98 (1H, t, *J*=9 Hz, C3–H), 4.36 (1H, t, *J*=7 Hz, C3–H), 5.98 (2H, m, OCH_2O), 6.73 (1H, dd, *J*=7, 2 Hz, ArH), 6.73 (1H, s, ArH), 6.76 (1H, s, ArH), 6.78 (1H, d, *J*=8 Hz, ArH), 7.32 (1H, d, *J*=3.5 Hz, alkene) ppm; δ_C (75 MHz, $CDCl_3$) 169.9, 153.1, 153.0, 148.1, 146.3, 138.8, 132.5, 129.4, 125.6, 124.2, 120.1, 109.6, 108.5, 107.7, 101.2, 72.6, 61.0, 60.2, 60.7, 56.3, 48.1, 44.0 ppm; ν_{max} (evaporated film) 1771, 1510, 1472, 1287 cm^{-1}; *m/z* (EI); 396 (M^+, 100%); *m/z* (CI) 414 ($[M+NH_4]^+$, 100%). HRMS $C_{22}H_{20}O_7$ (M^+) requires: 396.1209; found: 396.1204. The more polar product was identified as the aryltetralin, **16**, an amorphous, white solid. Yield 0.011 g (12%), R_f 0.31 (silica, 1:4 EtOAc–hexanes). δ_H (300 MHz, $CDCl_3$) 2.66–2.80 (1H, m, C8a–H), 3.48 (1H, dd, *J*=14, 11 Hz, C5a–H), 3.75 (6H, 2× overlapping s, OCH_3), 3.92 (3H, s, OCH_3), 4.05 (1H, d, *J*= 11 Hz, C5–H), 4.34–4.44 (2H, m, 2×C8–H), 4.55 (1H, d, *J*=2 Hz, C9–H), 4.62 (1H, d, *J*=12 Hz, OCH_2Ph) 4.75 (1H, d, *J*=12 Hz, OCH_2Ph), 5.98–6.00 (2H, m, OCH_2O), 6.46 (2H, s, ArH), 6.51 (1H, s, ArH), 6.74–6.80 (2H, m, ArH), 7.34–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 176.3, 153.3, 148.6, 146.1, 139.6, 138.1, 136.9, 134.4, 132.5, 129.4, 128.7, 128.3, 128.1, 127.5, 111.0, 109.9, 106.3, 101.6, 101.2, 73.2, 70.3, 67.4, 61.0, 60.2, 56.2, 48.1, 46.5, 45.1, 42.4 ppm; *m/z* (EI) 504 (M^+, 5%), 230 (50%); *m/z* (CI) 522 ($[M+NH_4]^+$, 100%), 414 (40%). HRMS (CI) $C_{29}H_{32}NO_8$ ($[M+NH_4]^+$) requires: 522.2122; found: 522.2116

4.1.10. (3a*R,4*S**,9a*S**)-4-(1,3-Benzodioxol-5-yl)-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 17.** A solution of the unsaturated lactone **15** (0.050 g, 0.132 mmol) in ethyl acetate (2 mL) was hydrogenated over 5% Pd–C (0.025 g, 50 wt%) at room temperature and atmospheric pressure for 2 h. The reaction mixture was filtered through a pad of Celite®, and the filtrate concentrated in vacuo. Chromatography of the crude product (silica, 17:3 EtOAc/hexanes) afforded the title compound as a colourless oil. Yield 0.043 g (86%). δ_H (500 MHz, $CDCl_3$) 2.83 (1H, dd, *J*=15, 8 Hz, C9–H), 2.95

(1H, J=15, 2 Hz, C9–H), 3.03 (1H, ddd, J=11, 7, 2 Hz, C9a–H), 3.55–3.64 (1H, ddt, J=11, 7, 2 Hz, C3a–H), 3.64 (1H, dd, J=7, 3 Hz, C3–H), 3.78 (3H, s, OCH_3), 3.88 (6H, 2×overlapping s, 2×OCH_3), 4.48 (1H, br s, C4–H), 4.60 (1H, t, J=7 Hz, C3–H), 5.95 (2H, s, OCH_2O), 6.45 (1H, ddd, J=8, 1.5, 1 Hz, ArH), 6.47 (1H, br s, ArH), 6.53 (1H, d, J=1.5 Hz, ArH), 6.63 (1H, d, J=8 Hz, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 178.5, 153.0, 152.2, 148.2, 146.3, 141.3, 135.9, 131.3, 122.4, 120.3 108.4, 108.2, 101.3, 72.9, 61.4, 61.1, 59.2, 40.1, 39.5, 38.8, 29.9, 29.6 ppm; ν_{max} (evaporated film); 1765, 1501, 1379 cm^{-1}; *m/z* (EI); 398 (M^+, 100%), 277 (20%), 135 (50%); *m/z* (CI); 416 ($[M+NH_4]^+$, 100%), 399 ($[M+H]^+$, 20%). HRMS $C_{22}H_{22}O_7$ (M^+) requires: 398.1365; found: 398.1360.

4.1.11. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-3,3-bis[3,4,5-trimethoxyphenyl)methyl]dihydrofuran-2(3*H*)-one, 24.** To potassium hexamethyldisilazide (3.92 mL, 1.96 mmol, 0.5 M solution in toluene) was added slowly by syringe, at −78 °C, a solution of the lactone **12** (0.32 g, 0.98 mmol) in anhydrous tetrahydrofuran (3 mL) and the resulting mixture was stirred for 2 h whilst warming up to 20 °C. To this solution was added, slowly by syringe at 0 °C, 3,4,5-trimethoxybenzyl bromide[33] (0.512 g, 1.96 mmol) in anhydrous tetrahydrofuran (3 mL) and the resulting mixture was stirred for 2 h at 20 °C. The reaction was quenched by the addition of saturated ammonium chloride solution (5 mL) and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine, dried $MgSO_4$ and concentrated in vacuo and the residue was purified by column chromatography (silica, 40% EtOAc/hexanes) affording the bisalkylated lactone, **24** as a glass (0.370 g, 55%). δ_H (300 MHz, $CDCl_3$) 2.19 (1H, d, J=12 Hz, CH_2Ar), 2.90–2.98 (1H, m, C4–H), 2.95 (1H, d, J=12 Hz, CH_2Ar), 3.16 (2H, dd, J=14, 7 Hz, CH_2Ar), 3.78–3.85 (1H, m, C5–H), 3.85 (6H, s, OCH_3), 3.86 (6H, s, OCH_3), 3.88 (6H, s, OCH_3), 4.18 (1H, d, J=12 Hz, OCH_2Ph), 4.31 (1H, t, J=7 Hz, C5–H), 4.40 (1H, d, J=12 Hz, OCH_2Ph), 4.72 (1H, d, J=7 Hz, C*H*OCH_2Ph), 6.08 (2H, s, O–CH_2–O), 6.38 (2H, s, ArH), 6.46 (2H, s, ArH), 6.95–7.00 (3H, m, ArH), 7.18–7.24 (2H, m, ArH), 7.32–7.38 (3H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 179.8, 171.4, 153.2, 153.1, 148.8, 148.3, 137.5, 137.4, 137.1, 133.6, 132.2, 131.7, 129.1, 129.0, 128.8, 128.3, 128.1, 121.6, 108.6, 107.9, 107.8, 107.7, 101.8, 78.5, 70.2, 67.9, 61.2, 61.1, 60.6, 56.4, 56.4, 56.1, 51.5, 46.6, 41.1, 40.5, 34.1, 28.7, 24.1 ppm; ν_{max} (evaporated film) 3067, 2937, 2838, 1766, 1590, 1505, 1459 cm^{-1}; *m/z* (EI); 686 (M^+, 5%), 578 (5%), 455 (5%), 399 (25%), 314 (20%), 181 (100%). HRMS (CI) $C_{39}H_{46}NO_{11}$ ($[M+NH_4]^+$) requires: 704.3065; found: 704.3079.

4.1.12. (3a*R,4*S**,9a*R**)-4-[(1,3-Benzodioxol-5-yl)-((3,4,5-trimethoxyphenyl)methyl)]-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 25.** To a solution of the bis-alkylated lactone **24** (0.071 g, 0.1035 mmol) in anhydrous dichloromethane (2 mL) was added, at 0 °C, a solution of molybdenum pentachloride (0.056 g, 0.207 mmol) in anhydrous dichloromethane (1 mL). The resulting solution was stirred for 2 h and was then quenched by the addition of saturated sodium hydrogencarbonate solution (2 mL). The aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica, 3:7 EtOAc/hexanes) affording compound **25** as an oil. Yield (0.030 g, 50%). δ_H (300 MHz, $CDCl_3$) 2.22 (1H, d, J=15 Hz, ArCH), 2.75 (1H, d, J=15 Hz, ArCH), 3.08 (1H, d, J=15 Hz, ArCH), 3.25 (1H, d, J=15 Hz, ArCH), 3.30–3.40 (1H, m, C3a–H), 3.45–3.55 (1H, m, C3–H), 3.76 (3H, s, OCH_3), 3.86–3.95 (15H, m, OCH_3), 4.08 (1H, t, J=9 Hz, C3–H), 4.50 (1H, br s, C4–H), 6.0 (2H, s, O–CH_2–O), 6.35 (2H, s, ArH), 6.46 (1H, d, J=9 Hz, ArH), 6.65 (2H, d, J=4 Hz, ArH), 6.75 (1H, d, J=9 Hz, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 182.7, 153.3, 153.1, 152.4, 148.3, 146.4, 141.4, 137.1, 135.0, 132.3, 131.4, 122.2, 120.6, 108.3, 108.1, 107.0, 101.4, 71.7, 61.6, 61.2, 61.1, 56.3, 56.2, 51.2, 45.4, 42.3, 41.1, 39.0, 24.0, 21.3 ppm; ν_{max} 2938, 1763, 1590, 1488, 1462 cm^{-1}; *m/z* (CI); 596 ($[M+NH_4]^+$, 50%), 578 (M^+, 40%). APCI 579 (30%), 491 (30%), 458 (100%), 411 (65%). HRMS (APCI) $C_{32}H_{34}O_{10}$ ($[M+H]^+$) requires: 579.2225; found: 579.2225.

4.1.13. (3a*S,4*S**,9a*R**)-4-(Benzo-1,3-dioxol-5-yl)-5,6,7-trimethoxy-9a-hydroxy-3a,4,9,9a-tetrahydro-naphtho-[2,3-*c*]furan-1(3*H*)-one, 18.** To a stirred solution of **17** (0.067 g, 0.17 mmol) in THF (5 mL) was added potassium hexamethyldisilazide (0.034 mL, 0.17 mmol of a 2.0 M soln in THF), at −78 °C. After 1 h at 78 °C a solution of (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (0.085 g, 0.37 mmol) in THF (1 mL) was added dropwise by syringe before stirring for a further 3 h. The reaction was quenched by the addition of saturated ammonium chloride solution (5 mL), the phases separated, and the aqueous phase extracted repeatedly with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the crude residue residue chromatographed (3:7 ethyl acetate/hexanes) affording the title compound as a colourless viscous oil. Yield 0.046 g (67%). R_f 0.25 (3:7 EtOAc/hexanes). δ_H (300 MHz, $CDCl_3$) 2.88 (1H, d, J=2 Hz, OH), 2.95 (1H, dd, J=13, 1 Hz, C9–H), 3.12 (1H, d, J=13 Hz, C9–H), 3.48–3.55 (1H, m, C3a–H), 3.62 (1H, dd, J=9, 7 Hz, C3–H), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.58 (1H, d, J=2 Hz, C4–H), 4.68 (1H, t, J=9 Hz, C3–H), 5.95 (2H, apparent t, J=2 Hz, OCH_2O), 6.54 (1H, s, ArH), 6.75–80 (3H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 180.4, 153.2, 152.1, 148.1, 146.3, 141.5, 135.1, 128.8, 122.6, 120.7, 108.5, 108.3, 108.2, 101.2, 71.4, 61.4, 61.1, 56.2, 49.6, 46.5, 43.0, 41.0, 38.8 ppm; ν_{max} (evaporated film) 3458 (br), 2960, 1772 (s), 1646, 1600, 1489 cm^{-1}; *m/z* (EI); 414 (M^+, 5%), 398 (5%), 108 (60%); *m/z* (CI); 432 ($[M+NH_4]^+$, 50%), 231 (100%). HRMS (CI) $C_{22}H_{26}NO_8$ ($[M+NH_4]^+$) requires: 432.1662; found: 432.1653.

4.1.14. (1*S,3a*S**,4*S**,9a*R**)-4-(Benzo-1,3-dioxol-5-yl-5,6,7-trimethoxy)-3,3a,4,9-tetrahydronaphtho[2,3-*c*]-furan-1,9a-diol, 19.** To a solution of **18** (0.030 g, 0.072 mmol) in anhydrous THF (1 mL) was added lithium aluminium hydride (0.072 ml, 0.072 mmol, 1.0 M in THF) at 0 °C. After 15 min the reaction was quenched by the addition of saturated aqueous sodium potassium tartrate solution (1 mL) and diluted with ethyl acetate (10 mL).

The organic layer was separated and the aqueous phase extracted repeatedly with ethyl acetate (3×5 mL). The combined organic extracts were washed (brine; 10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (silica; 2:3 ethyl acetate/hexanes) affording the title compound as a colourless, viscous oil. Yield 0.026 g (87%). δ_H (300 MHz, $CDCl_3$) 2.80 (1H, d, J=13 Hz, C9–H), 2.93 (1H, dd, J=13, 1 Hz, C9–H), 3.02 (1H, td, J=8.5, 2 Hz, C3a–H), 3.17 (1H, apparent triplet, J=9 Hz, C3–H), 3.76 (3H, s, OCH_3), 3.89 (6H, 2×overlapping s, OCH_3), 4.35 (1H, apparent t, J=9 Hz, C3–H), 4.40 (1H, br s, C4–H), 4.62 (1H, s, C1–H), 5.95 (2H, s, OCH_2O), 6.54 (1H, s, ArH), 6.67 (1H, ddd, J=8, 2, 1 Hz ArH), 6.74 (1H, d, J=8 Hz, ArH), 6.74–6.76 (1H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 153.3, 151.8, 149.4, 145.9, 141.3, 135.2, 127.4, 123.5, 120.7, 108.6, 108.3, 108.1, 101.2, 101.1, 69.5, 61.2, 61.1, 56.2, 51.0, 46.5, 40.0, 37.8 ppm; ν_{max} (evaporated film) 3449 (br), 2945, 1659, 1639, 1475, 1372 cm^{-1}; *m/z* (CI); 434 ($M+NH_4^+$, 30%), 416 (M^+, 30%), 221 (40%), 161 (100%). HRMS (CI) $C_{22}H_{28}NO_8$ ($[M+NH_4]^+$) requires: 434.1809; found: 434.1796.

4.1.15. (3a*S,4*S**,9*R**,9a*S**)-4-(1,3-Benzodioxol-5-yl)-9,9a-dihydroxy-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 20.** To a solution of **15** (0.050 g, 0.126 mmol) in anhydrous pyridine (2 mL) was added OsO_4 (0.038 g, 0.15 mmol, 1.2 equiv) (CARE) at room temperature. The solution was allowed to stir overnight and was then quenched by the addition saturated aqueous sodium sulfite (10 mL) and left to stir at ambient temperature for 3 h. Ether (20 mL) was then added and the organic phase was separated, washed [satd sodium sulfite (5 mL), copper (II) sulfate (5 mL) then and brine (5 mL)], dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue (silica; 4:5 ethyl acetate/hexanes) afforded the title compound as an off-white crystalline compound. Yield 0.035 g (65%), mp 152–154 °C (from DCM–hexanes). δ_H (300 MHz, $CDCl_3$) 2.81 (1H, br s, OH), 3.25 (1H, td, J=9, 2 Hz, C3a–H), 3.54 (3H, s, C5–OMe), 3.86 (3H, s, C6–OMe), 3.92 (3H, s, C7–OMe), 3.93 (1H, t J=8 Hz, C3–H), 4.28 (1H, d, J=2 Hz, C4–H), 4.70 (1H, t, J=9 Hz, C3–H), 4.80 (1H, s, C9–H), 5.95, (2 H, s, OCH_2O), 6.62 (1H, dd, J=8, 1.5 Hz, ArH), 6.73 (1H, d, J=8 Hz, ArH), 6.75 (1H, d, J=2 Hz, ArH), 6.88 (1H, s, ArH); δ_C (75 MHz, $CDCl_3$) 40.5, 46.9, 56.3, 60.8, 60.9, 69.8, 71.5, 75.2, 101.4, 108.1, 108.4, 108.5, 120.7, 122.7, 129.9, 139.0, 143.1, 146.5, 148.2, 152.1, 153.6, 177.8 ppm; ν_{max} (evaporated film) 3368, 1709 (s), 1504, 1491, 1449, 1251 cm^{-1}; *m/z* (EI) 430 (M^+, 98%), 412 (20%), 395 (30%), 313 45%); *m/z* (CI) 448 ($[M+NH_4]^+$). HRMS (CI) $C_{22}H_{26}NO_9$ ($[M+NH_4]^+$) requires: 448.1602; found: 448.1605.

4.1.16. Isolation of osmate ester 20′. To a stirred solution of **15** (0.050 g, 0.13 mmol) in anhydrous pyridine (2 mL) was added OsO_4 (0.038 g, 0.15 mmol, 1.2 equiv) (CARE) at room temperature. This solution was allowed to stir overnight at 20 °C and then the reaction was quenched by the addition of a saturated aqueous solution of sodium sulfite (10 mL) and ethyl acetate (10 mL). The organic phase was separated then washed with sodium sulfite (5 mL), brine (5 mL) and dried (MgSO4). Removal of the solvent in vacuo afforded the crude osmate ester **20′** as a brown amorphous solid. Attempted purification of **20′** by column chromatography led to its partial decomposition. Crude yield 0.072 g (87%). δ_H (300 MHz, $CDCl_3$) 8.89 (4H, apparent t, J=5 Hz, py), 7.92 (2H, apparent q, J=7 Hz, py), 7.53 (4H, apparent q, J=8 Hz, py), 6.98 (1H, d, J=2 Hz, ArH), 6.85 (1H, dd, J=8, 2 Hz, ArH), 6.72 (1H, d, J=8 Hz, ArH), 5.94 (1H, d, J=1.5 Hz, OCH_2O), 5.90 (1H, d, J=1.5 Hz, OCH_2O), 5.65 (1H, s, ArCHO), 4.78 (1H, dd, J=10, 6 Hz, C3–H), 4.28 (1H, dd, J=9, 2.5 Hz, C3–H), 4.25 (1H, d, J=5 Hz, C4–H), 3.91 (3H, s, OMe), 3.82 (3H, s, OMe), 3.38 (3H, s, OMe), 3.25–3.30 (1H, m, C3a–H) ppm; δ_C (75 MHz, $CDCl_3$) 175.5, 153.1, 151.7, 150.0, 149.9, 147.7, 145.7, 143.2, 141.8, 141.1, 141.0, 129.9, 125.7, 125.6, 124.7, 121.7, 109.3, 109.1, 107.8 100.9, 91.3, 90.5, 74.7, 60.8, 60.4, 56.1, 46.6, 46.1 ppm; ν_{max} (evaporated film) 2937, 1774, 1608, 1486, 1413, 1245, 1035, 838 cm^{-1}.

4.1.17. (3a*R,4*S**,9*S***R**,9a*R**)-4-(1,3-Benzodioxol-5-yl)-9-hydroxy-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 21a,b.** A dry Schlenck tube was charged with **15** (0.030 g, 0.070 mmol and 'wet' THF (1 mL) and the resulting solution degassed (three times using freeze–thaw cycle) to which was added, by syringe, a 0.1 M solution SmI_2 in THF (1.5 ml, 0.15 mmol, 3 equiv). The deep blue solution of Sm(II) was immediately discharged, turning first to a red and then a pale-yellow coloured solution within 5 min. This solution was allowed to stir for a further 30 min at 20 °C and then quenched by the addition of water (20 mL). The organic layer was separated, the aqueous layer extracted (EtOAc, 2×20 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue (silica; 100% ethyl acetate) afforded the title compound (3:1 mixture of diastereoisomers) as an off-white crystalline solid. Yield 0.025 g (86%), mp 138–140 °C (from DCM–hexanes). Major isomer, **21a**: δ_H (300 MHz, $CDCl_3$) 3.31 (1H, dd, J=9, 2.5 Hz, C9a–H), 3.40–3.50 (1H, m, C3a–H), 3.62 (3H, s, OMe), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 4.15 (1H, dd, J=9, 5 Hz, C3–H), 4.35 (1H, d. J=2.5 Hz), 4.59 (1H, dd, J=9, 7.5 Hz, C3–H), 5.01 (1H, d, J=2.5 Hz, C9–H), 5.95 (2 H, s, OCH_2O), 6.62 (1H, br d, J=7 Hz, ArH), 6.74 (1H, d, J=7 Hz, ArH), 6.77 (2H, 2×overlapping s, ArH); δ_C (75 MHz, $CDCl_3$) 177.0, 153.4, 152.3, 152.2, 148.4, 146.6, 139.4, 143.1, 131.5, 122.7, 120.4, 108.5, 108.4, 101.4, 73.8, 69.2, 61.0, 60.9, 56.3, 46.8, 40.8, 39.6 ppm; ν_{max} (evaporated film) 3418, 2915, 1775, 1501, 1487, 1243, 1122, 1036 cm^{-1}; *m/z* (ES^+) 437 (100%). HRMS (ES^+) $C_{22}H_{22}NaO_8$ ($[M+Na]^+$) requires 437.1207; found: 437.1200. Minor isomer **21b** exhibits resonances at δ_H (300 MHz, $CDCl_3$) 6.86 (1H, s, ArH), 4.76 (1H, br s, C9–H), 4.70 (1H, t, J=9 Hz, C3–H), 4.30 (1H, d, J=2 Hz, C4–H), 3.86–3.96 (1H, m, C3–H), 3.57 (3H, s, OMe); ν_{max} (evaporated film) 1769 cm^{-1}.

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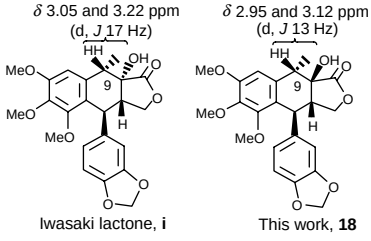
19. (a) Paquette, L. A.; Hong, F.-T. *J. Org. Chem.* **2003**, *68*, 6905–6918. Clive, D. L. J.; Manning, H. W.; Boivin, T. L. B. *J. Chem. Soc., Chem. Commun.* **1990**, 972–974. Mostler, U.; Urban, E. *Monatshefte für Chemie* **1989**, *120*, 349–355. For exceptions see: Glinski, M. B.; Freed, J. C.; Durst, T. *J. Org. Chem.* **1987**, *52*, 2749–2753. Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem.* **2000**, *65*, 847–860. Gensler, W. J.; Gatsoni, C. D. *J. Org. Chem.* **1966**, *31*, 4004–4008. (b) Iwasaki et al.[22] have prepared the isomeric lactone **i**



whose spectral data exhibits minor, yet significant, differences compared to that for lactone **18**.

20. cf. Nishibe, S.; Tsukamoto, H.; Hisada, S.; Yamanouchi, S.; Takido, M. *Chem. Pharm. Bull.* **1981**, *29*, 2082–2085.
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23. (a) Criegee, R.; Marchand, B.; Wannowius, H. *Ann.* **1942**, *550*, 99–133. See also: Hashimoto, S.-I.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670–3672. (b) Sarett, L. H. *J. Am. Chem. Soc.* **1948**, *70*, 1454–1458.

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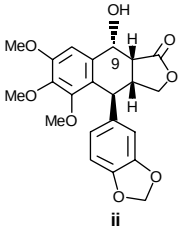
25. Tobinaga et al.[16] previously reported the isolation of a compound assigned as **ii**, which has identical spectroscopic data to **21a**. We tentatively suggest, on the basis of NOE and other data, that its structure be more correctly represented as the 9β-alcohol, **21a** and not the 9α-epimer, **21b**.



ii

26. For a related aldol reaction see: Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902–921.
27. See: Abe, H.; Takeda, S.; Fujita, T.; Nishioka, K.; Takeuchi, Y.; Harayama, T. *Tetrahedron Lett.* **2004**, *45*, 2327–2329 and references therein.
28. Lessene, G.; Feldman, K. S. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 479–538. Quideau, S.; Pouysegu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113–148.
29. Kramer, B.; Averhoff, A.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2981–2982. Mirk, D.; Wibbeling, B.; Fröhlich, R.; Waldvogel, S. R. *Synlett* **2005**, 1970–1974.
30. cf. Tanaka, M.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4161–4164. Eklund, P. C.; Rainer, E. S. *Tetrahedron* **2003**, *59*, 4515–4523.
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32. The ^{1}H NMR spectrum of our sample is in agreement with that previously reported (although stereochemical assignments were not made by these groups): Ishiguro, T.; Mizuguchi, H.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 609–617. Lewis, S. N.; Popper, T. L. *Tetrahedron* **1967**, *23*, 4197–4208. Curiously Coelho's[14] data for this compound does not match that in the literature or that from our study whilst his data for the silylether derivative **13** is identical to that reported here.
33. Ohta, A.; Tonomura, Y.; Sawaki, J.; Sato, N.; Akiike, H.; Ikuta, M.; Shimazaki, M. *Heterocycles* **1991**, *32*, 965–973.

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Reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of strong CH-acids: one-pot synthesis of highly functionalized annulated 4*H*-pyrans

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Abstract—The highly reactive 1:1 adduct, produced from the reaction between dialkyl acetylenedicarboxylates and alkyl isocyanides, was trapped by strong cyclic CH-acids such as 4-hydroxy-6-methyl-2*H*-pyran-2-one or 4-hydroxycoumarin to yield dialkyl 2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylates or dialkyl 7-methyl-2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3,4-dicarboxylates in good yields at room temperature.

1. Introduction

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity.[1] One of the ways to fulfill these goals is the development and use of multicomponent reactions, which consist of several simultaneous bond-forming reactions and allow the highly efficient synthesis of complex molecules starting from simple substrates in a one-pot manner.[2] Multicomponent reactions (MCRs), which can produce a diversity of compounds, provide one of the most efficient methods for the combinatorial synthesis of compound sortiments.[3] Multicomponent reactions can also lead to an increase in molecular complexity by combining a series of reactions in one synthetic operation.[4]

In recent years, isocyanide-based multicomponent condensation reactions (IMCRs) by virtue of their synthetic potential, their inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity, have attracted much attention because of the advantages that they offer to the field of combinatorial chemistry.[5,6]The fact that complex products can be formed in a single operation by simultaneous reactions of several reagents has caused IMCRs to be among the most powerful methods for the synthesis of organic molecules.[7]

It has been shown that alkyl or aryl isocyanides add to dialkyl acetylenedicarboxylates to generate zwitterionic species, which serve as intermediates in many different reactions.[8–11] Recently, these highly reactive zwitterionic intermediates have been captured by suitable CH–,[9] NH–,[10] and OH–acids[11] substrates such as 3-methylcyclopentane-1,2,4-trione,[9d] maleimide[10b] and naphthol,[11a] which produced tetrahydrocyclopenta[*b*]pyrans, 2-aminofuranes and benzochromene derivatives, respectively.

Continuing our interest in isocyanide-based multicomponent reactions,[12] involving electron deficient acetylenic esters,[13] and 4-hydroxycoumarin or 4-hydroxy-6-methyl-2*H*-pyran-2-one[12d,f] we disclose herein three-component reactions, starting from simple and readily available precursors affording products containing highly functionalized annulated 4*H*-pyrans as an expanded paper that includes more results to another report.[9e] Addition of the zwitterionic intermediate generated from alkyl isocyanides **1** and dialkyl acetylenedicarboxylates **2** to 4-hydroxy-6-methyl-2*H*-pyran-2-one or 4-hydroxycoumarin **3** afforded the annulated 4*H*-pyrans **4** in good yields. The reaction can be represented as in Scheme 1.

2. Results and discussion

The one-pot three-component condensation reactions of alkyl isocyanides **1** with dialkyl acetylenedicarboxylates **2** in the presence of 4-hydroxy-6-methyl-2*H*-pyran-2-one or

Keywords: Acetylenic ester; Annulated 4*H*-pyran; CH-acid; Isocyanide; Multicomponent reaction.
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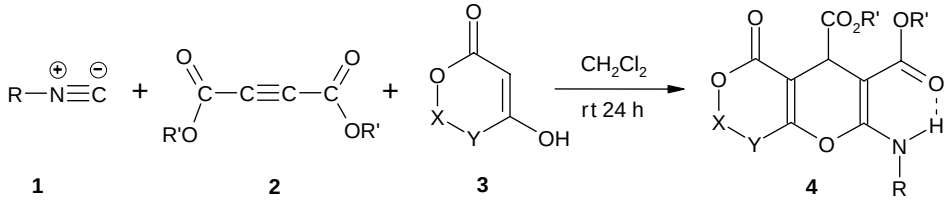


R

1a *tert*-Butyl
1b Cyclohexyl
1c 2-Morpholinoethyl
1d 1,1,3,3-Tetramethylbutyl

R'

2a Methyl
2b Ethyl

X-Y

3a
3b

	X-Y	R'	R	Yield (%)
4a		Methyl	*tert*-Butyl	71
4b		Methyl	Cyclohexyl	64
4c		Methyl	2-Morpholinoethyl	74
4d		Ethyl	Cyclohexyl	62
4e		Ethyl	1,1,3,3-Tetramethylbutyl	58
4f		Methyl	*tert*-Butyl	88
4g		Methyl	Cyclohexyl	78
4h		Methyl	2-Morpholinoethyl	63
4i		Ethyl	*tert*-Butyl	90
4j		Ethyl	1,1,3,3-Tetramethylbutyl	55

Scheme 1.

4-hydroxycoumarin **3** proceeded spontaneously at room temperature in dichloromethane and were complete after 1 day to afford corresponding dialkyl 2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylates or dialkyl 7-methyl-2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano-[4,3-*b*]pyran-3,4-dicarboxylates **4**, in moderate to good yields (55–90%). ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of annulated 4*H*-pyrans **4**. No product other than **4** could not be detected by NMR spectroscopy. The structures of the products **4a–j** were deduced from their elemental analyses and IR, ^{1}H and ^{13}C NMR spectra.

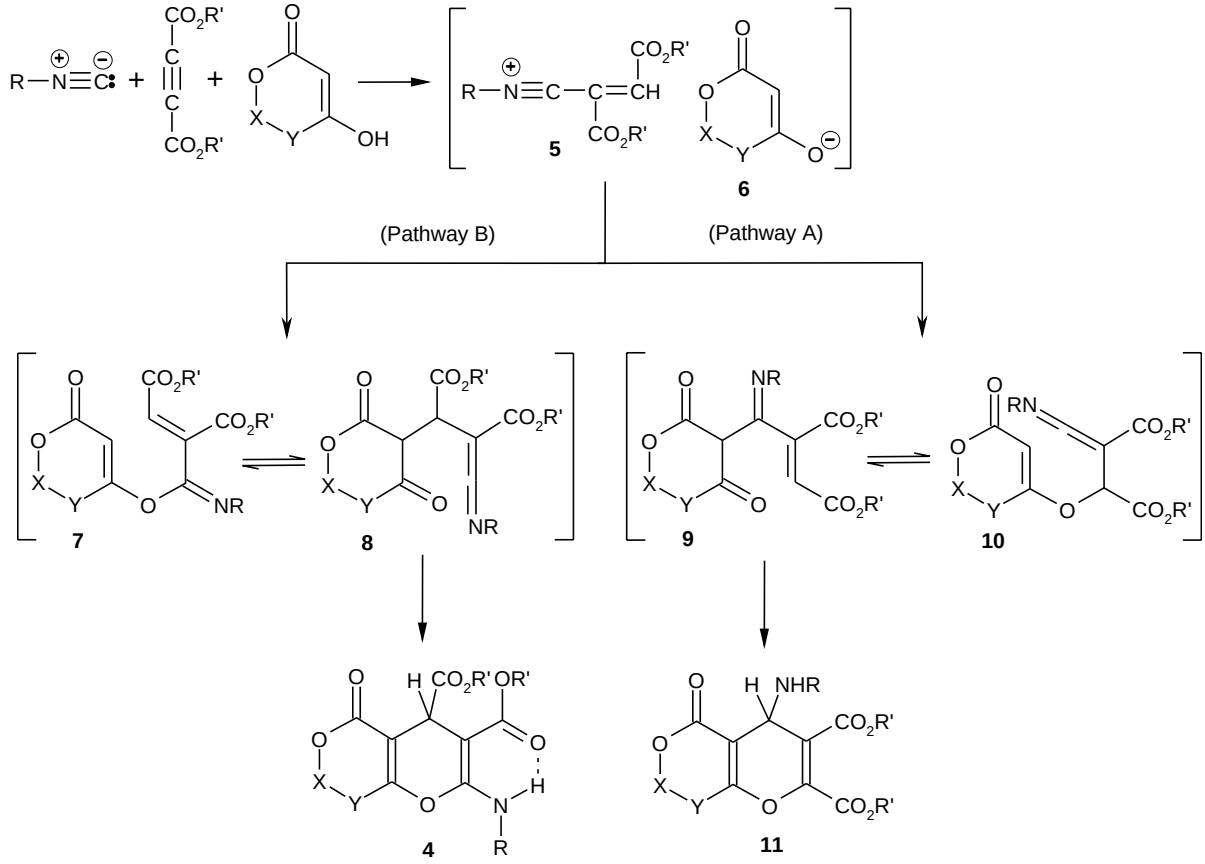
The ^{1}H NMR spectrum of **4a** exhibited six single sharp lines readily recognized as arising from *tert*-butyl (δ 1.40 ppm), methyl (δ 2.25 ppm), two methoxy protons (δ 3.67 and 3.68 ppm), allylic methine (δ 4.54 ppm) and olefinic methine (δ 5.93 ppm). A fairly broad singlet (δ 8.75 ppm) was observed for the NH group. The presence of an amine proton was confirmed by exchange with D_2O. The chemical shift of the NH group indicates that this moiety must have participated in a six-membered intramolecular hydrogen bond formation with the vicinal carbonyl group as shown in Scheme 1.

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the suggested structure. Partial assignment of these resonances is given in Section 3.

The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **4a** was supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorptions at 1724, 1676 and 1615 cm^{-1} due to the carbonyls and the amino group at 3220 cm^{-1} as a weak broad band.

The ^{1}H and ^{13}C NMR spectra of **4b–j** are similar to those of **4a** and the results are summarized in Section 3. Although the mechanism of this reaction has not been established experimentally, the formation of these heterocycles can be rationalized by initial Michael-type addition[14] of the isocyanide to the acetylenic ester and subsequent protonation of the highly reactive 1:1 zwitterionic intermediate by strong CH-acid leads to vinylisonitrilium cation **5**, which could have undergone addition reactions with bidentate enolate anion **6** on two possible electrophilic sites to produce four possible intermediates **7–10**. Adducts **7** and **8**, as well as, **9** and **10** can be interconverted by Claisen rearrangement. Intermediates **8** and **9** can be cyclized under the reaction conditions employed to produce the annulated 4*H*-pyrans **4** and **11**, respectively (Scheme 2). Since the ^{1}H NMR signal of the allylic saturated methine proton exhibited a sharp singlet in different solvents, the structure **11**, which is expected to show vicinal coupling for the HC–NH moiety, is excluded. Moreover, the ^{1}H and ^{13}C chemical shifts of the allylic methine group are in better agreement with the structure **4**. Interestingly, it has been found that this reaction is highly chemoselective in the preparation of fused heterocyclic enaminoester **4**, since no other detectable product is formed under the described reaction conditions.

In conclusion, we have found that the one-pot three-component chemoselective reaction of isocyanides, with



Scheme 2.

dialkyl acetylenedicarboxylate in the presence of relatively strong cyclic CH-acids such as 4-hydroxy-6-methyl-2*H*-pyran-2-one or 4-hydroxycoumarin leads to a facile synthesis of highly functionalized dialkyl 2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylates or dialkyl 7-methyl-2-(alkylamino)-5-oxo-4*H*,5*H*-pyrano-[4,3-*b*]pyran-3,4-dicarboxylates **4** in good yields, respectively. The present method has advantages that, not only the reaction is performed under neutral conditions, but the substances can be mixed without any activation or modification.

3. Experimental

3.1. General

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR Spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, respectively. NMR spectra were obtained by solutions made in $CDCl_3$. The solvents, strong CH-acids, dialkyl acetylenedicarboxylates, cyclohexyl and 1,1,3,3-tetramethylbutyl isocyanides used in this work were purchased from Merck and the *tert*-butyl and 2-morpholinoethyl isocyanides were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

3.1.1. Typical procedure for preparation of dimethyl 7-methyl-2-(*tert*-butylamino)-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]-pyran-3,4-dicarboxylate (4a). To a magnetically stirred solution of 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.127 g, 1.0 mmol) and dimethyl acetylenedicarboxylate (0.143 g, 1.0 mmol) in dichloromethane (40 mL) was added dropwise a mixture of *tert*-butyl isocyanide (0.084 g, 1.0 mmol) in dichloromethane (10 mL) at room temperature over 10 min via a syringe. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under vacuum and the solid residue was washed with diethyl ether and crystallized from CH_2Cl_2–*n*-hexane (1/2) to give **4a** as white crystals (0.250 g, 71%); mp 183–185 °C; IR (KBr) (ν_{max}, cm^{-1}): 3220 (N–H), 1724, 1676 and 1615 (C=O), 1604 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.40 (9H, s, $C(CH_3)_3$), 2.25 (3H, s, =C—CH_3), 3.67 and 3.68 (6H, 2s, $2OCH_3$), 4.54 (1H, s, CH), 5.93 (1H, s, =CH), 8.76 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 20.02 (CH_3), 30.55 ($2CMe_3$), 35.52 (CH), 51.17 (CMe_3), 52.56 and 52.89 ($2OCH_3$), 72.95 (*C*=C–N), 98.16 (*C*H=C—CH_3), 99.86 (C=*C*–CH), 159.04, 159.69, 162.41, 162.76, 169.43 and 173.29 (3C=O, 2O–*C*=C and =*C*–N). Anal. Calcd for $C_{17}H_{21}NO_7$ (351.35): C, 58.11; H, 6.02; N, 3.99%. Found: C, 58.20; H, 5.96; N, 3.95%.

3.1.2. Dimethyl 7-methyl-2-(cyclohexylamino)-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3,4-dicarboxylate (4b). Cream crystals (0.242 g, 64%); mp 118–120 °C; IR (KBr) (ν_{max}, cm^{-1}): 3245 (N–H), 1719, 1682 and 1612 (C=O), 1603 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.24–2.18 (10H, m,

5CH_2), 2.23 (3H, s, =C—CH_3), 3.66 and 3.67 (6H, 2s, 2OCH_3), 3.75 (1H, m, N–CH), 4.51 (1H, s, CH), 5.93 (1H, s, =CH), 8.61 (1H, d, $^3J_{HH}$=6.2 Hz, NH···O=C). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 19.99 (CH_3), 24.41, 25.36, 32.10, 33.50 and 33.77 (5CH_2), 35.71 (CH), 50.13 (N–CH), 51.10 and 52.56 (2OCH_3), 72.00 (*C*=C–N), 98.33 (*C*H=C—CH_3), 99.80 (C=*C*–CH), 158.34, 159.73, 162.49, 162.63, 169.35 and 173.48 (3C=O, 2O–*C*=C and =*C*–N). Anal. Calcd for $C_{19}H_{23}NO_7$ (377.38): C, 60.47; H, 6.14; N, 3.71%. Found: C, 60.55; H, 6.20; N, 3.69%.

3.1.3. Dimethyl 7-methyl-2-[(2-morpholinoethyl)amino]-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3,4-dicarboxylate (4c). Cream crystals (0.303 g, 74%); mp 154–156 °C; IR (KBr) (ν_{max}, cm^{-1}): 3220 (N–H), 1722, 1687 and 1662 (C=O), 1619 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 2.23 (3H, s, =C—CH_3), 2.49 (4H, m, CH_2NCH_2), 2.55 (2H, t, $^3J_{HH}$= 5.6 Hz, NCH_2), 3.45 (2H, d of t, $^3J_{HH}$=5.6, 5.0 Hz, NHCH_2), 3.66 and 3.67 (6H, 2s, 2OCH_3), 3.71 (4H, m, CH_2OCH_2), 4.51 (1H, s, CH), 5.92 (1H, s, =CH), 8.73 (1H, t, $^3J_{HH}$=5.0 Hz, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 20.02 (CH_3), 35.81 ($NHCH_2$), 37.76 (CH), 51.15 and 52.56 (2OCH_3), 53.37 (CH_2NCH_2), 57.34 (NCH_2), 66.80 (CH_2OCH_2), 72.77 (*C*=C–N), 98.21 (*C*H=C—CH_3), 99.79 (C=*C*–CH), 158.56, 159.24, 162.37, 162.66, 169.00 and 173.46 (3C=O, 2O–*C*=C and =*C*–N). Anal. Calcd for $C_{19}H_{24}N_2O_8$ (408.40): C, 55.88; H, 5.92; N, 6.86%. Found: C, 56.00; H, 6.01; N, 6.83%.

3.1.4. Diethyl 7-methyl-2-(cyclohexylamino)-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3,4-dicarboxylate (4d). Cream crystals (0.252 g, 62%); mp 139–141 °C; IR (KBr) (ν_{max}, cm^{-1}): 3260 (N–H), 1730, 1680 and 1636 (C=O), 1609 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.22–2.21 (10H, m, 5CH_2), 1.24 and 1.25 (6H, 2t, $^3J_{HH}$=7.0 Hz, 2OCH_2CH_3), 2.24 (3H, s, =C—CH_3), 3.63 (1H, m, N–CH), 4.08–4.25 (4H, m, 2ABX_3 overlapping systems, 2O*C*$H_2$$CH_3$), 4.52 (1H, s, CH), 5.93 (1H, s, =CH), 8.65 (1H, br s, NH··· O=C). ^{13}C NMR ($CDCl_3$): δ_C 14.18 and 14.43 (2OCH_2CH_3), 19.97 (CH_3), 24.45, 25.39, 32.36, 33.53 and 33.81 (5CH_2), 35.97 (CH), 50.12 (N–CH), 59.74 and 61.29 (2OCH_2), 72.18 (*C*=C–N), 98.35 (*C*H=C—CH_3), 99.90 (C=*C*–CH), 158.25, 159.36, 162.49, 162.57, 169.07 and 173.37 (3C=O, 2O–*C*=C and =*C*–N). Anal. Calcd for $C_{21}H_{27}NO_7$ (405.44): C, 62.21; H, 6.71; N, 3.45%. Found: C, 60.24; H, 6.65; N, 3.49%.

3.1.5. Diethyl 7-methyl-2-[(1,1,3,3-tetramethylbutyl)-amino]-5-oxo-4*H*,5*H*-pyrano[4,3-*b*]pyran-3,4-dicarboxylate (4e). White crystals (0.253 g, 58%); mp 120–122 °C; IR (KBr) (ν_{max}, cm^{-1}): 3231 (N–H), 1733, 1680 and 1648 (C=O), 1606 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 0.97 (9H, s, $C(CH_3)_3$), 1.22 and 1.24 (6H, 2t, $^3J_{HH}$=7.1 Hz, 2OCH_2CH_3), 1.42 and 1.43 (6H, 2s, $C(CH_3)_2$), 1.69 (2H, s, CH_2), 2.25 (3H, s, =C—CH_3), 4.08–4.18 (4H, m, 2ABX_3 overlapping systems, 2O*C*$H_2$$CH_3$), 4.53 (1H, s, CH), 5.91 (1H, s, =CH), 8.83 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 14.16 and 14.41 (2OCH_2CH_3), 20.01 (CH_3), 31.22 (*C*Me_3), 31.42 (C*Me*$_3$), 31.66 (C*Me*$_2$), 35.80 (CH), 53.57 (CH_2), 56.37 (*C*Me_2), 59.76 and 61.24 (2OCH_2), 72.76 (*C*=C–N), 98.13 (*C*H=C—CH_3), 99.97 (C=*C*–CH), 159.00, 159.44, 162.51, 162.71, 169.13 and 173.05 (3C=O, 2O–*C*=C and =*C*–N). Anal. Calcd for $C_{23}H_{33}NO_7$ (435.51): C, 63.43; H, 7.64; N, 3.22%. Found: C, 63.50; H, 7.59; N, 3.25%.

3.1.6. Dimethyl 2-(*tert*-butylamino)-5-oxo-4*H*,5*H*-pyrano-[3,2-*c*]chromene-3,4-dicarboxylate (4f). Pale yellow crystals (0.341 g, 88%); mp 214–216 °C; IR (KBr) (ν_{max}, cm^{-1}): 3225 (N–H), 1726, 1681 and 1643 (C=O), 1607 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.53 (9H, s, $C(CH_3)_3$), 3.69 and 3.73 (6H, 2s, 2OCH_3), 4.73 (1H, s, CH), 7.35–7.84 (4H, m, arom.), 8.99 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 30.55 (2C*Me*$_3$), 36.11 (CH), 51.24 (*C*Me_3), 52.61 and 52.85 (2OCH_3), 72.88 (*C*=C–N), 103.04 (=*C*–CH), 113.50, 117.17, 122.32, 124.32, 132.68 and 152.71 (six arom. carbons), 154.97 (*C*=C–CH), 159.55, 160.64, 169.43 and 172.94 (3C=O and =*C*–N). Anal. Calcd for $C_{20}H_{21}NO_7$ (387.38): C, 62.01; H, 5.46; N, 3.62%. Found: C, 61.90; H, 5.40; N, 3.66%.

3.1.7. Dimethyl 2-(cyclohexylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylate (4g). White crystals (0.323 g, 78%); mp 199–201 °C; IR (KBr) (ν_{max}, cm^{-1}): 3250 (N–H), 1731, 1690 and 1662 (C=O), 1603 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.14–2.05 (10H, m, 5CH_2), 3.66 and 3.70 (6H, 2s, 2OCH_3), 3.84 (1H, m, N–CH), 4.68 (1H, s, CH), 7.22–7.79 (4H, m, arom.), 8.68 (1H, br s, NH··· O=C). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.45, 25.39, 32.05, 33.46 and 33.73 (5CH_2), 36.30 (CH), 50.65 (N–CH), 51.20 and 52.67 (2OCH_3), 72.13 (*C*=C–N), 102.97 (=*C*–CH), 113.59, 117.08, 121.94, 124.62, 132.47 and 152.75 (six arom. carbons), 154.89 (*C*=C–CH), 158.26, 160.67, 169.30 and 173.09 (3C=O and =*C*–N). Anal. Calcd for $C_{22}H_{23}NO_7$ (413.42): C, 63.91; H, 5.61; N, 3.39%. Found: C, 64.02; H, 5.65; N, 3.44%.

3.1.8. Dimethyl 2-[(2-morpholinoethyl)amino]-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylate (4h). Cream crystals (0.280 g, 63%); mp 218–220 °C; IR (KBr) (ν_{max}, cm^{-1}): 3195 (N–H), 1730, 1679, 1644 (C=O), 1607 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 2.51 (4H, m, CH_2NCH_2), 2.63 (2H, t, $^3J_{HH}$=5.1 Hz, NCH_2), 3.63 (2H, d of t, $^3J_{HH}$= 5.1, 4.3 Hz, NHCH_2), 3.67 and 3.71 (6H, 2s, 2OCH_3), 3.72 (4H, m, CH_2OCH_2), 4.68 (1H, s, CH), 6.87–7.75 (4H, m, arom.), 8.81 (1H, t, $^3J_{HH}$=4.3 Hz, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 36.43 ($NHCH_2$), 38.13 (CH), 51.24 and 52.68 (2OCH_3), 53.40 (CH_2NCH_2), 57.16 (NCH_2), 66.88 (CH_2OCH_2), 72.78 (*C*=C–N), 102.96 (=*C*–CH), 113.49, 117.06, 122.11, 124.51, 132.77 and 152.72 (six arom. carbons), 154.81 (*C*=C–CH), 158.47, 160.61, 168.91 and 173.10 (3C=O and =*C*–N). Anal. Calcd for $C_{22}H_{24}N_2O_8$ (444.43): C, 59.45; H, 5.44; N, 6.30%. Found: C, 59.54; H, 5.40; N, 6.26%.

3.1.9. Diethyl 2-(*tert*-butylamino)-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylate (4i). White crystals (0.374 g, 90%); mp 192–194 °C; IR (KBr) (ν_{max}, cm^{-1}): 3231 (N–H), 1732, 1684 and 1644 (C=O), 1601 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 1.23 and 1.28 (6H, 2t, $^3J_{HH}$=7.1 Hz, 2OCH_2CH_3), 1.52 (9H, s, $C(CH_3)_3$), 4.11–4.22 (4H, m, 2ABX_3 overlapping systems, 2O*C*$H_2$$CH_3$), 4.71 (1H, s, CH), 7.34–7.83 (4H, m, arom.), 9.01 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 14.16 and 14.46 (2CH_3), 30.60 (2C*Me*$_3$), 36.41 (CH), 51.81 (*C*Me_3), 59.98 and 61.47 (2OCH_2), 73.06 (*C*=C–N),

103.16 (=*C*–CH), 113.62, 117.22, 122.37, 124.61, 132.63 and 152.76 (six arom. carbons), 155.06 (*C*=C–CH), 159.48, 160.85, 169.19 and 172.99 (3C=O and =*C*–N). Anal. Calcd for $C_{22}H_{25}NO_7$ (415.43): C, 63.61; H, 6.07; N, 3.37%. Found: C, 63.54; H, 6.04; N, 3.40%.

3.1.10. Diethyl 2-[(1,1,3,3-tetramethylbutyl)amino]-5-oxo-4*H*,5*H*-pyrano[3,2-*c*]chromene-3,4-dicarboxylate (4j). White crystals (0.260 g, 55%); mp 152–154 °C; 3225 (N–H), 1728, 1676 and 1654 (C=O), 1600 (C=C). ^{1}H NMR ($CDCl_3$): δ_H 0.98 (9H, s, $C(CH_3)_3$), 1.23 and 1.28 (6H, 2t, $^3J_{HH}$=7.1 Hz, $2OCH_2CH_3$), 1.54 and 1.57 (6H, 2s, $C(CH_3)_2$), 1.87 (2H, s, CH_2), 4.09–4.23 (4H, m, $2ABX_3$ overlapping systems, $2OCH_2CH_3$), 4.71 (1H, s, CH), 7.35–7.86 (4H, m, arom.), 9.09 (1H, br s, NH···O=C). ^{13}C NMR ($CDCl_3$): δ_C 14.16 and 14.44 ($2OCH_2CH_3$), 31.18 (CMe_3), 31.42 (CMe_3), 31.57 and 31.74 (CMe_2), 36.43 (CH), 53.48 (CH_2), 56.43 (CMe_2), 59.94 and 61.42 ($2OCH_2$), 72.74 (*C*=C–N), 103.28 (=*C*–CH), 113.61, 117.27, 122.38, 124.58, 132.62 and 152.78 (six arom. carbons), 155.07 (*C*=C–CH), 159.43, 160.83, 169.24 and 172.86 (3C=O and =*C*–N). Anal. Calcd for $C_{26}H_{33}NO_7$ (471.54): C, 66.23; H, 7.05; N, 2.97%. Found: C, 66.28; H, 7.00; N, 3.01%.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.039.

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Addition of 2-*tert*-butyldimethylsilyloxythiophene to activated quinones: an approach to thia analogues of kalafungin

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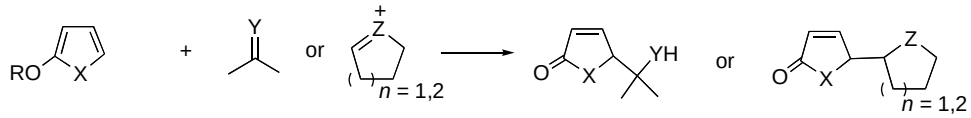
Abstract—The uncatalyzed reaction of 2-*tert*-butyldimethylsilyloxythiophene **2** with 1,4-quinones bearing either an electron withdrawing acetyl or a carbomethoxy group at C-2, was investigated. No reaction was observed using 1,4-quinones **8** and **9** bearing an ester group at C-2 whereas use of 1,4-quinones **10** and **11** bearing an acetyl group at C-2 only provided low yields of the silyloxythiophenes **15** and **16** resulting from electrophilic substitution of the silyloxythiophene by the 1,4-quinone. Use of the Lewis acids $InCl_3$, $Cu(OTf)_2$ and $BF_3 \cdot Et_2O$ were investigated in an effort to improve the yield of the desired annulation reaction. $BF_3 \cdot Et_2O$ proved to be the optimum catalyst for the synthesis of thiolactone naphthofuran adducts **14** and **18** from 1,4-naphthoquinones **9** and **11**, respectively. Reaction of 2-*tert*-butyldimethylsilyloxythiophene **2** with 1,4-benzoquinones **8** and **10** bearing a carbomethoxy or an acetyl group at C-2, respectively, afforded thiolactone benzofuran adducts **13** and **17**, respectively, catalyzed by either $InCl_3$ or $Cu(OTf)_2$. Addition of 2-*tert*-butyldimethylsilyloxythiophene **2** to 3-acetyl-5-methoxy-1,4-naphthoquinone **12** afforded adduct **19** that underwent oxidative rearrangement to thiolactone pyranonaphthoquinone **20** using ceric ammonium nitrate in acetonitrile, thus providing a novel approach for the synthesis of a thia analogue of the pyranonaphthoquinone antibiotic kalafungin.

1. Introduction

The silyl enolate d^4 synthons 2-trimethylsilyloxyfuran (TMSOF) **1**, 2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** and *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole (TBSOP) **3** readily undergo vinylogous aldol-like reactions[1] with aldehydes, vinylogous imino-aldol reactions[2] (Mannich type addition) with imines and vinylogous addition to heteroatom-stablized carbenium ions (Scheme 1).[3] The resultant aldol-like products provide ready access to many bioactive molecules including the Annonaceous acetogenins,[4,5] carbasugars,[6] densely hydroxylated indolizidine alkaloids,[7] hydroxylated prolines,[8] aminosugars[9] and peptidyl *C*-glycosides.[10]

We have studied the reaction of the silyl enolate d^4 synthons, TMSOF **1** and TBSOP **3** with 1,4-benzoquinones and 1,4-naphthoquinones bearing electron withdrawing groups at C-2 in which initial conjugate addition to the quinone is followed by intramolecular cyclization to afford either a furobenzofuran or pyrrolobenzofuran or a furonaphthofuran or pyrrolonaphthofuran, respectively (Scheme 2). This annulation step formed a key step in our synthesis of the pyranonaphthoquinone antibiotic kalafungin[11] and the synthesis of aza analogues[12] thereof, by effecting a facile oxidative cyclization of the initial annulation product.

As an extension to this work, we now herein report the results of our studies on the hitherto unreported addition of



1: X = O; R = $SiMe_3$ Y = O, NH; Z = O, N
2: X = S; R= Si^tBuMe_2
3: X = $NCO_2{}^tBu$; R= Si^tBuMe_2

Scheme 1.

Keywords: Silyloxythiophene; Quinones; Pyranonaphthoquinone antibiotics; Annulation.
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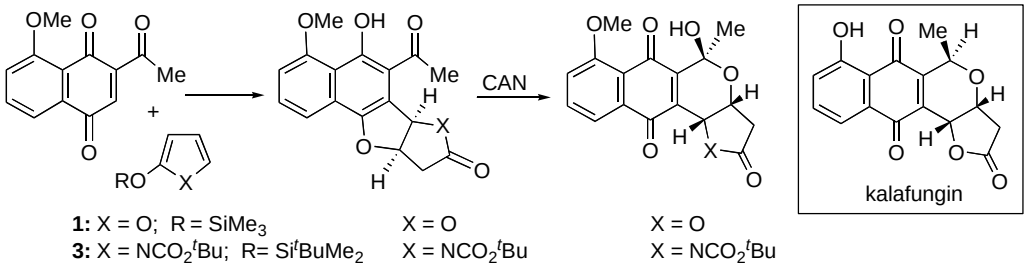


Scheme 2.

2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** to a series of benzoquinones and naphthoquinones bearing either an acetyl group or a carbomethoxy group at C-2. The resultant annulation products would provide access to thia analogues of the kalafungin skeleton that were of interest due to their potential bioactivity as bioreductive alkylating agents.[13]

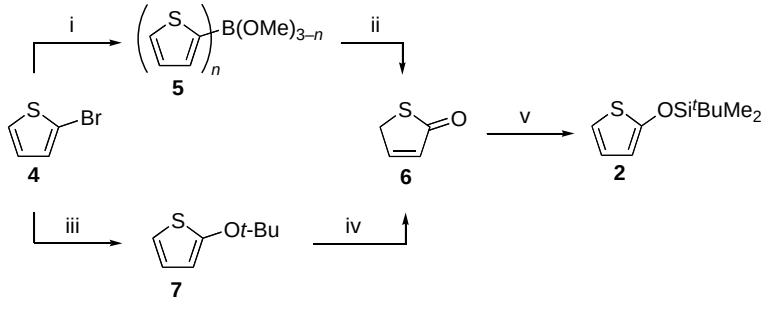
2. Results and discussion

It was proposed that addition of 2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** to 1,4-quinones bearing an electron withdrawing group at C-2 would follow a similar pathway to the addition of TMSOF **1** and TBSOP **3** affording thia analogues of the corresponding furo[3,2-*b*]-benzofuran and furo[3,2-*b*]naphthofuran adducts. Initial synthesis of TBSOT **2** was therefore required.

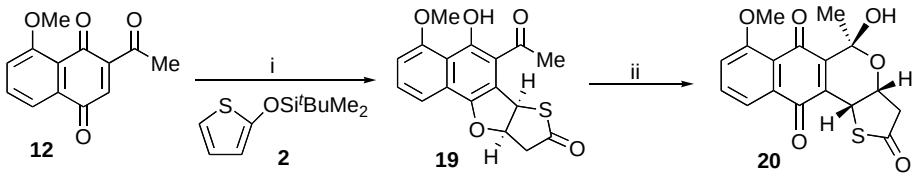
It was envisaged that TBSOT **2** could be prepared from thiolactone **6** using the procedure reported by Casiraghi et al.[14] (Scheme 3). The thiolactone precursor **6** was originally prepared by Hawkins[15] from 2-bromothiophene **4** via the boronate ester **5**. Following the procedure of Hawkins[15] 2-bromothiophene **4** was treated with *n*-butyllithium followed by trimethylborate. Oxidative work-up of the resultant boronate **5**, however, furnished thiolactone **6** in only 26% yield. Frisell and Lawesson[16] reported an alternative procedure for the preparation of thiolactone **6** employing *tert*-butyl ether **7**. Accordingly, the Grignard generated from 2-bromothiophene **4** was treated with *tert*-butyl peroxybenzoate and the resultant *tert*-butyl ether **7** hydrolyzed with *p*-toluenesulfonic acid at 160 °C. Gratifyingly, thiolactone **6** was isolated in 61% yield. Silyl enol ether formation[14] using *tert*-butyldimethylsilyl trifluoromethane sulfonate and 2,6-lutidine proceeded smoothly to furnish TBSOT **2** in 84% yield.

With TBSOT **2** in hand, the conjugate addition reactions to several readily accessible quinones **8**, **9**, **10**, **11**, similar in structure to the quinone precursor **12** required to prepare a thia analogue of kalafungin (Scheme 4), were next investigated (Table 1). Our previous paper describing the addition of silyloxypyrrole **3** to activated quinones reports the syntheses of the quinone starting materials.[12]

It was anticipated that the uncatalyzed addition of TBSOT **2** to 2-carbomethoxyquinones **8** and **9** would provide thiolactone adducts **13** and **14**, respectively. However, after stirring the quinones **8** and **9** with TBSOT **2** at room temperature in acetonitrile for 16 h, no reaction was observed (Table 1). Treatment of the more electron withdrawing 2-acetylquinones **10** and **11** with TBSOT **2** was more encouraging, providing substituted silyloxythiophenes **15** and **16**, arising from direct eletrophilic aromatic

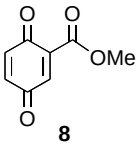
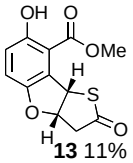
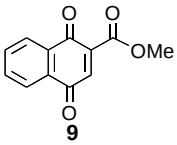
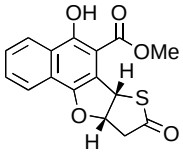
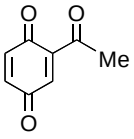
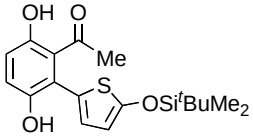
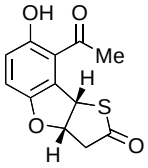
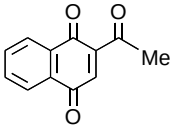
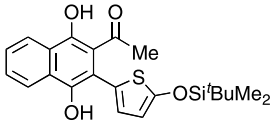
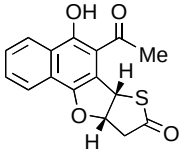


Scheme 3. Reagents and conditions: (i) *n*-BuLi, THF, reflux 1 h then $B(OMe)_3$, 60 °C, 2 h; (ii) H_2O_2, 0 °C to rt, 26% over two steps; (iii) Mg, Et_2O, rt, 3 h, reflux, 0.5 h then $PhCO_2O^tBu$, 0 °C, 12 h; (iv) *p*-TsOH, 160 °C, 10 min, 61% over two steps; (v) $^tBuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 1 h, 84%.



Scheme 4. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 1 h, 45%; (ii) CAN (2.0 equiv), MeCN–H_2O (1:1), 21%.

Table 1. Addition of TBSOT **2** to 1,4-quinones **8**, **9**, **10** and **11**

Quinone	Uncatalyzed[a]	$InCl_3$[b]	$Cu(OTf)_2$[c]	$BF_3 \cdot OEt_2$[d]
 **8**	No reaction	 **13** 11%	**13** 13%	—
 **9**	No reaction	 **14** 27%	**14** 30%	**14** 31%
 **10**	 **15** 35%	 **17** 35%	**17** 22%	—
 **11**	 **16** 11%	 **18** 9%	**18** 33%	**18** 48%

[a] Reactions carried out using **2** (1.1 equiv) in acetonitrile at rt for 16 h.
[b] Reactions carried out using **2** (1.0 equiv) $InCl_3$ (5%) in acetonitrile at rt, 0 °C then rt, 16 h.
[c] Reactions carried out using **2** (1.0 equiv), $Cu(OTf)_2$ (1.0 equiv) in dichloromethane, −78 °C then rt, 2 h.
[d] Reactions carried out using **2** (1.0 equiv), $BF_3 \cdot Et_2O$ (1.1 equiv) in dichloromethane, −78 °C then rt, 1 h.

substitution of the thiophene ring, in 35 and 11% yield, respectively.

Whilst the uncatalyzed addition of TBSOT **2** to the aforementioned quinones **8**, **9**, **10** and **11** failed to furnish the desired thiolactone adducts **13**, **14**, **17** and **18**, it was hoped that use of a Lewis acid to promote the desired annulation reaction would be more fruitful. Yadav et al.[17,18,19,20] and Loh and Wei[21,22] have reported the catalysis of conjugate addition reactions using indium(III) chloride, however, neither group had investigated the use of 2-silyloxythiophenes as nucleophiles or quinones as Michael acceptors. Accordingly, quinones **8**, **9**, **10** and **11** were treated with TBSOT **2** in the presence of indium(III) chloride (5 mol%) in acetonitile at 0 °C. After allowing the reaction mixture to warm to room temperature and stirring for 16 h gratifyingly, the desired corresponding thiolactone adducts **13**, **14**, **17** and **18** were isolated in modest yield after purification by flash chromatography.

In an effort to improve the yields of the desired adducts **13**, **14**, **17** and **18**, the use of an alternative Lewis acid was next investigated. Brimble et al.[23] have employed copper(II) trifluoromethanesulfonate as a Lewis acid in the Michael addition of TMSOF **1** to various chiral naphthoquinones. Following this precedent, a solution of each of the quinones **8**, **9**, **10** and **11** in dichloromethane was added to a suspension of copper(II) trifluoromethanesulfonate (1.0 equiv) in dichloromethane at −78 °C and the resultant mixture then treated with TBSOT **2**. Although the reactions proceeded cleanly to completion, as monitored by thin-layer chromatography, it was nevertheless disappointing to observe no significant improvement in the isolated yields of the desired adducts **13**, **14**, **17** and **18**.

The desired adducts were highly susceptible to degradation upon flash chromatography presumably accounting for the low yields of the isolated products. Efforts to try to improve the stability of the adducts via protection of the free phenol as either an acetate or a *tert*-butyldimethylsilyl ether were unsuccessful, and led only to the formation of a complex mixture of products in both instances. Use of reverse phase HPLC and alumina or florisil as solid supports for chromatography also did not offer any improvement.

Catalysis of the conjugate addition reaction using boron trifluoride etherate was next investigated. Accordingly, a solution of each of the quinones **8**, **9**, **10** and **11** and TBSOT **2** in dichloromethane at −78 °C was treated with boron trifluoride etherate (1.1 equiv). The reaction of benzoquinones **8** and **10** led to the formation of a complex mixture of products, whilst naphthoquinones **9** and **11** afforded thiolactone naphthofurans **14** and **18** in 31 and 48% yield, respectively; possibly reflecting the lower reactivity of the naphthoquinones **9** and **11** compared to the corresponding benzoquinones **8** and **10**.

Having successfully prepared thiolactone naphthofuran **18** in a modest 48% yield using boron trifluoride etherate as a Lewis acid, the synthesis of a thia analogue of kalafungin was next undertaken (Scheme 4). Following the procedure established for the preparation of **18**, a solution of naphthoquinone **12** and TBSOT **2** in dichloromethane at −78 °C was treated with boron trifluoride etherate (1.1 equiv) affording thiolactone naphthofuran **19** in 45% yield. Facile oxidative cyclization of **19** to the desired thiolactone pyranonaphthoquinone **20** using ceric ammonium nitrate proceeded in 21% yield. Use of alternative oxidants was unsuccessful affording none of the desired oxidative cyclization product. Disappointingly, the thia analogue **20** of kalafungin thus prepared was unstable rapidly degrading to a complex mixture of products.

3. Conclusions

In summary, a study of the addition of TBSOT **2** to several electron deficient quinones is reported. Uncatalyzed addition of TBSOP **2** to 1,4-quinones **8** and **9** bearing carbomethoxy substituents at C-2 was unsuccessful whilst use of the 2-acetylquinones **10** and **11** afforded the electrophilic substitution products **15** and **16**, respectively. Use of the Lewis acids $InCl_3$, $Cu(OTf)_2$ and $BF_3 \cdot Et_2O$ to promote the annulation reaction afforded the desired thiolactone adducts **13**, **14**, **17** and **18**. $BF_3 \cdot Et_2O$ proved to be the optimum catalyst for the reaction of TBSOT **2** with the naphthoquinones **9** and **11** to provide adducts **14** and **18**, respectively, whilst $InCl_3$ and $Cu(OTf)_2$ were more effective for the reaction of TBSOT **2** with the benzoquinones **9** and **11** to provide adducts **13** and **17**, respectively. These thiolactone benzofuran and naphthofuran adducts provide novel heterocyclic ring systems that can be further elaborated to provide thia analogues of natural products as demonstrated by the conversion of adduct **19** to a thia analogue **20** of the bioreductive alkylating agent kalafungin.

4. Experimental

4.1. General details

All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere using standard syringe and septum techniques unless otherwise stated. Diethyl ether and tetrahydrofuran were freshly distilled from sodium/benzophenone. Hexane, pentane, dichloromethane, triethylamine and diethylamine were distilled from calcium hydride. Thin-layer chromatography was performed on precoated 0.2 mm Merck Kieselgel 60 F_{254} silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Flash column chromatography was performed using Reidel-de Häen Kieselgel or Merck Kieselgel 60 F (both 230–400 mesh) with the indicated solvents. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Spectrum One Fourier Transform IR spectrophotometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained using either a Bruker DRX-400 spectrophotometer operating at either 400 or 100 MHz or a Bruker Avance 300 spectrometer operating at 300 or 75 MHz, respectively. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard or relative to $CDCl_3$. All J values are given in Hertz. Assignments are made with the aid of DEPT 135, COSY and HSQC experiments. High-resolution mass spectra were recorded using a VG70-SE spectrometer operating at a nominal accelerating voltage of 70 eV. Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Quinones **8**, **9**, **10** and **11** were prepared as described in our previous paper.[12]

4.2. Preparation of 2-(*tert*-butyldimethylsilyloxy) thiophene 2

4.2.1. 3-Thiolen-2-one 6. *Procedure A*. In an adaptation of the procedure used by Hawkins,[15] 2-bromothiophene **4** (2.00 mL, 20.7 mmol) was dissolved in dry tetrahydrofuran (25 mL) at room temperature under an atmosphere of nitrogen. To this stirred solution was added *n*-butyllithium (15.2 mL, 22.7 mmol, 1.50 M) dropwise slowly over 20 min. The resultant solution was heated at reflux for 1 h, cooled to 45 °C then trimethylborate (1.6 mL, 13.8 mmol) added via syringe. After heating for 2 h at 60 °C the reaction was cooled to 0 °C. Water (5 mL) was added followed by hydrogen peroxide (4.9 mL, 161.1 mmol) dropwise and the solution allowed to warm to room temperature. After 2 h the mixture was acidified and extracted with diethyl ether (3×50 mL). The combined organic extracts were dried over magnesium sulphate, filtered and the solvent removed at reduced pressure. Purification by flash column chromatography using hexane–ethyl acetate (8/2) as eluent provided the title compound **6** (538 mg, 26%) as a yellow oil; δ_H (300 MHz, $CDCl_3$) 4.15 (2H, dd, J=2.7, 2.0 Hz, H5), 6.43 (1H, dt, J=5.9, 2.0 Hz, H3) and 7.58 (1H, dt, J=5.9, 2.7 Hz, H4). This data was in agreement with that reported in the literature.[24]

Procedure B. In an adaptation of the procedure used by Frisell and Lawesson,[16] a two-necked flask was charged with magnesium turnings (527 mg, 21.7 mmol) and a single crystal of iodine then covered with dry diethyl ether (40 mL). To this stirred mixture was added 10% of a solution of 2-bromothiophene **4** (2.0 mL, 20.7 mmol) in diethyl ether (70 mL). After gently heating the mixture to initiate a reaction the remainder of the 2-bromothiophene solution was then added dropwise. The mixture was stirred for 3 h at room temperature then 0.5 h under reflux before cooling to 0 °C in an ice-bath. *tert*-Butylperoxy benzoate (3.3 cm^3, 17.6 mmol) was added dropwise and the mixture allowed to warm to room temperature. After 12 h the mixture was poured into ice-water (30 mL) and acidified with concentrated hydrochloric acid. The aqueous layer was extracted with diethyl ether (3×100 mL) and the combined extracts dried over magnesium sulphate. Filtration and removal of the solvent afforded a crude oil that was purified by flash column chromatography using hexane as eluent. The resultant 2-*tert*-butoxythiophene **7** was treated with *p*-toluenesulfonic acid (10 mg) and heated at 160 °C for 10 min. Purification by flash column chromatography using hexane–ethyl acetate (8/2) as eluent gave the title compound

6 (1.26 g, 61%) as a yellow oil. The spectroscopic data was identical to that reported above and was in agreement with that reported in the literature.[24]

4.2.2. 2-(*tert*-Butyldimethylsilyloxy)thiophene 2. Following the procedure reported by Casiraghi et al.[14] 3-thiolen-2-one **6** (1.25 g, 12.5 mmol) was dissolved in dichloromethane (25 mL) under an atmosphere of nitrogen and the solution cooled to 0 °C. To this stirred solution was added 2,6-lutidine (4.4 mL, 37.4 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.30 mL, 18.7 mmol). The mixture was allowed to warm to room temperature, stirred for 1 h then the solvent was removed under reduced pressure. Purification of the resultant residue by flash column chromatography using hexane as eluent provided the title compound **2** (2.24 g, 84%) as a colourless oil; δ_H (300 MHz, $CDCl_3$) 0.22 (6H, s, $^tBuMe_2Si$), 0.98 (9H, s, $^tBuMe_2Si$), 6.14 (1H, dd, $J=3.1$, 1.6 Hz, H3), 6.50 (1H, dd, $J=5.9$, 1.6 Hz, H5), 6.65 (1H, dd, $J=5.9$, 3.1 Hz, H4). This data was in agreement with that reported in the literature.[14]

4.3. Addition of 2-(*tert*-butyldimethylsilyloxy)thiophene 2 to quinones

4.3.1. Representative experimental procedures. *A. Uncatalyzed conjugate addition*. To a stirred solution of quinone (0.10 mmol) in acetonitrile (15 mL) at 0 °C under an atmosphere of nitrogen was added a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (24 mg, 0.11 mmol) in acetonitrile (6 mL). The mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed at reduced pressure and the resultant residue purified by flash column chromatography to afford the title compound.

B. Indium(III) chloride catalyzed conjugate addition. To a suspension of indium(III) chloride (11 mg, 0.05 mmol) in acetonitrile (2 cm^3) at 0 °C under an atmosphere of nitrogen was added a solution of quinone (1.00 mmol) in acetonitrile (3 mL) followed by a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (236 mg, 1.10 mmol) in acetonitrile (3 mL). The mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed at reduced pressure and the resultant residue purified by flash column chromatography to afford the title compound.

C. Copper(II) trifluoromethane sulfonate catalyzed conjugate addition. To a stirred suspension of copper(II) trifluoromethanesulfonate (362 mg, 1.00 mmol) in dichloromethane (2 mL) at −78 °C under an atmosphere of nitrogen was added a solution of quinone (1.00 mmol) in dichloromethane (3 mL) followed by a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (214 mg, 1.00 mmol) in dichloromethane (3 mL). After stirring for 2 h, the mixture was allowed to warm to room temperature then filtered through a pad of Celite®. The solvent was removed at reduced pressure and the resultant residue purified by flash column chromatography to afford the title compound.

D. Boron trifluoride etherate catalyzed conjugate addition. To a stirred solution of quinone (1.00 mmol) in dichloromethane (5 mL) at −78 °C under an atmosphere of nitrogen was added a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (214 mg, 1.00 mmol) in dichloromethane (5 mL). Boron trifluoride etherate (0.14 mL, 1.10 mmol) was added dropwise and the mixture stirred for 1 h. The reaction was quenched by the addition of water (3 cm^3) and allowed to warm to room temperature. The aqueous layer was extracted with dichloromethane (3×15 mL) and the combined organic extracts dried over magnesium sulphate. Filtration and removal of the solvent at reduced pressure gave a residue that was purified by flash column chromatography to afford the title compound.

4.3.2. *cis*-8-Carbomethoxy-7-hydroxy-2-oxo-2,3,3a,8b-tetrahydro-1*H*-[1]benzofuro[3,2-*b*]thiophene 13. Flash column chromatography using hexane–ethyl acetate (8/2) as the eluent gave the title compound **13** (Procedure B 11%; Procedure C 13%) as a red solid; mp 160–162 °C; ν_{max}(film)/cm^{-1} 3426br (OH) and 1644s (CO); δ_H (400 MHz, $CDCl_3$), 3.12 (1H, dd, $J=18.2$, 6.2 Hz, H3), 3.23 (1H, d, $J=18.2$ Hz, H3), 3.98 (3H, s, Me), 5.31 (1H, t, $J=6.2$ Hz, H3a), 5.76 (1H, d, $J=6.2$ Hz, H8b), 6.92 (1H, d, $J=8.9$ Hz, H6), 7.03 (1H, d, $J=8.9$ Hz, H5) and 10.44 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 47.8 (CH_2, C3), 52.6 (CH_3, Me), 56.2 (CH, C8b), 83.2 (CH, C3a), 108.5 (quat., C8), 118.2 (CH, C6), 119.4 (CH, C5), 127.4 (quat., C8a), 152.3 (quat., C7), 157.1 (quat., C4a), 169.3 (quat., CO) and 204.4 (quat., C2); *m/z* (EI): 266 (M^+, 100), 234 (M−CH_3OH, 78), 224 (M−CH_2CO), 207 (M−CO_2Me, 2), 192 (M−CH_2SCO, 16) and 57 (C_4H_9, 14); HRMS (EI): Found M^+, 266.0239. $C_{12}H_{10}O_5S$ requires 266.0249.

4.3.3. *cis*-10-Carbomethoxy-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]thiophene 14. Flash column chromatography using hexane–ethyl acetate (7/3) as the eluent gave the title compound **14** (Procedure B 27%; Procedure C 30%; Procedure D 31%) as pale yellow needles; mp 221–223 °C; ν_{max}(film)/cm^{-1} 3376br (OH), 1697s (CO), 1665s (CO) and 1233s; δ_H (400 MHz, $CHCl_3$) 3.22 (1H, dd, $J=18.4$, 6.3 Hz, H3), 3.37 (1H, d, $J=18.4$ Hz, H3), 4.00 (3H, s, OMe), 5.46 (1H, t, $J=6.3$ Hz, H3a), 5.91 (1H, d, $J=6.3$ Hz, H10b), 7.58 (1H, t, $J=7.7$ Hz, H7), 7.66 (1H, t, $J=7.7$ Hz, H6), 7.90 (1H, d, $J=7.7$ Hz, H5), 8.40 (1H, d, $J=7.7$ Hz, H8) and 11.83 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 48.0 (CH_2, C3), 52.5 (CH_3, OMe), 57.8 (CH, C10b), 83.2 (CH, C3a), 101.5 (quat., C10), 117.3 (quat., C10a), 121.7 (CH, C5), 124.2 (quat., C8a), 125.6 (quat., C4b), 127.0 (CH, C7), 129.9 (CH, C6), 148.3 (quat., C9), 157.3 (quat., C4a), 170.5 (quat., CO_2Me) and 204.9 (quat., C2); *m/z* (FAB): 316 (M^+, 42%) and 89 (100); HRMS (FAB): Found M^+, 316.04008. $C_{16}H_{12}O_3S$ requires 316.04055.

4.3.4. 2-(2-Acetyl-1,4-dihydroxy-3-phenyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-thiophene 15. Flash column chromatography using hexane−ethyl acetate (7/3) as the eluent gave the title compound **15** (Procedure A 35%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 3384br (OH) and 1635s (CO); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, $^tBuMe_2Si$), 1.00 (9H, s, $^tBuMe_2Si$), 2.12 (3H, s, Me), 5.28 (1H, s, OH), 6.26 (1H, d, $J=3.7$ Hz, H4), 6.69 (1H, d, $J=3.7$ Hz, H3), 6.98 (1H, d, $J=9.0$ Hz, H6′), 7.13 (1H, d, $J=9.0$ Hz, H5′) and 11.36 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) −5.0 (CH_3, $^tBuMe_2Si$), 18.2 (quat., $^tBuMe_2Si$), 20.9 (CH_3, $^tBuMe_2Si$), 60.3 (CH_3, Me), 110.3 (CH, C4), 119.8 (quat., C2′), 119.8

(CH, C6′), 122.2 (quat., C3′), 122.2 (quat., C2), 122.7 (CH, C5′), 127.8 (CH, C3), 147.2 (quat., C4′), 155.1 (quat., C1′), 171.1 (quat., C5) and 205.8 (quat., CO); *m/z* (EI): 364 (M^+, 66%), 349 (M−Me, 2), 307 (M−C_4H_9, 6), 233 (12), 115 (6) and 43 (18); HRMS (EI): Found M^+, 364.11671. $C_{18}H_{24}O_4SSi$ requires 364.11646.

4.3.5. 2-(2-Acetyl-1,4-dihydroxy-3-naphthyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-thiophene 16. Flash column chromatography using hexane–ethyl acetate (8/2) as the eluent gave the title compound **16** (Procedure A 11%) as a yellow oil; ν_{max}(film)/cm^{-1} 3434br (OH) and 1675s (CO); δ_H (400 MHz, $CDCl_3$) 0.29 (6H, s, ^{t}Bu*Me*$_2$Si), 1.00 (9H, s, ^{t}*Bu*Me$_2$Si), 2.19 (3H, s, Me), 5.85 (1H, s, OH), 6.29 (1H, d, *J*=3.6 Hz, H4), 6.78 (1H, d, *J*=3.6 Hz, H3), 7.60 (1H, ddd, *J*=7.6, 7.6, 1.2 Hz, H7′), 7.69 (1H, ddd, *J*=7.6, 7.6, 1.2 Hz, H6′), 8.20 (1H, d, *J*=7.6 Hz, H5′), 8.47 (1H, d, *J*=7.6 Hz, H8′) and 13.82 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) −4.9 (CH_3, ^{t}Bu*Me*$_2$Si), 18.3 (quat., ^{t}*Bu*Me$_2$Si), 25.5 (CH_3, ^{t}*Bu*Me$_2$Si), 30.1 (CH_3, Me), 109.0 (quat., C2′), 109.5 (CH, C4), 114.7 (quat., C3′), 122.6 (CH, C5′), 123.5 (quat., C2), 124.6 (CH, C8′), 126.2 (quat., C4a′), 127.2 (CH, C3), 127.6 (CH, C7′), 130.1 (CH, C6′), 130.9 (quat., C8a′), 143.3 (quat., C4′), 156.9 (quat., C1′), 163.7 (quat., C5) and 205.3 (quat., CO); *m/z* (EI): 414 (M^+, 78), 399 (M−Me, 3), 371 (M−COMe, 7), 282 (12), 115 (9) and 43 (17); HRMS (EI): Found M^+, 414.13198. $C_{22}H_{26}O_4SSi$ requires 414.13211.

4.3.6. *cis*-8-Acetyl-7-hydroxy-2-oxo-2,3,3a,8b-tetrahydro-1*H*-[1]benzofuro[3,2-*b*]thiophene 17. Flash column chromatography using hexane–ethyl acetate (7/3) as the eluent gave the title compound **17** (Procedure B 35%; Procedure C 22%) as a pale-yellow solid; mp 125–127 °C (degradation); ν_{max}(film)/cm^{-1} 3376br (OH), 1716s (CO), 1637s (CO), 1472 and 1210; δ_H (400 MHz, $CHCl_3$) 2.68 (3H, s, Me), 3.13 (1H, dd, *J*=18.2, 5.6 Hz, H3), 3.30 (1H, d, *J*=18.2 Hz, H3), 5.31 (1H, t, *J*=5.6 Hz, H3a), 5.70 (1H, d, *J*=5.6 Hz, H8b), 6.94 (1H, d, *J*=9.0 Hz, H6), 7.07 (1H, d, *J*=9.0 Hz, H5) and 12.25 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 31.2 (CH_3, Me), 47.3 (CH_2, C3), 56.6 (CH, C8b), 83.2 (CH, C3a), 116.1 (quat., C8), 119.4 (CH, C5), 120.8 (CH, C6), 126.2 (quat., C8a), 152.5 (quat., C7), 158.7 (quat., C4a) 202.4 (quat., CO_2Me or C2) and 202.5 (quat., CO_2Me or C2); *m/z* (EI): 250 (M^+, 100%), 208 (37), 189 (44), 175 (27), 152 (18), 147 (18), 137 (28) and 43 (49); HRMS (EI): Found M^+, 250.03021. $C_{12}H_{10}O_4S$ requires 250.02998.

4.3.7. *cis*-10-Acetyl-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]thiophene 18. Flash column chromatography using hexane–ethyl acetate (1/1) as the eluent gave the title compound **18** (Procedure B 9%; Procedure C 33%; Procedure D 48%) as orange needles; mp 210–212 °C; ν_{max}(film)/cm^{-1} 3345br (OH), 1677s (CO) and 1593s (CO); δ_H (400 MHz, $CDCl_3$) 2.74 (3H, s, Me), 3.26 (1H, dd, *J*=18.3, 5.7 Hz, H3), 3.43 (1H, d, *J*=18.3 Hz, H3), 5.48 (1H, dd, *J*=5.7, 6.4 Hz, H3a), 5.87 (1H, d, *J*=6.4 Hz, H10b), 7.58 (1H, ddd, *J*=7.6, 7.6, 1.1 Hz, H7), 7.70 (1H, ddd, *J*=7.6, 7.6, 1.1 Hz, H6), 7.92 (1H, d, *J*=7.6 Hz, H5), 8.48 (1H, d, *J*=7.6 Hz, H8) and 14.56 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 30.7 (CH_3, Me), 47.5 (CH_2, C3), 58.2 (CH, C10b), 83.1 (CH, C3a), 109.5 (quat., C10a), 116.3 (quat., C10), 121.6 (CH, C5), 124.3 (quat., C8a), 124.8 (CH, C8), 125.4 (quat., C4b), 126.4 (CH, C7), 130.7 (CH, C6), 133.4 (quat., C9), 160.3 (quat., C4a), 202.1 (quat., CO) and 202.8 (quat., C2); *m/z* (EI): 300 (M^+, 100), 257 (M−COMe, 2), 256 (4), 57 (7) and 43 (37); HRMS (EI): Found M^+, 300.04557. $C_{16}H_{12}O_4S$ requires 300.04563.

4.3.8. *cis*-10-Acetyl-9-hydroxy-8-methoxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]thiophene 19. Flash column chromatography using hexane–ethyl acetate (7/3) as the eluent gave the title compound **19** (Procedure D 45%) as a brown solid; mp 230–233 °C (degradation); ν_{max}(film)/cm^{-1} 3439br (OH), 1694s (CO), 1649, 1631, 1450, 1399, 1244, and 1229; δ_H (300 MHz, $CHCl_3$) 2.75 (3H, s, Me), 3.20 (1H, dd, *J*=18.2, 5.9 Hz, H3), 3.31 (1H, d, *J*=18.2 Hz, H3), 4.13 (3H, s, OMe), 5.39 (1H, t, *J*=5.9 Hz, H3a), 5.92 (1H, d, *J*=5.9 Hz, H10b), 6.92 (1H, d, *J*=8.0 Hz, H7), 7.49 (1H, t, *J*=8.0 Hz, H6), 7.55 (1H, dd, *J*=8.0, 1.0 Hz, H5) and 10.38 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 33.2 (CH_3, Me), 48.1 (CH_2, C3), 56.6 (CH_3, OMe), 57.1 (CH, C10b), 83.4 (CH, C3a), 106.5 (CH, C7), 115.5 (quat., C8), 115.7 (quat., C10a), 116.0 (CH, C5), 121.7 (quat., C10), 124.9 (quat., C4b), 129.1 (CH, C6), 148.2 (quat., C4a), 153.6 (quat., C9), 157.4 (quat., C8), 199.5 (quat., CO) and 205.8 (quat., C1); *m/z* (FAB): 331 (MH^+, 23%), 330 (M, 18), 120 (59) and 89 (100); HRMS (FAB): Found M^+, 330.05675. $C_{17}H_{14}O_5S$ requires 330.05620.

4.3.9. *cis*-(3a,5,9b)-3,3a,5,11b-Tetrahydro-5-hydroxy-7-methoxy-5-methyl-1*H*-[1]naptho[2,3-*c*]pyran-2,6,11-trione thiophene 20. To a stirred solution of thienylnaphthofuran **11** (40 mg, 0.12 mmol) in acetonitrile (2 cm^3) and water (2 cm^3) at 0 °C was added ceric ammonium nitrate (133 mg, 0.24 mmol). After stirring for 20 min, water (2 cm^3) was added and the aqueous layer extracted with dichloromethane (3×10 cm^3). The combined extracts were dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. Purification of the resultant residue by flash column chromatography using hexane–ethyl acetate (8/2) as eluent gave the title compound **20** (9 mg, 21%) as an unstable red-brown oil that rapidly degraded to a complex mixture of products; δ_H (300 MHz, $CHCl_3$) 1.78 (3H, s, Me), 2.88 (1H, d, *J*=17.1 Hz, H3), 2.99 (1H, dd, *J*=17.1, 3.8 Hz, H3), 4.04 (3H, s, OMe), 4.87 (1H, t, *J*=3.8 Hz, 3a), 4.92 (1H, d, *J*=3.8 Hz, 11b), 7.34–7.38 (1H, m, H8), 7.70–7.78 (2H, m, H9 and H10).

Acknowledgements

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X-ray crystallographic analysis of *N*,*N*-diallylcoumarincarboxamides and the solid-state photochemical reaction

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Abstract—X-ray crystallographic analysis and the photochemical aspects of *N*,*N*-diallylcoumarincarboxamides were investigated. Irradiation of the corresponding amides promoted stereoselective intramolecular cyclobutane formation exclusively. The solid-state photoreaction of the coumarinamide without substituent on the 4-position proceeded in a crystal-to-crystal manner. On the other hand, photolysis of the amide possessing a methyl group at the 4-position also effected 2+2 cycloaddition; however, the reaction proceeded much slower. The difference in the reactivity was explainable on the basis of the molecular conformation in the crystal lattice.

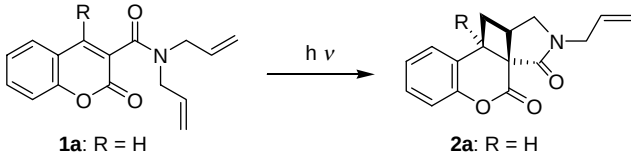
1. Introduction

Solid-state photoreaction provides product- and stereoselectivity compared to reactions that occur in solution due to restriction of molecular movement imposed by the environment.[1] Many examples are reported of topochemical intermolecular 2+2 cyclobutane formation of alkenes, and the geometrical studies are well-known as Schmidt's rule, which means that the reactive alkenyl groups locate within 4.2 Å of the center-to-center distance in parallel to promoted cycloaddition.[2] Compared to a large amount of data for intermolecular cycloaddition reactions,[3] there is little information on intramolecular reactions.[4] Intermolecular reactions are strongly affected by the molecular arrangement in the crystal; on the other hand, molecular conformation in the ground-, excited- and transition-state also plays an important role in the intramolecular photoprocess. To investigate the geometrical aspects of intramolecular 2+2 photocycloaddition and the difference between photochemical reactivity with the reaction media, photochemical reaction of *N*,*N*-diallylcoumarin-3-carboxamides was examined, because coumarin is well-known as not only one of the photoreactive molecules for dimerization and 2+2 cycloaddition with alkenes,[5] but also natural products and biologically active materials.[6] Now we have found that *N*,*N*-diallylcoumarin-3-caboxamides showed effective photochemical reactivity and gave cylobutanes selectively, and one of the reactions proceeded in a crystal-to-crystal manner.

2. Results and discussion

N,*N*-Diallylcoumarin-3-carboxamide **1a** and the 4-methyl derivative **1b** were conveniently prepared from the

Table 1. Photochemical reaction of *N*,*N*-diallylcoumarincarboxamides **1**



1a: R = H
1b: R = Me

2a: R = H
2b: R = Me

Entry	Amide **1**	Conditions[a]	Conversion (%)	Yield (%) of **2**[b]
1	**1a**	Benzene (5 h)[c]	100	98
2	**1a**	Solid-state (2 h)	100	100
3	**1b**	Benzene (12 h)[c]	47	50
4	**1b**	Solid-state (6 h)	46	100
5	**1b**	Solid-state (12 h)	99	74

[a] A 0.02 M benzene solution in a Pyrex vessel under argon was irradiated with a 500 W high pressure mercury lamp.
[b] Chemical yields were determined on the basis of consumed coumarins.
[c] Number in parentheses is irradiation time.

Keywords: Coumarincarboxamide derivatives; Solid-state reaction; 2+2 Cycloaddition; X-ray crystallography; Photochemical reaction.
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corresponding carboxylic acids (Table 1).[7] Recrystallization of the amide **1a** from a mixture of chloroform and hexane gave colorless plates, and **1b** afforded colorless needles. Both amides were subjected to X-ray single crystal analysis, and Figure 1 shows the ORTEP view of the amides **1a–b**. Each amide plane twisted almost orthogonally to the coumarin chromophore, and the torsion resulted in closed orientation of the reacting alkenyl bonds.

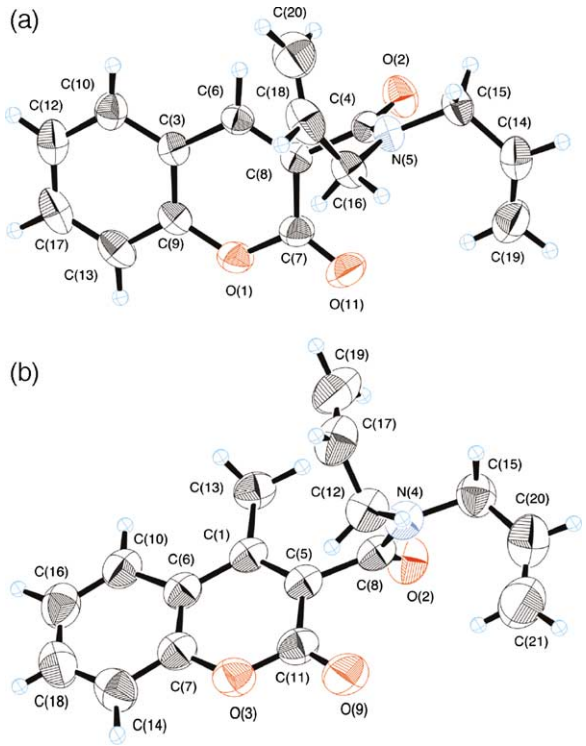


Figure 1. (a) ORTEP view of **1a**. (b) ORTEP view of **1b**.

When a 0.02 M benzene solution of the amide **1a** was irradiated with a 500 W high-pressure mercury lamp under argon atmosphere, intermolecular 2+2 photocyclization proceeded and multi-cyclic cyclobutane **2a** was obtained in 98% yield (Table 1, entry 1). The structure of **2a** was determined on the basis of its spectral data. Finally, the structure was unequivocally established by single crystal X-ray crystallographic analysis (Fig. 2).

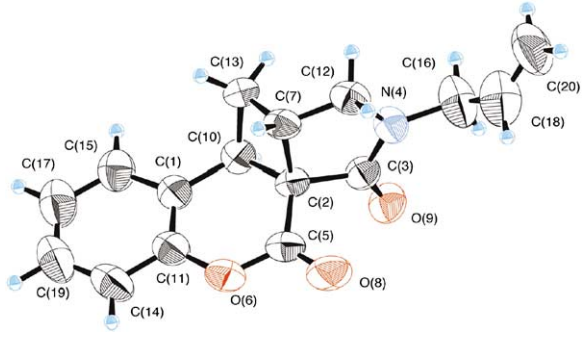


Figure 2. ORTEP view of the photoproduct **2a**.

When the powdered crystals of **1a** were irradiated, the solid-state photoreaction proceeded more effectively than the reaction in solution (Table 1, entries 1–2). Furthermore, the crystal-to-crystal behavior was confirmed on the basis of the X-ray powder diffraction as shown in Figure 3. Figure 3a shows the spectrum of starting material **1a**; Figure 3b exhibited the reflection pattern of 100% conversion yield, and still shows sharp reflections. Figure 3c, derived from recrystallized **2a** shows almost same reflections as Figure 3b. We attempted a single crystal X-ray analysis of the photolyzed crystals; however, sufficient reflections for the analysis were not obtained.

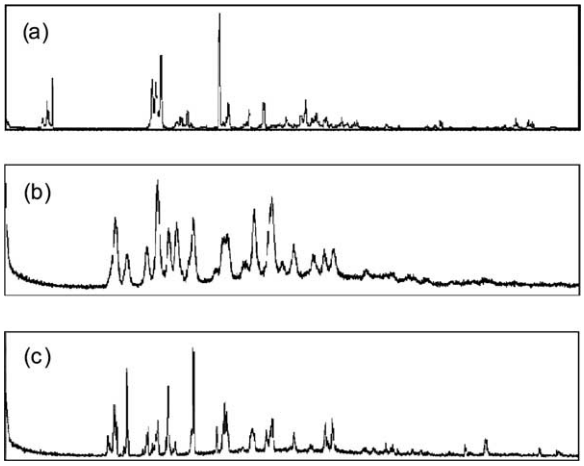


Figure 3. X-ray diffraction pattern for the transformation of **1a** to **2a**. (a) Starting material **1a**. (b) Irradiated crystals at 100% conversion. (c) Recrystallized **2a** from $CHCl_3$–hexane solution.

In the case of **1b**, photolysis of a 0.02 M benzene solution gave the corresponding cyclobutane **2b** in 50% yield accompanied by a complex mixture (Table 1, entry 3). Decreasing the concentration to 0.01 M did not improve the chemical yield. On the other hand, when the powdered crystals of **1b** were irradiated, a chemoselective reaction occurred and only cyclobutane **2b** was isolated. However, the reaction was slower than that of **1a**; furthermore, the solid gradually became amorphous by prolonged irradiation, The solid melts down after 6 h of irradiation; cyclobutane **2b** was formed in 100% yield (46% conversion yield) at this point (entry 4). Prolonged irradiation resulted in decreasing the chemical yield of **2b** (entry 5), because of the formation of a complex mixture. Figure 4a shows the XRD pattern of **1b**, and Figure 4b exhibits those of 46% conversion yield, which shows that the reflections derived from **1b** decreased with no new reflection. In all cases, no coumarin dimer was detected at all.

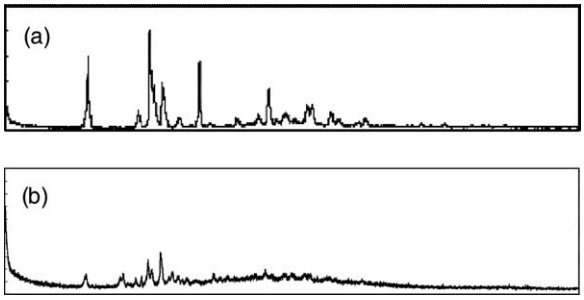


Figure 4. X-ray diffraction pattern for the transformation of **1b** to **2b**. (a) Starting material **1b**. (b) Transition pattern (irradiated for 6 h, 46% conversion).

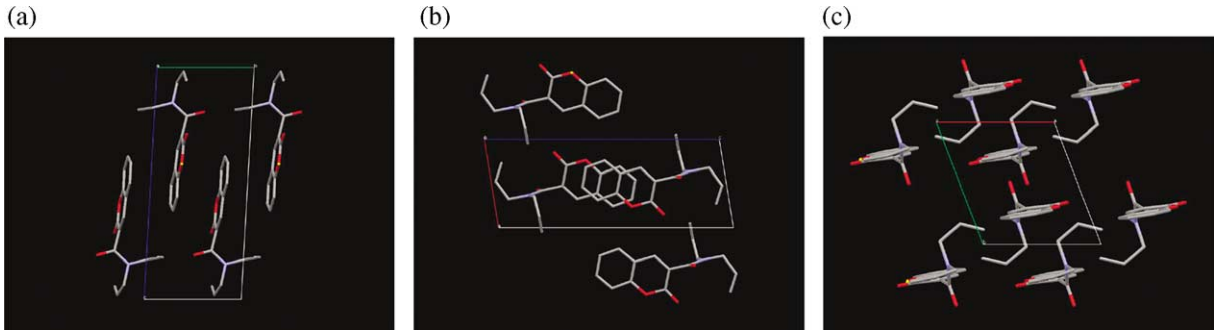


Figure 5. Packing diagram of **1a**. (a) A view from *a*-axis. (b) A view from *b*-axis. (c) A view from *c*-axis.

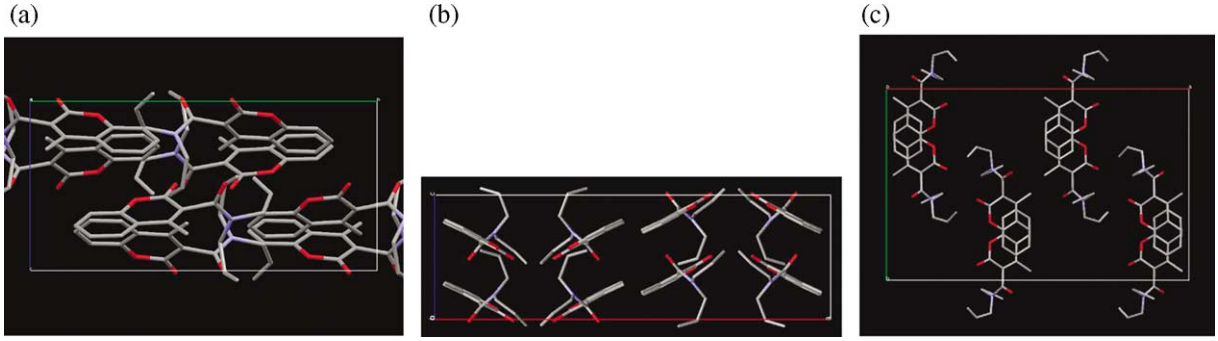
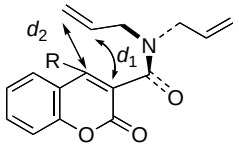


Figure 6. Packing diagram of **1b**. (a) A view from *a*-axis. (b) A view from *b*-axis. (c) A view from *c*-axis.

In both cases, the solid-state irradiation did not give coumarin dimer but yielded cyclobutane via intramolecular cycloaddition. Matsuura and Venkatesan independently reported photodimerization of coumarin derivatives in the solid-state.[5a,d] In Venkatesan's case, the distance between each reacting alkenyl bond was 3.81–3.87 Å, which is much shorter than the Schmidt's rule, <4.2 Å. In the cases of **1a** and **1b**, photodimerization was not observed and effective intramolecular cycloaddition occurred exclusively. The packing diagram clearly indicates the reason for their reactivities. Figures 5 and 6 show the packing image of **1a** and **1b**, respectively. In both cases, planes of coumarin make parallel position in the crystal; however, the reacting double bonds were placed far away. In the case of **1a**, the center-to-center distance was 7.0 Å, and 5.1 Å for **1b**; their value was over 4.2 Å.

The conformational factor plays a very important role in the intramolecular cycloaddition reaction in the solid-state reaction, because interconversion involving a dramatic movement of the atoms cannot usually occur. Table 2 shows the distances between each reacting alkenyl carbon atom. In the case of **1a**, the reaction proceeded retaining the crystallinity, where both reacting carbon atoms are placed closely, 3.59 and 3.83 Å for d_1 and d_2, respectively. Then the C–C bond formation leading to a cyclobutane ring does not need drastic atomic reorientation. However, the reaction of **1b** occurred rather more slowly than that of **1a**, and the solid changed to amorphous according to the progress of the reaction. The fact is reasonably explainable on the basis of the molecular conformation of which the d_2 value for **1b** exceeds 4.2 Å. This is because of the steric repulsion between the methyl group at the 4-position and the allyl group, which keep away each reacting double bond. Furthermore, the formation of cyclobutane, in which the sp^2 carbon atom at the C4 position transformed to sp^3 hybridization, needs considerably dramatic movement of the methyl group at the C4 position. The difference in photochemical reactivity was explainable on the basis of the molecular conformation in the crystal lattice.

Table 2. Distances between the reacting carbon atoms



Coumarin	Distance (Å)	
	d_1	d_2
1a	3.59	3.83
1b	3.68	4.21

In conclusion, when *N*,*N*-diallylcoumarin-3-carboxamides were irradiated in solution and in the solid-state. The stereoselective cyclobutane formation was observed because of the reacting alkenyl group was placed intramolecularly, and was proceeded more effectively than the dimerization of coumarin chromophore. Whereas the solid-state photolysis of the coumarincarboxamide with a methyl group at the 4-position afforded an amorphous compound according to the progress of the reaction, that of the corresponding amide with no substituent gave quantitative yield of cyclobutane, where the crystallinity was maintained after 100% conversion, and the crystal-to-crystal manner was confirmed by XRD analysis. This reaction provides a fine example of stereo-controlled intramolecular photocycloaddition reaction of hetero aromatics.

3. Experimental

NMR spectra were recorded on $CDCl_3$ solutions on a BRUKER 300 operating 300 MHz, respectively, for ^1H and ^{13}C NMR spectroscopy. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standards. UV spectra were measured with a JASCO model V-570 UV/VIS/NIR spectrophotometer. IR spectra were recorded on a JASCO FT/IR-230 spectrometers as KBr disks, unless otherwise noted.

3.1. General procedure for the preparation of *N*,*N*-diallylcoumarincarboxamides 1a and 1b

Both coumarincarboxamides **1a**–**1b** were provided from corresponding coumarincarboxylic acid[7] and diallyl amine. A synthesis of **1a** was exemplified as follows. To a toluene solution containing 1.5 g (5.5 mmol) of coumarincarboxylic acid and triethylamine 0.80 g (8.0 mmol) was added 0.79 g (6.6 mmol) of thionyl chloride at 0 °C. The reaction mixture was stirred for 0.5 h, and then diallylamine 1.4 g (14.0 mmol) was added dropwise. After the reaction mixture was stirred for 1 h, water was added, and extracted as a usual manner. After toluene was evaporated in vacuo and the residual mixture was subjected to chromatography on silica gel and the crystalline amide **1a** was recrystallized from ethanol; afforded colorless plates. The structures of **1a** and **1b** were determined on the basis of spectral data, mass spectroscopy, and unequivocally X-ray crystallographic analyses.

3.1.1. *N*,*N*-Diallylcoumarincarboxamides 1a. The title compound was obtained colorless plates from ethanol; mp 127–129 °C; IR (cm^{-1}, KBr) 1631, 1712; ^1H NMR ($CDCl_3$) δ 3.87 (d, $J=5.6$ Hz, 2H, CH_2), 4.15 (d, $J=5.4$ Hz, 2H, CH_2), 5.14–5.36 (m, 4H, 2×C=CH_2), 5.78–5.84 (m, 2H, 2×CH=CH_2), 7.28–7.38 (m, 2H, ArH), 7.51–7.59 (m, 2H, ArH), 7.83 (s, 1H, 4-CH); ^{13}C NMR 47.2, 51.2, 117.2, 118.3, 118.6, 125.3, 125.9, 128.9, 132.2, 133.1, 133.4, 142.3, 154.4, 158.5, 165.4; HR-MS (FAB). Anal. 270.1130 Calcd for $C_{16}H_{15}NO_3$ (MH^+). Found: *m*/*z* 270.1124 (MH^+).

X-ray crystallographic data of **1a**. Triclinic space group *P*-1, $a=6.516(2)$ Å, $b=7.101(3)$ Å, $c=16.027(4)$ Å, $\alpha=89.93(3)°$, $\beta=81.48(2)°$, $\gamma=69.12(3)°$, $V=684.1(4)$ Å^3, $Z=2$, $\rho=1.307$ g/cm^3, μ(Cu Kα)$=0.74$ mm^{-1}. The structure was solved by the direct method of full-matrix least-squares, where the final *R* and *Rw* were 0.051 and 0.226 for 2345 reflection. CCDC 268496 contains crystallographic data. These crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 (e-mail: deposit@ccdc.cam.ac.uk).

3.1.2. *N*,*N*-Diallyl-4-methylcoumarincarboxamides 1b. The title compound was obtained colorless needles from a mixture of $CHCl_3$–hexane; mp 85–87 °C; IR (cm^{-1}, KBr) 1630, 1714; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 3.85 (d, $J=5.8$ Hz, 2H, CH_2), 4.14–4.25 (m, 2H, CH_2), 5.10–5.38 (m, 4H, 2×C=CH_2), 5.69–5.78 (m, 1H, CH=CH_2), 5.83–5.91 (m, 1H, CH=CH_2), 7.30–7.38 (m, 2H, ArH), 7.51–7.59 (m, 1H, ArH), 7.64–7.68 (m, 1H, ArH); ^{13}C NMR 16.7, 46.9, 51.2, 117.5, 118.4, 119.1, 119.9, 124.0, 125.1, 125.5, 132.4, 132.7, 133.3, 149.4, 153.3, 158.6; HR-MS (FAB). Anal. 284.1287 Calcd for $C_{17}H_{17}NO_3$ (MH^+). Found: *m*/*z* 284.1275 (MH^+).

X-ray crystallographic data of **1b**. Orthorhombic space group *Pbca*, $a=24.705(9)$ Å, $b=15.742(6)$ Å, $c=7.728(4)$ Å, $V=3005.0(2)$ Å^3, $Z=8$, $\rho=1.252$ g/cm^3, μ(Cu Kα)$=0.70$ mm^{-1}. The structure was solved by the direct method of full-matrix least-squares, where the final *R* and *Rw* were 0.056 and 0.180 for 1712 reflections, CCDC 268497 contains crystallographic data.

3.2. General procedure for the photochemical reaction in benzene

A benzene solution of amides **1a**–**1b** (0.02 M) was purged with deoxygenated and dried argon for 15 min prior to photolysis and was irradiated with a 500-W Eikosha high-pressure mercury lamp through a Pyrex filter. After irradiation, benzene was evaporated and the photolysate was chromatographed on silica gel (Merk Kieseigel 60) with ethyl acetate–hexane (10/1) as the eluent.

3.3. General procedure for the photochemical reaction in the solid-state

Solid samples were irradiated as a powder sandwiched between Pyrex glasses in the inside of a polyethylene bags and was fixed out side of a emersion well apparatus. After irradiation, the photolysate was treated as same as that in solution photochemistry.

3.3.1. Photoproduct 2a. The title compound was obtained colorless prisms from a mixture of $CHCl_3$–hexane; mp 162–163 °C; IR (cm^{-1}, KBr) 1691, 1745; ^1H NMR ($CDCl_3$) δ 2.37–2.66 (m, 2H, CH_2), 3.23 (d, $J=10.5$ Hz, 1H, CH), 3.44 (dd, $J=22.4$, 7.8 Hz, 1H, CH), 3.68 (m, 1H, CH), 3.92, (d, $J=6.2$ Hz, 1H, CH), 3.97–4.18 (m, 2H, CH), 5.28–5.37 (m, 2H, C=CH_2), 5.77–5.88 (m, 1H, CH=C), 7.04–7.30 (m, 4H, ArH); ^{13}C NMR 35.2, 36.5, 37.2, 46.2, 51.9, 52.1, 118.0, 119.2, 123.5, 125.9, 128.6, 129.2, 131.9, 150.4, 164.6, 171.1; HR-MS (FAB). Anal. 270.1130 Calcd for $C_{16}H_{16}NO_3$ (MH^+). Found: *m*/*z* 270.1124 (MH^+).

X-ray crystallographic data of **2a**. Orthorhombic space group *Pbca*, $a=16.019(3)$ Å, $b=15.451(3)$ Å, $c=10.799(3)$ Å, $V=2672.7(10)$ Å^3, $Z=8$, $\rho=1.339$ g/cm^3, μ(Cu Kα)$=0.76$ mm^{-1}. The structure was solved by the direct method of full-matrix least-squares, where the final *R* and *Rw* were 0.058 and 0.119 for 2881 reflections, CCDC 268498 contains crystallographic data.

3.3.2. Photoproduct 2b. The title compound was obtained colorless prisms from a mixture of $CHCl_3$–hexane; mp 80–82 °C; IR (cm^{-1}, KBr) 1685, 1750; ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H), 2.18–2.24 (dd, $J=8.0$, 12.0 Hz, 1H), 2.55–2.62 (dd, $J=8.5$, 12.0 Hz, 1H), 3.16–3.24 (m, 1H), 3.58–3.64 (m, 1H), 3.91–3.98 (m, 1H), 4.20–4.27 (m, 2H), 5.27–5.36 (m, 2H), 5.77–5.88 (m, 1H), 7.03–7.06 (m, 1H), 7.21–7.30 (m, 3H); ^{13}C NMR 27.2, 34.0, 41.8, 42.6, 46.1, 51.8, 56.1, 118.0, 119.0, 126.0, 119.1, 126.0, 127.7, 128.6, 129.2,

132.2, 149.4, 169.5; HR-MS (FAB). Anal. 284.1287 Calcd for $C_{17}H_{18}NO_3$ (MH^+). Found: *m/z* 284.1274 (MH^+).

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Synthesis of 3,3′-disubstituted-2,2′-biindolyls through sequential palladium-catalysed reactions of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide with organic halides/triflates

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Dedicated to the memory of Prof. Bianca Rosa Pietroni

Abstract—Palladium-catalysed reactions of aryl iodides/vinyl triflates with 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide provide a straightforward entry into 3,3′-disubstituted-2,2′-biindolyls. Subsequent application of the procedure to homochiral aryl iodides affords the corresponding chiral 3,3′-disubstituted-2,2′-biindolyls. The methodology can also be applied to the synthesis of benzo[*c*]indolo[2,3-*a*]carbazoles.

1. Introduction

Palladium-catalysed routes to heterocyclic compounds represent well-exploited synthetic approaches.[1] In particular, palladium-catalysed annulations involving both formation of carbon–carbon and carbon–nitrogen bonds, have proven to be very useful in the synthesis of a variety of heterocyclic systems.[2]

The aminopalladation/reductive elimination domino reaction of alkynes containing proximate nitrogen nucleophiles is a versatile synthetic methodology to build up complex indole and polycyclic indole derivatives.[3] The trifluoroacetamido group was shown to act as the proximate nitrogen nucleophile of choice for favouring palladium-catalysed cyclisations of *o*-alkynylaniline derivatives involving η^2-alkyne organopalladium intermediates. In addition, it allows the formation of free N–H indoles (the amide bond is broken during the reaction or/and the work-up), avoiding troublesome and time-consuming deprotection steps.[4]

This chemistry has been employed in the preparation of biologically active compounds.[5] It has also been adapted to a solid-supported synthesis for the preparation of combinatorial libraries of indoles with three variable components.[6]

However, while a variety of indole derivatives could be prepared in good to excellent yield by using aryl/vinyl halides/triflates as σ-donors,[7] the extension of the procedure to the synthesis of 3,3′-disubstituted-2,2′-biindolyl derivatives was limited to the synthesis of indolo[2,3-*a*]carbazole alkaloids[5c] by using *N*-benzyl-3,4-dibromomaleimide as the σ-donor. Products containing the biindolyl unit are of considerable interest, not only for their chemical architecture, but also due to their diverse pharmacological profiles.[8] Biindolyl-based red fluorescent materials have been prepared and used as non-doping red emitters.[9] The juxtaposition of the two nitrogens in 2,2′-biindolyls has also been exploited in the construction of various ligand systems.[10]

In connection with our current research interests in this area and in order to widen the scope and generality of the methodology, we decided to develop a procedure for the preparation of 3,3′-disubstituted-2,2′-biindolyl derivatives **3** through the palladium-catalysed reaction of readily

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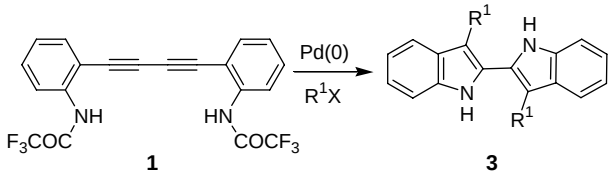
available 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide[5c] **1** with organic halides/triflates (Scheme 1). Despite its importance, synthetic methodologies for the construction of 3,3′-disubstituted-2,2′-biindolyl derivatives are scarce.[11]



Scheme 1.

Herein, we report the results of this study. The methodology was also applied to the synthesis of benzo[*c*]indolo[2,3-*a*]carbazole.

2. Results and discussion

Initial palladium-catalysed polyannulation attempts were focused on finding a general set of reaction conditions that could be used with a variety of aryl/vinyl halides/triflates. Based on the results obtained in the palladium-catalysed synthesis of 2,3-disubstituted indoles,[12] we initially examined the reaction of **1** (1 equiv) with aryl iodides (2.2 equiv) in the presence of $Pd(PPh_3)_4$ (0.05 equiv) and K_2CO_3 (5 equiv) in acetonitrile at 80 °C. Under these conditions, target 3,3′-disubstituted-2,2′-biindolyls **3a–e** can be prepared in satisfactory yields from aryl iodides **2a–e**, (Table 1, entries 1–5). As shown in Table 1, the reaction tolerates both electron-withdrawing or electron-donating substituents in the C_{sp2} donors. In a few cases, the 3-substituted biindolyls **5a–c** (Fig. 1) were also isolated in significant yields (Table 1, entries 6–9), and a tendency towards the production of 2,2′-biindolyl **4** (Fig. 1) was also observed (Table 1, entries 9 and 10).

Moreover, the 2,2′-biindol **4** was isolated as the main reaction product, when we extended the same procedure to include aryl bromides and aryl triflates (Table 1, entries 12 and 13). It was previously reported[7] that the reaction of *o*-alkynyltrifluoro-acetanilides with aryl bromides and triflates preferably afford 2-substituted 3-arylindoles rather than 2-substituted-indoles by increasing the temperature to 100 °C. However, when we tried to perform the reaction of **1** with **2j** and **2k** under the same reaction conditions we failed to obtain the corresponding derivatives **3b**,**f** in satisfactory yields and the cyclisation of **1** to **4** was a significant side reaction or even the main reaction path. Presumably, this different reactivity could be a consequence of higher acidity of **1** compared to that of *o*-alkynyltrifluoroacetanilides [calculations at the HF/4-31G+PCM show that ΔpK_a (H_2O) at 300 K between **1** and the *o*-ethynyltrifluoroacetanilide is $=-1.5$].[13]

Finally, when vinyl triflates were used as σ-donors, best results in the synthesis of the title derivatives **3** could be achieved by decreasing the reaction temperature at 45 °C (Table 1, entries 16 and 17).

The cyclisation of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide **1** to give the 2,2′-biindolyl **4** involves a palladium-catalysed process rather than a base-promoted process. Thus, when **1** was reacted in CH_3CN at reflux for 24 h under the presence of $Pd(PPh_3)_4$ and K_2CO_3 the corresponding 2,2′-biindolyl **4** was isolated in 75% yield (the starting alkyne **1** was recovered in 21% yield). The involvement of a base-promoted cyclisation[14] of **1** to **4** could be ruled out since the starting reagent **1** was recovered (90% yield) when the same reaction was carried out omitting the palladium catalyst.

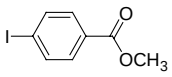
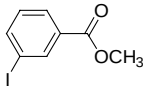
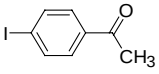
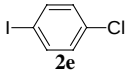
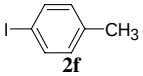
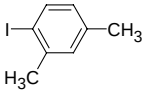
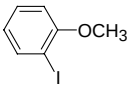
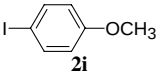
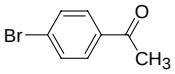
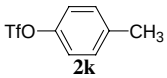
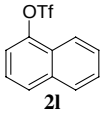
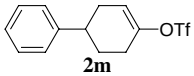
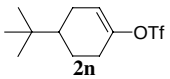
A plausible rationale, which accounts for the obtained results may involve two competing mechanisms. The sequential aminopalladation/reductive elimination reaction leading to the target derivatives **3** most probably proceeds through a mechanism most frequently found in the literature.[2d,e,3] Oxidative addition of palladium(0) in the aryl/vinyl halide/triflate bond affords a σ-organopalladium(II) intermediate, which can coordinate to the triple bond to give the η^2-alkyne-organopalladium intermediate **6**. The acetylene is then sufficiently electrophilic to undergo nucleophilic attack by the tethered nitrogen to give the σ-indolylpalladium complex **7** (5 *endo-dig* process). As far as the aniline moiety is concerned, no 3,3′-disubstituted-2,2′-biindolyl derivatives were obtained using the 2-[4-(2-aminophenyl)buta-1,3-diynyl]aniline containing free amino groups. Presumably, when carbon–carbon triple bonds are activated via coordination to organopalladiums, anionic nitrogen nucleophiles, or nitrogen atoms whose nucleophilic attack can be assisted by proton removal in the transition state leading to the aminopalladation adduct, are required to produce the desired cyclisation products.[12b] Reductive elimination of palladium(0) from the intermediate **7** regenerates the catalyst and affords product **3** after an iterative aminopalladation/reductive elimination reaction and protective group cleavage (Scheme 2).

Alternatively, a competitive oxidative addition of Pd(0) into the N–H bond of **1** to form a Pd–H species can take place under the reaction conditions. Then, intramolecular insertion of the triple bond can result in a 3-indolylpalladium derivative **8**. Sequential reductive elimination of the Pd–H intermediates/oxidative addition into N–H will provide 2,2′-biindolyl **4** (Scheme 3).

The activation of Pd(0) via oxidative addition into NH bond has been previously reported to take place with more acidic amides.[15] A similar mechanism has been suggested for the palladium-catalysed cyclisations of acetylene-containing *N*-protected α-aminoesters.[16] The formation of amido complexes directly from amines has also been observed.[17] Nevertheless, as demonstrated by the results obtained in the experiments performed in the presence either of Pd(II)[18] and Au(III),[19] a mechanism that leads to the 2,2′-biindolyl **4** involving a palladium catalyst that acts simultaneously[20] both as transition metal in the Pd(0) oxidation state and as Lewis acid in the Pd(II) oxidation state can not be ruled out.[21]

It is possible that the two different reaction paths afford the formation of derivative **5** when operating together.

Table 1. Synthesis of 2,2′-biindolyls **3**

Entry	σ-Donor **2**	Time (h)	**3** (%)[a,b]	**4** (%)[a,b]	**5** (%)[a,b]
1	 **2a**	24	**3a** 82	—	—
2	 **2b**	3.5	**3b** 77	—	—
3	 **2c**	4	**3c** 63	—	—
4	 **2d**	24	**3d** 73	—	—
5	 **2e**	1.5	**3e** 82	—	—
6	 **2f**	16	**3f** 50	—	**5a** 47
7	**2f**	4	**3f** 79[c]	—	**5a** 14[c]
8	 **2g**	4.5	**3g** 23	—	**5b** 67
9	 **2h**	24	**3h** 38	23	**5c** 30
10	 **2i**	17	**3i** 75	15	—
11	**2i**	2	**3i** 90[c]	—	—
12	 **2j**	24	**3b** 15[d]	65[d]	—
13	 **2k**	16	**3f** 15[e]	33[e]	—
14	**2k**	16	**3f** 34[f]	—	—
15	 **2l**	24	**3j** 51[g]	—	—
16	 **2m**	4	**3k** 45[g]	—	—
17	 **2n**	5	**3l** 61[g]	—	—

[a] Yields refer to single runs and are given for isolated products.
[b] Unless otherwise stated, reactions were carried out under a nitrogen atmosphere according to the following procedure: **1/2**/K_2CO_3/$Pd(PPh_3)_4$ = 1:2.2:5:0.07 in CH_3CN at 80 °C (0.12–0.35 mmol scale).
[c] Reaction was carried out at 80 °C in CH_3CN under a nitrogen atmosphere using the following molar ratios: **1/2**/K_2CO_3/$Pd(PPh_3)_4$ = 1:4.4:5:0.07.
[d] The reaction was carried out in CH_3CN at 100 °C under a nitrogen atmosphere using the following molar ratios: **1/2c**/Cs_2CO_3/$Pd(PPh_3)_4$ = 1:3:3:0.07.
[e] The reaction was carried out in CH_3CN at 100 °C under a nitrogen atmosphere using the following molar ratios: **1/2g**/Cs_2CO_3/$Pd(PPh_3)_4$ = 1:2.2:3:0.07.
[f] The reaction was carried out in CH_3CN at 100 °C under a nitrogen atmosphere using the following molar ratios: **1/2g**/Cs_2CO_3/$Pd(PPh_3)_4$ = 1:3:3:0.07.
[g] The reaction was carried out in CH_3CN at 45 °C under a nitrogen atmosphere using the following molar ratios: **1/2**/K_2CO_3/$Pd(PPh_3)_4$ = 1:2.2:3:0.07.

The feature of the σ-donor **2**, the reaction temperature and the **1**:σ-donor ratio were found to play a pivotal role in controlling the balance of the reaction paths. The preferential formation of 2,2′-biindolyl **4** is observed when aryl bromides/triflates are used as σ-donor precursors. Apparently, at the temperature of 80 °C the oxidative addition of aryl bromides/triflates is relatively slow and the cyclisation of **1** to **4** is the main reaction. According to that

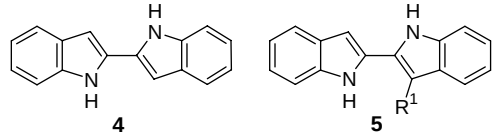
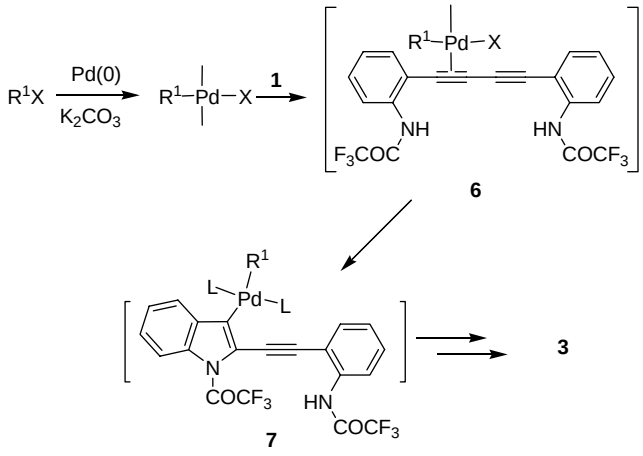
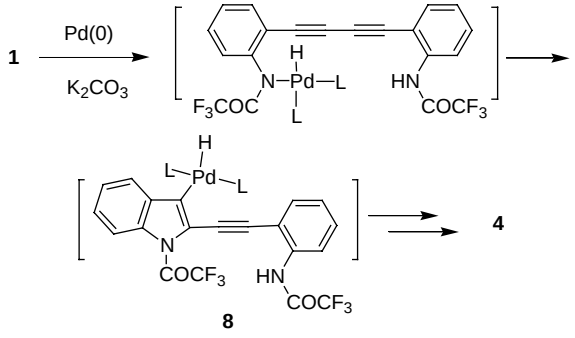


Figure 1.



Scheme 2.

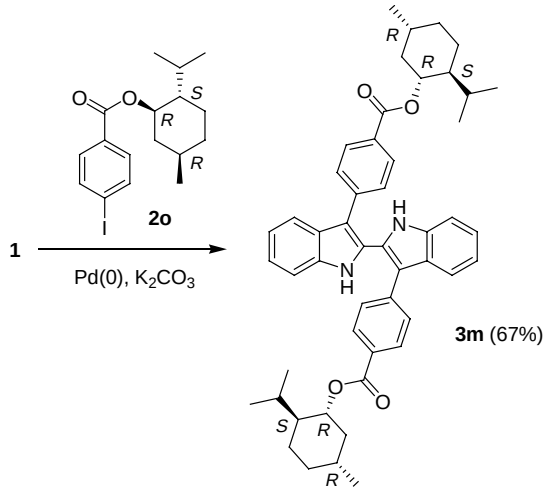


Scheme 3.

the reaction of **1** with the 5-bromopyrimidine under the same reaction conditions used for aryl iodides led only to the formation of **4** (75% yield). However, under the conditions previously reported to successfully give 2-substituted 3-aryl- and 3-heteroarylindoles by the palladium-catalysed reaction of *o*-alkynyltrifluoroacetanilides with aryl bromides and triflates[7] the formation of **3** was disappointing from a synthetic point of view (Table 1, entries 12 and 13). Very likely, at 100 °C the oxidative addition of Pd(0) into the N–H bond is the fastest process. According to that the formation of the 2,2′-biindolyl **4** was the main reaction product (88% yield) when **1** was reacted with the more reactive vinyl triflate **2m** in CH_3CN at 100 °C in the presence of $Pd(PPh_3)_4$ and K_2CO_3. Consequently, we failed to shift the reaction towards the aminopalladation/reductive elimination mechanism when aryl/heteroaryl bromides were used as σ-donors, even if the formation of the target derivatives **3** can be achieved in moderate yield by increasing the **1**:**2** molar ratio (Table 1, entry 14).

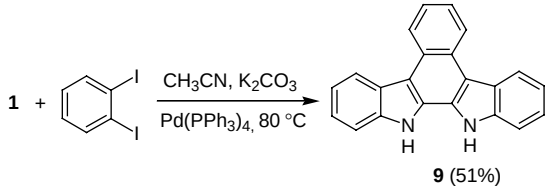
The increasing of the 1:2 molar ratio also limited the formation of the derivates **5** (Table 1, entries 7 and 11).

Interestingly, application of the procedure to (−)-menthyl *p*-iodobenzoate **2o** (Scheme 4) and (+)-menthyl *p*-iodobenzoate **2o′** led to the formation in good yields of corresponding chiral 3,3′-disubstituted-biindolyls **3m** (67% yield) and **3m′** (61% yield) derivatives, respectively. The absolute stereochemistry of **3m** and **3m′** can be assigned on the assumption that the stereogenic centres in the starting aryl iodide are not affected during this transformation.



Scheme 4.

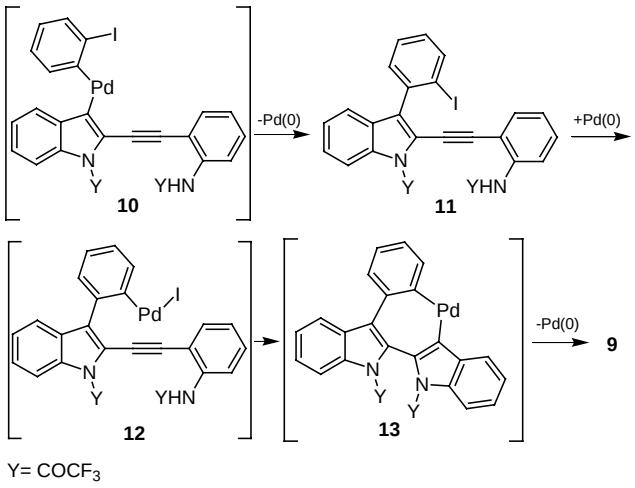
Moreover, treating **1** with 1,2-diiodobenzene provides an easy entry into the benzo[*c*]indolo[2,3-*a*]carbazole **9** (Scheme 5).



Scheme 5.

To the best of our knowledge, the synthesis of this heterocyclic system has not been reported previously. Intermediates **10**–**13** are suggested to be involved in a palladium(0)/palladium(II) catalytic cycle (Scheme 6).

In conclusion, because of the simple experimental procedure, easy availability of starting materials, and ability to incorporate a variety of functional groups, the present methods represents a valuable tool for the synthesis of 3,3′-disubstituted-2,2′-biindolys through the palladium-catalysed reaction of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide with aryl iodides/vinyl triflates. Subsequent application of the procedure to homochiral aryl iodides affords the corresponding chiral 3,3′-disubstituted-2,2′-biindolys. It is worth noting that the here reported protocol could allow a versatile access to indolobenzocarbazole fused derivatives from 1,2-diiodoarenes.



Scheme 6.

3. Experimental

3.1. General

Temperatures are reported as bath temperature. Solvents used in extraction and purification were distilled prior to use. Compounds were visualised on analytical thin-layer chromatograms (TLC) by UV light (254 nm). The products, after usual work-up, were purified by flash chromatography on silica gel (230–400 mesh) eluting with *n*-hexane/ethyl acetate mixtures. ^{1}H and ^{13}C NMR spectra were recorded with a Varian-Gemini at 200 MHz and a Bruker AC 200 E spectrometers. ESI mass spectra were recorded with a ThermoFinnigan LCQ Deca XP Plus equipped with an orthogonal ESI source and ESI accurate mass measurements were recorded with a Mass spectrometer Finnigan TSQ Quantum Ultra with accurate mass options instrument. IR were recorded with Perkin-Elmer 683 and 16 PC spectrometers. Only the most significant IR absorptions are given. Optical rotations were measured on a Perkin Elmer 343 plus polarimeter. CHN analyses were recorded with an Eager 200 analyser. All starting materials, catalysts, and solvents if not otherwise stated, are commercially available and were used as purchased, without further purification. The 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide[5c] **1**, triflates[22] **2f**, **l**–**n**, (−)-menthyl *p*-iodobenzoate[23] **2o** and (+)-menthyl *p*-iodobenzoate were prepared according to described methods. The following products were identified by comparison of their physical and spectral data with those given in the cited references: 2,2′biindolyl[14b] **4** and 3,3′-diphenyl-1*H*,1′*H*-[2,2′]biindolyl[11a] **3a**.

3.1.1. General procedure for the preparation of 3,3′-disubstituted-2,2′-biindolys 3. A typical procedure is as follows: to a stirred solution of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide **1** (0.150 g, 0.35 mmol) in boiling acetonitrile (7 mL) were added methyl 4-iodobenzoate **2b** (0.195 g, 0.78 mmol), K_2CO_3 (0.244 g, 1.77 mmol) and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol). The reaction mixture was stirred at 80 °C (bath temperature) under a nitrogen atmosphere for 3.5 h and poured in a separatory funnel containing water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with a 80:20 *n*-hexane/EtOAc mixture to give 0.117 g (77%) of **3b**: Yellow solid; IR (KBr) 3340, 1720, 1610, 770, 740 cm^{-1}; ^{1}H NMR (DMSO) δ 3.74 (s, 6H), 7.05–7.20 (m, 8H), 7.45–7.56 (m, 8H), 11.83 (s, 2H); ^{13}C NMR δ 57.9, 117.9, 121.0, 124.4, 126.1, 128.5, 132.1, 132.6, 133.0, 134.3, 135.4, 135.5, 139.3, 141.2, 142.6, 172.1; ESI-MS: *m*/*z* (% relative intensity) 499.3 (93) $(M-H)^-$; ESI-HRMS calcd for $C_{32}H_{23}N_2O_4$ 499.544, Found 499.541.

3.1.2. 3,3′-Bis-(3-benzoic acid methyl ester)-1*H*,1′*H*-[2,2′]biindolyl 3c. Yield: 144.0 mg, 63%; Yellow solid; IR (KBr) 3320, 1710, 860 cm^{-1}; ^{1}H NMR (DMSO) δ 3.74 (s, 6H), 7.06–7.20 (m, 8H), 7.45–7.56 (m, 8H), 11.83 (br s, 2H); ^{13}C NMR (DMSO) δ 57.9, 117.9, 121.0, 124.4, 126.1, 128.5, 132.1, 132.6, 133.0, 134.4, 135.4, 135.5, 139.3, 141.2, 142.6, 172.0. Anal. Calcd for $C_{32}H_{24}N_2O_4$ C, 76.78; H, 4.83; N, 5.60; Found C, 76.63; H, 4.86; N, 5.55.

3.1.3. 1-{4-[3′-(4-Acetyl-phenyl)-1*H*,1′*H*-[2,2′]biindolyl-3-yl]-phenyl}-ethanone 3d. Yield: 166.0 mg, 73%; Yellow solid; IR (KBr) 3320, 1740, 730 cm^{-1}; ^{1}H NMR (DMSO) δ 2.50 (s, 6H), 7.06–7.21 (m, 6H), 7.19 (d, J=8.3 Hz, 4H), 7.48 (d, J=7.7 Hz, 2H), 7.64 (d, J=8.3 Hz, 4H), δ 11.64 (br s, 2H); ^{13}C NMR δ 26.4, 111.8, 115.3, 118.8, 120.2, 122.5, 126.5, 127.4, 127.9, 128.5, 133.7, 136.7, 140.2, 196.8; ESI-MS: *m*/*z* (% relative intensity) 467.4 (100) $(M-H)^-$; ESI-HRMS calcd for $C_{32}H_{23}N_2O_2$ 467.551, Found 467.553.

3.1.4. 3,3′-Bis-(4-chloro-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 3e. Yield: 172.0 mg, 82%; Yellow solid; IR (KBr) 3425, 1620, 1020, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.95–7.26 (m, 12H), 7.36–7.46 (m, 2H), 7.54–7.61 (m, 2H), 11.69 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 111.8, 114.6, 118.6, 120.0, 122.4, 126.4, 126.8, 127.6, 130.1, 133.6, 136.5; ESI-MS: *m*/*z* (% relative intensity) 453.4 (65) $(M-H)^-$, 451.4 (100) $(M-H)^-$. Anal. Calcd for $C_{28}H_{18}Cl_2N_2$ C, 74.18; H, 4.00; N, 6.18; Found C, 74.05; H, 4.16; N, 6.25.

3.1.5. 3,3′-Di-*p*-tolyl-1*H*,1′*H*-[2,2′]biindolyl 3f. Yield: 148.0 mg, 79%; Yellow solid; IR (KBr) 3300, 1520, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 6H), 7.08–7.28 (m, 6H), 7.26 (d, J=7.9 Hz, 4H), 7.48 (d, J=7.9 Hz, 4H), 7.60 (d, J=7.3 Hz, 2H), 8.05 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 110.8, 115.6, 119.4, 120.2, 122.9, 125.9, 127.9, 129.7, 130.1, 131.3, 135.8, 136.8. Anal. Calcd for $C_{30}H_{24}N_2$ C, 87.35; H, 5.86; N, 6.79; Found C, 87.40; H, 5.68; N, 6.89.

3.1.6. 3,3′-Bis-(2,4-dimethyl-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 3g. Yield: 100.0 mg, 23%; Dark brown solid; IR (KBr) 3480, 750 cm^{-1}; ^{1}H NMR (DMSO) δ 2.21 (s, 6H), 2.22 (s, 6H), 6.46 (d, J=7.7 Hz, 1H), 6.58–6.68 (m, 3H), 6.79 (s, 2H), 6.091–7.16 (m, 6H), 7.44 (d, J=8.0 Hz, 2H), 11.48 (br s, 1H), 11.55 (br s, 1H); ^{13}C NMR (DMSO) δ 19.8, 20.8, 111.4, 115.6, 116.1, 119.0, 121.6, 125.5, 125.6, 127.7, 130.0, 130.2, 130.4, 136.0, 136.1, 136.7; ESI-MS: *m*/*z* (% relative intensity) 439.6 (94) $(M-H)^-$, ESI-HRMS calcd for $C_{32}H_{27}N_2$ 439.579, Found 439.577.

3.1.7. 3,3′-Bis-(2-methoxy-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 3h. Yield: 84.0 mg, 38%; Dark brown solid; IR (KBr) 3490, 750 cm^{-1}; ^1H NMR (DMSO) δ 3.40 (s, 6H), 6.65–6.70 (m, 2H), 6.80–6.82 (m, 2H), 6.98–7.186 (m, 8H), 7.39 (d, $J=8.0$ Hz, 4H), 11.30 (br s, 2H); ^{13}C NMR (DMSO) δ 55.1, 100.3, 111.2, 116.4, 126.9, 127.7, 128.1, 128.8, 131.1, 136.0, 156.7, 157.6. Anal. Calcd for $C_{30}H_{24}N_2O_2$ C, 81.06; H, 5.44; N, 6.30; Found C, 81.04; H, 5.71; N, 6.27.

3.1.8. 3,3′-Bis-(4-methoxy-phenyl)-1*H*,1′*H*-[2,2′]-biindolyl 3i. Yield: 108.0 mg, 75%; Brown solid; IR (KBr) 3300, 1730, 820 cm^{-1}; ^1H NMR (DMSO) δ 3.60 (s, 6H), 6.69 (d, $J=8.3$ Hz, 4H), 6.93–7.12 (m, 8H), 7.32 (d, $J=7.6$ Hz, 2H), 7.54 (d, $J=7.6$ Hz, 2H), 11.37 (br s, 2H); ^{13}C NMR (DMSO) δ 54.9, 111.6, 113.8, 115.8, 118.9, 119.5, 122.0, 126.5, 126.7, 127.2, 129.5, 136.2, 157.3; ESI-MS: *m/z* (% relative intensity) 445.3 (100) $(M+H)^+$, 339.3 (84); ESI-HRMS calcd for $C_{30}H_{25}N_2O_2$ 445.540, Found 445.535.

3.1.9. 3,3′-Di-naphthalen-1-yl-1*H*,1′*H*-[2,2′]biindolyl 3j. Yield: 120.0 mg, 51%; Dark brown solid; IR (KBr) 3200, 740 cm^{-1}; ^1H NMR (DMSO) δ 6.51–7.63 (m, 22H), 7.86 (d, $J=8.6$ Hz, 2H), 11.64 (br s, 2H); ^{13}C NMR δ 101.4, 111.8, 113.9, 118.7, 119.4, 119.9, 120.0, 121.7, 122.4, 125.1, 126.1, 126.7, 127.3, 127.6, 127.8, 128.1, 128.5, 131.3, 132.5, 136.5; ESI-MS: *m/z* (% relative intensity) 483.4 (100) $(M-H)^-$, ESI-HRMS calcd for $C_{36}H_{23}N_2$ 483.592, Found 483.589.

3.1.10. 3,3′-Bis-(4-phenyl-cyclohex-1-enyl)-1*H*,1′*H*-[2,2′]biindolyl 3k. Yield: 86.0 mg, 45%; Brown solid; IR (KBr) 3180, 1480, 740 cm^{-1}; ^1H NMR (DMSO) δ 1.85–1.95 (m, 4H), 2.03–2.07 (m, 4H), 2.53–2.59 (m, 6H), 6.15 (br s, 2H), 7.05–7.49 (m, 16H), 7.76 (d, $J=7.6$ Hz, 2H), 10.35 (br s, 2H); ^{13}C NMR (DMSO) δ 28.9, 30.0, 34.2, 111.4, 117.8, 119.5, 121.8, 125.9, 126.6, 126.7, 126.9, 128.4, 131.5, 136.0, 136.3, 147.0; ESI-MS: *m/z* (% relative intensity) 543.4 (100) $(M-H)^-$, ESI-HRMS calcd for $C_{40}H_{35}N_2$ 543.731, Found 543.730.

3.1.11. 3,3′-Bis-(4-*tert*-butyl-cyclohex-1-enyl)-1*H*,1′*H*-[2,2′]biindolyl 3l. Yield: 150.0 mg, 61%; Yellow solid; IR (KBr) 3415, 1614, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (s, 18H), 1.01–1.55 (m, 6H), 1.93–2.05 (m, 4H), 2.35 (br s, 4H), 6.10 (m, 2H), 7.08–7.25 (m, 4H), 7.33 (d, $J=7.3$ Hz, 2H), 7.59 (d, $J=7.7$ Hz, 2H), 8.71 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1, 27.5, 27.8, 31.7, 32.6, 44.4, 110.9, 117.6, 119.8, 120.0, 122.8, 126.3, 128.3, 129.6, 132.9, 135.9; ESI-MS: *m/z* (% relative intensity) 505.5 (43) $(M+H)^+$, 504.4 (100) $(M)^+$, 503.3 (73) $(M-H)^+$, 367 (21). Anal. Calcd for $C_{36}H_{44}N_2$ C, 85.66; H, 8.79; N, 5.55; Found C, 85.49; H, 8.73; N, 5.58.

3.1.12. (−)-3,3′-Bis[benzoic(1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl ester]-1*H*,1′*H*-[2,2′]biindolyl 3m. Yield: 216.0 mg, 67%; Yellow solid; $[\alpha]_D$ −20.8 (5.45 mg/mL, $CHCl_3$); IR (KBr) 3350, 1720, 1600, 1270, 740 cm^{-1}; ^1H NMR (DMSO) δ 0.83 (d, $J=5.8$ Hz, 6H), 0.89 (d, $J=3.6$ Hz, 6H), 0.93 (d, $J=4.1$ Hz, 6H), 1.02–2.13 (m, 18H), 4.85–5.04 (m, 2H), 7.13–7.24 (m, 6H), 7.52 (d, $J=8.3$ Hz, 4H), 7.72 (d, $J=8.0$ Hz, 2H), 7.98 (d, $J=8.3$ Hz, 4H), 8.46 (br s, 2H); ^{13}C NMR (DMSO) δ 16.5, 20.8, 22.0, 23.6, 26.5, 31.4, 34.3, 40.9, 42.2, 74.9, 111.4, 115.7, 119.4, 120.9, 123.5, 126.3, 127.2, 128.6, 129.5, 130.0, 136.3, 139.1, 166.1; ESI-MS: *m/z* (% relative intensity) 749.2 (100) $(M+H)^+$. Anal. Calcd for $C_{50}H_{56}N_2O_4$ C, 80.18; H, 7.54; N, 3.74; Found C, 80.15; H, 7.48; N, 7.60.

3.1.13. (+)-3,3′-Bis[benzoic(1*S*,2*R*,5*S*)-2-isopropyl-5-methyl-cyclohexyl ester]-1*H*,1′*H*-[2,2′]biindolyl 3m′. Yield: 468.0 mg, 61%; Yellow solid; $[\alpha]_D$ +20.5 (5.24 mg/mL, $CHCl_3$).

3.1.14. 3-*p*-Tolyl-1*H*,1′*H*-[2,2′]biindolyl 5a. Yield: 20.0 mg, 14%; Brown solid; IR (KBr) 3400, 820 cm^{-1}; ^1H NMR (DMSO) δ 2.37 (s, 3H), 6.48 (s, 1H), 6.98–7.49 (m, 12H), 11.06 (br s, 1H), 11.48 (br s, 1H); mass spectrum (EI): *m/z* (% relative intensity) 323 (100) $(M+H)^+$, Anal. Calcd for $C_{23}H_{18}N_2$ C, 85.68; H, 5.63; N, 8.69; Found C, 85.70; H, 5.82; N, 8.57.

3.1.15. 3-(2,4-Dimethyl-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 5b. Yield: 222.0 mg, 67%; Dark yellow solid; IR (KBr) 3490, 750 cm^{-1}; ^1H NMR (DMSO) δ 1.97 (s, 3H), 2.38 (s, 3H), 6.10 (s, 1H), 6.94–7.19 (m, 9H), 7.37–7.50 (m, 6H), 10.99 (br s, 1H), 11.38 (br s, 1H); ^{13}C NMR (DMSO) δ 19.6, 20.8, 100.0, 111.2, 113.5, 118.6, 119.4, 119.6, 119.8, 121.5, 121.9, 126.7, 127.2, 128.1, 128.7, 130.7, 130.9, 131.1, 131.3, 135.7, 136.1, 136.3, 136.9; (EI): *m/z* (% relative intensity) 337 (100) $(M+H)^+$, 322 (34). Anal. Calcd for $C_{24}H_{20}N_2$ C, 85.68; H, 5.99; N, 8.33; Found C, 85.59; H, 5.84; N, 8.41.

3.1.16. 3-(2-Methoxy-phenyl)-1*H*,1′*H*-[2,2′]biindolyl 5c. Yield: 36.0 mg, 30%; Yellow solid; ^1H NMR (DMSO) δ 3.60 (s, 3H), 6.60–7.41 (m, 13H), 10.95 (br s, 11.35H); EI-MS: *m/z* (% relative intensity) 339.2 (100) $(M+H)^+$; ESI-HRMS calcd for $C_{23}H_{19}N_2O$ 339.409, Found 339.405.

3.1.17. Experimental procedure for the preparation of benzo[*c*]indolo[2,3-*a*]carbazole 9. To a stirred solution of 2,2,2-trifluoro-*N*-(2-(4-[2,2,2-trifluoro-acetylamino)-phenyl]-buta-1,3-diynyl)-phenyl)-acetamide **1** (0.100 g, 0.24 mmol) in acetonitrile/DMSO (7 mL/1 mL) were added 1,2-diiodobenzene (0.093 g, 0.28 mmol), K_2CO_3 (0.099 g, 0.72 mmol) and $Pd(PPh_3)_4$ (0.019 g, 0.017 mmol). The reaction mixture was stirred at 80 °C (bath temperature) under a nitrogen atmosphere for 20 h and poured in a separatory funnel containing water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with a 75:25 *n*-hexane/EtOAc mixture to give 0.037 g (51%) of **9**: Dark solid; IR (KBr) 3450, 820, 750 cm^{-1}; ^1H NMR (DMSO) δ 6.81–6.84 (m, 4H), 7.06–7.10 (m, 2H), 7.24–7.28 (d, $J=8.0$ Hz, 2H), 8.04–8.08 (d, $J=8.0$ Hz, 2H), 8.32–8.36 (m, 2H), 11.01 (s, 2H); ^{13}C NMR δ 112.1, 113.2, 119.0, 120.1, 121.2, 121.6, 123.6, 123.8, 125.8, 126.3, 138.4; ESI-MS *m/z* (% relative intensity) 329.2 (100) $(M+Na)^+$ ESI-HRMS calcd for $C_{22}H_{14}N_2Na$ 329.357, Found 329.353.

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Preparation of 3-hydroxyoxindoles with dimethyldioxirane and their use for the synthesis of natural products

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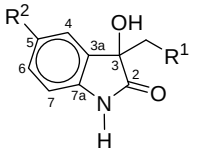
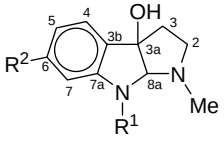
Abstract—This work describes a general protocol for the oxidation of indole and oxindole derivatives with dimethyldioxirane to give 3-hydroxyoxindoles present in many natural products. This strategy allowed us to synthesize the natural product **1**, to carry out the first total synthesis of **4**, a formal total synthesis of donaxaridine (**5**) and to achieve the synthesis of pyrroloindoline **8**, a debromo analogue of the natural product flustraminol B (**7**).

1. Introduction

A number of oxindole, pyrroloindole and furoindole alkaloids possessing a 3- and/or 3a-hydroxyl substituent, some of which possess interesting biological activities,[1] have been isolated from natural sources. Examples of these are metabolites **1**–**3** (Scheme 1) isolated from rice bran,[1a,b] which are putative intermediates in the oxidation of 3-indolylacetic acid. Particularly, **1** has also been isolated from *Hibiscus moscheutos* L.[1c] In addition, dioxindole **4** was isolated from cabbage inoculated with *Pseudomonas cichorii*,[1d] donaxaridine (**5**) was isolated from the giant reed *Arundo donax*,[1e] allina (**6**) was isolated from the epigeal part of *Allium odorum* L.,[1f] and flustraminol B (**7**) was isolated from the marine bryozoan *Flustra foliacea*.[1g] The tricyclic compounds **6**–**8** possess a physostigmine-like skeleton.



1: $R^1 = CO_2Me$, $R_2 = H$
2: $R^1 = CO_2H$, $R_2 = OH$
3: $R^1 = CO_2Me$, $R_2 = OH$
4: $R^1 = CN$, $R_2 = H$
5: $R^1 = CH_2NHMe$, $R_2 = H$



6: $R^1 = R^2 = H$
7: R^1 =  ; $R^2 = Br$
8: R^1 =  ; $R^2 = H$

Scheme 1.

The biological activity of oxindole derivatives and their structural relationship to indoles make these compounds important targets in medicinal and synthetic organic chemistry, as is reflected in the number of synthetic approaches hitherto. 3-Hydroxyoxindoles and 3a-hydroxypyrrolo- or furo-indole derivatives have been synthesized starting from isatins,[2] indoles,[1b,h,3] oxindoles,[4] 3-hydroxy-2,4-quinolinediones[5] and 2-allyloxyindolin-3-ones,[6] using different oxidating agents such as *m*-CPBA, H_2O_2/chloroperoxidase, *t*-BuOOH, NBS/SeO_2, DMSO, and $FeCl_3$/MeOH/H_2O. The use of oxone as the oxidant to prepare DMD in buffered acetone[7] has become popular due in part to its stability and cost-effectiveness.[8] Zhang et al. have demonstrated that indole derivatives with an *N*-electron withdrawing group can be oxidized to oxindoles with DMD via putative epoxide intermediates. Under these experimental conditions they reported that only minor amounts of 3-hydroxyindole derivatives were obtained.[9] On the other hand, Danishefsky et al. also successfully oxidized trytophan and dihydropyrroloindole derivatives with DMD in order to obtain 3a-hydroxypyrroloindoles.[10]

We report herein a general approach to 3-hydroxyoxindole derivatives based on the dimethyldioxirane (DMD)

Keywords: 3-Hydroxyoxindoles; 3-Hydroxyfuroindole; Donaxaridine; Dimethyldioxirane.
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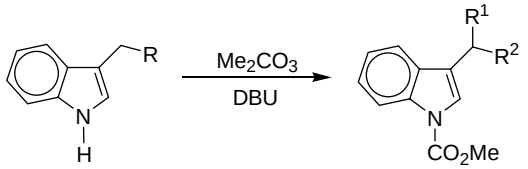
oxidation of *N*-substituted indoles and oxindoles and its application to the synthesis of natural product **1**, the first total synthesis of **4**, the formal total synthesis of donaxaridine (**5**) and the synthesis of pyrroloindoline **8**, a debromo analogue of the natural product flustraminol B (**7**).

2. Results and discussion

In order to improve the yield of 3-hydroxyoxindole derivatives using a DMD protocol, we oxidized the indole 2,3-double bond of *N*-carbomethoxy compounds **13–16** (Scheme 2) and oxindoles **23–29** (Scheme 3) with DMD prepared according to Corey.[7] These compounds were selected as starting materials in concordance to the functionality present in synthetic targets **1**, **4**, **5** and **8**.



9 : R = CO_2Me
10: R = CH_2OH
11: R = CONHMe
12: R = CN

13: R^1 = H, R^2 = CO_2Me
14: R^1 = H, R^2 = CH_2OCO_2Me
15: R^1 = H, R^2 = CONHMe
16: R^1 = H, R^2 = CN
17: R^1 = CO_2Me, R^2 = CN

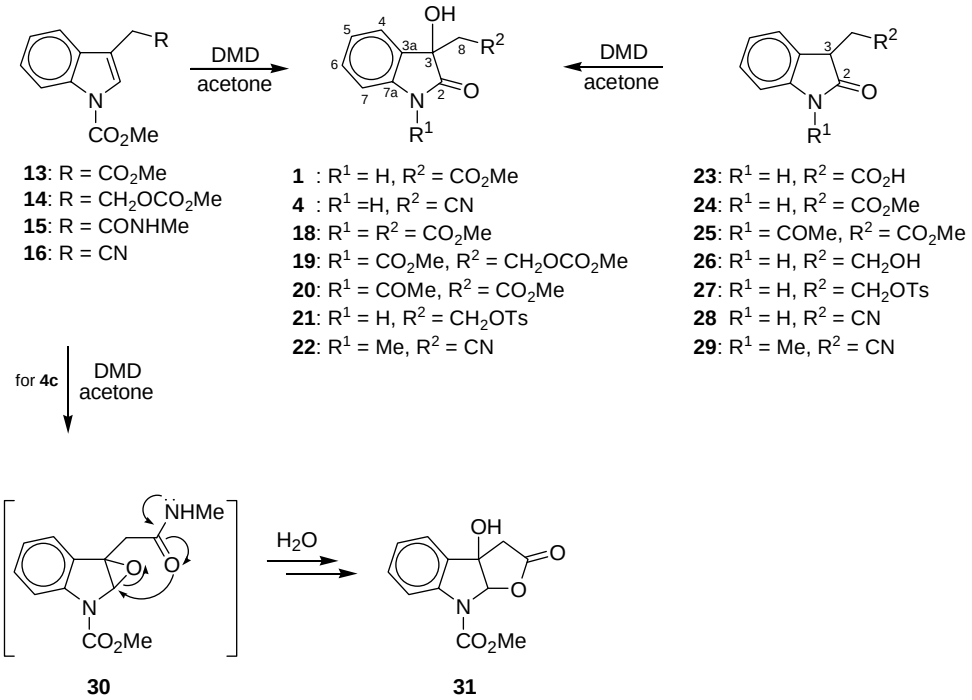
Scheme 2.

Compounds **13–15** were prepared from **9–11**[11] according to Scheme 2. When **9–11** were treated with Me_2CO_3, containing 0.1 equiv of 1,8-diazabicyclo[5.4.0]undecen-7-ene[12] (DBU) as the base, compounds **13–15** were obtained in 63–82% yield. When indole **12** was treated with DBU/Me_2CO_3 or Na/Me_2CO_3 compound **16** was obtained in low yields (15–21%) together with **17** (57–60%).[13] However, when compound **12** was treated with NaH/$ClCO_2Me$, then **16** was obtained in 73% yield and no traces of **17** were observed.

Oxidation of **13** with 2.5 equiv of DMD, generated in situ from oxone in acetone, afforded 3-hydroxyoxindole **18** in 63% yield (Scheme 3). The ^{1}H NMR spectrum of **18**, obtained in $(CD_3)_2SO$, showed an AB pattern at δ 3.25 and 3.19 (J_{AB} = 16.5 Hz) for the C8 methylene group and a singlet for the proton of the OH group at δ 6.60, which exchanged with D_2O. The structure of **18** was confirmed by X-ray crystallography (Fig. 1, Table 1).

Similarly, oxidation of **14** with 5 equiv of DMD afforded **19** in 94% yield. When **15** was oxidized with 2.5 equiv of DMD, the expected hydroxyoxindole was not formed, instead compound **31** was obtained in 96% yield. The formation of **31** can be rationalized by amide oxygen assisted cleavage of the intermediate epoxide in **30**, followed by hydrolysis of the intermediate iminolactone. Oxidation of indole **16** with DMD did not produced the corresponding oxindole, instead a complex mixture of products, as judged from ^{1}H NMR spectrum of the crude reaction product, was obtained.

We then turned our attention to synthesize the series of oxindole derivatives **23–29** (Scheme 3). Thus, oxidation of indole-3-acetic acid with DMSO/HCl[14] at room temperature gave oxindole **23**, which after treatment with MeOH/H^+ at reflux afforded ester **24**[15a] in 77% overall yield. Compound **24** was converted into the *N*-acetyl derivative **25** in 92% yield by acetylation with boiling acetic anhydride.[15b] Similarly, oxidation of indole **10** with DMSO/HCl afforded **26**[2a] (72%), which upon reaction with TsCl gave **27**[16]



13: R = CO_2Me
14: R = CH_2OCO_2Me
15: R = CONHMe
16: R = CN

1 : R^1 = H, R^2 = CO_2Me
4 : R^1 =H, R^2 = CN
18: R^1 = R^2 = CO_2Me
19: R^1 = CO_2Me, R^2 = CH_2OCO_2Me
20: R^1 = COMe, R^2 = CO_2Me
21: R^1 = H, R^2 = CH_2OTs
22: R^1 = Me, R^2 = CN

23: R^1 = H, R^2 = CO_2H
24: R^1 = H, R^2 = CO_2Me
25: R^1 = COMe, R^2 = CO_2Me
26: R^1 = H, R^2 = CH_2OH
27: R^1 = H, R^2 = CH_2OTs
28 R^1 = H, R^2 = CN
29: R^1 = Me, R^2 = CN

Scheme 3.

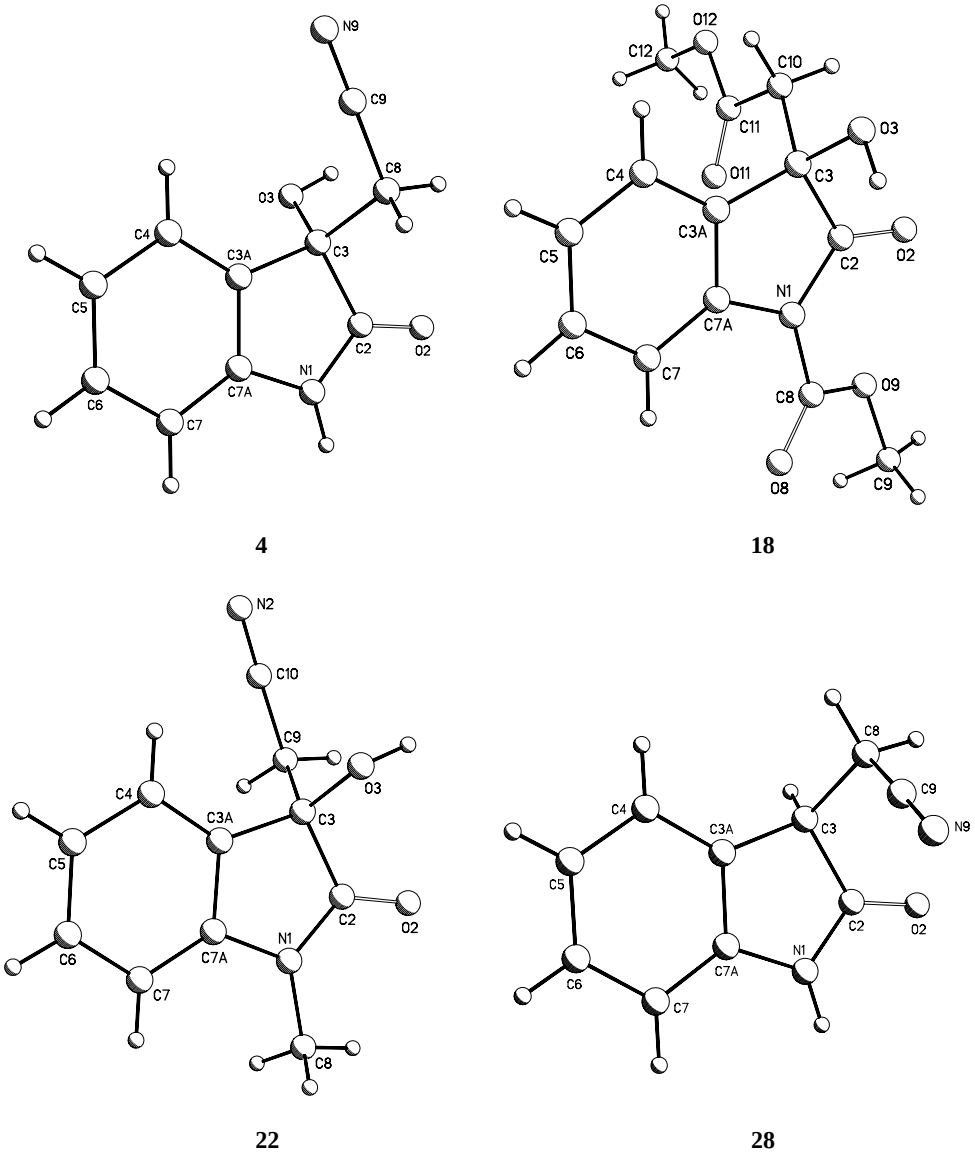


Figure 1.

(87%). Finally, treatment of **12** with DMSO/HCl afforded oxindole **28** in 78% yield. The X-ray structure of **28** is shown in Figure 1 (Table 1). The reaction of these oxindoles with DMD was then examined in order to gain more information about the oxidation process. Thus, **23** failed to oxidized with DMD even after prolonged reaction times. In contrast, reaction of **24** with 5 equiv of DMD at room temperature for 8 h afforded the natural product **1** in good yield (80%). This compound was carefully identified since some spectroscopic properties are ambiguous in the literature.[1a,1h]

The *N*-acylated oxindole **25** reacted much more rapidly (0.75 h) and with less oxidant (2.5 equiv) than **24**, to produce the dioxindole derivative **20** in 69% yield, a fact consistent with the expected easier enolization of the imide system present in **25**. These results suggest that the generation of **18** and **19** from **13** and **14**, respectively, involves two successive oxidations, where the hydroxyl group at C-3 is introduced via the enol derivative of an intermediate oxindole.[17]

When oxindole **26** was reacted with DMD no hydroxylated product was obtained even after 24 h. However, the *N*-tosyl derivative **27** smoothly gave the dioxindole derivative **21** in 65% yield. Since donaxaridine (**5**) has been previously prepared from **21**,[2b] the above procedure constitutes a formal total synthesis of **5**. Thus, the natural product **5** was obtained from **26** in 50% overall yield. Oxidation of **28** with 2.5 equiv of DMD completed the first total synthesis of the natural product **4** in 94% yield. Finally, oxidation of **29**[18] with 2.5 equiv of DMD yielded the analog **22** in 83% yield. The X-ray structures of **4** and **22** are shown in Figure 1 (Table 1).

In order to evaluate if oxidation of compounds **24**, **25**, **27**–**29** with DMD occurs either as a benzylic oxidation[19] or as an α-keto oxidation, *N*-carbomethoxy-2,3-dihydroindole was treated with DMD under the same reaction conditions used for the oxidation of **24**, after which no traces of the benzylic oxidated products could be detected even after 24 h, these results being consistent with the above proposed reaction

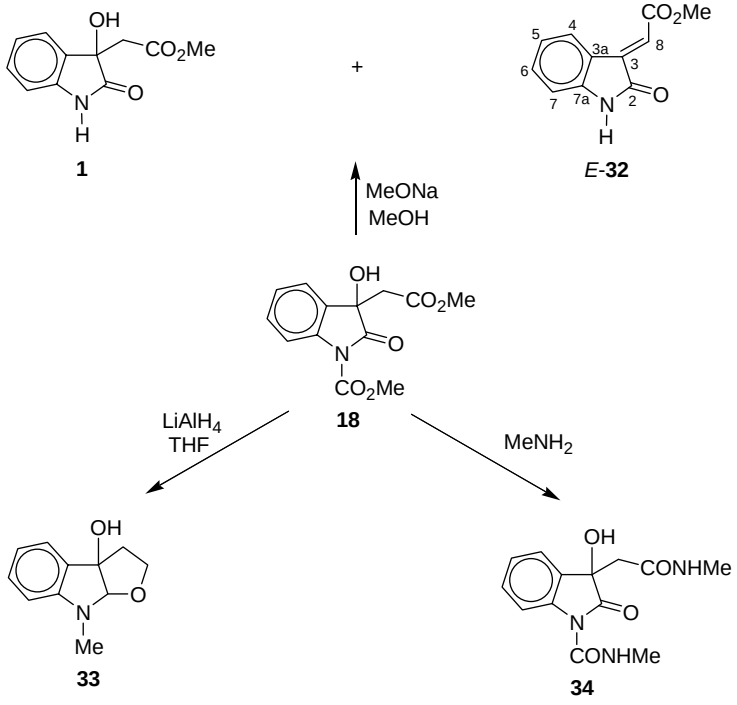
Table 1. X-ray data collection and processing parameters for **4**, **18**, **22**, **28**, **35** and **39**

Compound	**4**	**18**	**22**	**28**	**35**	**39**
Formula	$C_{10}H_8O_2N_2$	$C_{13}H_{13}O_6N$	$C_{11}H_{10}O_2N_2$	$C_{10}H_8O_1N_2$	$C_{16}H_{19}O_4N$	$C_{11}H_{14}ON_2$
Size (mm^3)	0.53×0.49×0.39	0.42×0.41×0.22	0.40×0.35×0.35	0.51×0.50×0.30	0.49×0.40×0.34	0.30×0.20×0.20
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1$	$P2_1/n$	$P2_1/c$	$P2_1/n$
a (Å)	5.839(1)	10.9983(5)	8.207(2)	7.292(1)	8.767(3)	8.530(2)
b (Å)	12.119(2)	8.1492(4)	4.857(1)	15.958(2)	22.314(7)	6.319(1)
c (Å)	12.566(3)	14.7280(6)	12.615(1)	7.612(1)	8.942(3)	19.197(4)
β (°)	92.06(3)	102.555(1)	93.10(3)	101.208(4)	114.168(8)	95.33(2)
V ($Å^3$)	888.5(3)	1288.47(10)	502.2(1)	869.0(2)	1595.9(9)	1030.4(3)
D_{calcd} (g cm^{-3})	1.41	1.44	1.34	1.19	1.20	1.23
Z	4	4	2	4	4	4
M (mm^{-1})	0.10 (Mo Kα)	0.12 (Mo Kα)	0.78 (Cu Kα)	0.07 (Mo Kα)	0.09 (Mo Kα)	0.64 (Cu Kα)
T (K)	293	293	293	293	293	293
$2\theta_{range}$ (°)	2.34–26.12	2.11–26.01	3.51–54.97	2.55–26.02	1.83–26.02	4.63–54.92
Total reflections	5706	8136	1339	5830	10,376	1595
Unique reflections	1751	2521	1337	1701	3116	1286
R_{int} (%)	0.05	0.03	0.001	0.001	0.08	0.03
Observed reflections	1351 $I\geq 4\sigma(I)$	1976 $I\geq 4\sigma(I)$	1266 $I\geq 4\sigma(I)$	1066 $I\geq 4\sigma(I)$	1367 $I\geq 4\sigma(I)$	1263 $I\geq 4\sigma(I)$
Parameters	160	234	141	126	198	140
R (%), R_w (%)	4.2, 11.4	3.8, 10	2.8, 7.5	3.7, 7.6	5.9, 15.2	3.8, 9.8
e_{max} (e $Å^{-3}$)	0.20	0.20	0.13	0.16	0.32	0.20
CCDC no.	295377	295378	295379	295380	295381	295382

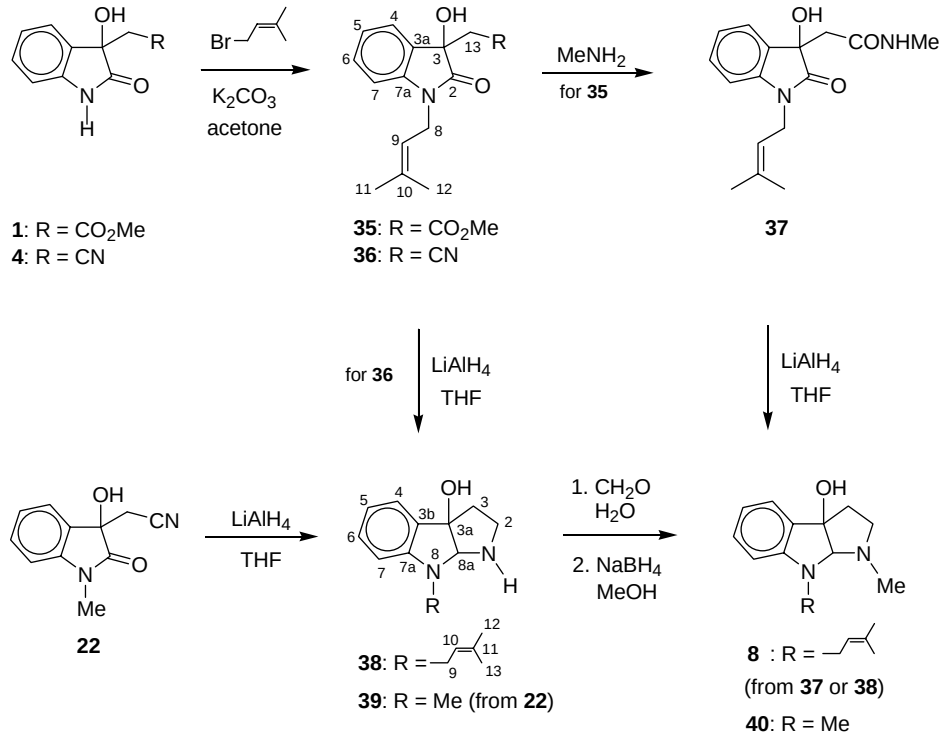
mechanism for the oxidation of **13** and **14** involving two successive oxidations to give **18** and **19**, respectively.

On the other hand, dioxindole **18** could also be used to produce **1**. The later was generated in modest yield (42%) by removal of the *N*-methoxycarbonyl group with methanolic sodium methoxide (reflux, 0.25 h, Scheme 4), which also afforded undesired dehydration product **32** (47%) as only the *E* isomer. The stereochemistry around the C3=C8 double bond in **32** was established on the basis of the marked deshielding of the H4 signal (8.54 ppm in $CDCl_3$ solution) caused by the proximity of the carbonyl ester group.[20]

In order to construct a trycyclic 3-hydroxyindole skeleton, dioxindole **18** was reduced with $LiAlH_4$ (THF/reflux/3 h) to afford 3-hydroxyfuroindole **33** in 21% yield, which has the furoindole skeleton found in natural occurring madindolines A and B.[21] In addition, compound **18** was quantitatively converted into the urea derivative **34**, however, it was insoluble for further chemical transformations (e.g., for $LiAlH_4$ reduction). The obtention of **33** from **18** suggested



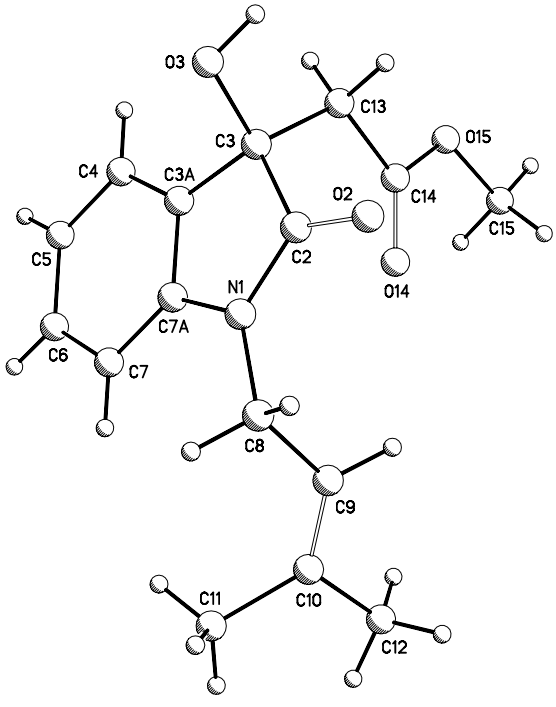
Scheme 4.



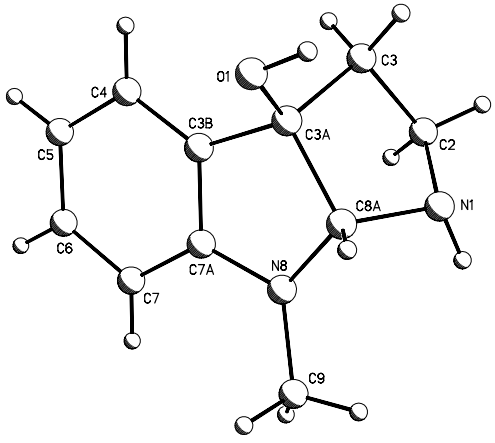
Scheme 5.

that the corresponding *N*-demethyl analog should likewise be available from **1**. However, tryptophol (**10**), was obtained instead, in quantitative yield.[22]

With **1** and **4** now being readily available, their conversion into **8**, containing a physostigmine-like skeleton, was examined (Scheme 5). Thus, N-alkylation of **1** and **4** with prenyl bromide (K_2CO_3/acetone/reflux 4 h) gave **35** and **36** in 97 and 96% yield, respectively. The X-ray structure of **35** is shown in Figure 2 (Table 1). Compound **35** reacted with $MeNH_2$ (room temperature/16 h) to give the oxindole **37** in 98% yield. Reduction of **37** with $LiAlH_4$ in refluxing THF



35



39

Figure 2.

gave debromoflustraminol **8** (55%) in 52% overall yield from **1**. On the other hand, reduction of **36** with $LiAlH_4$ in refluxing THF afforded **38** in 47% yield. Reductive alkylation of **38** was carried out with CH_2O/H_2O and $NaBH_4$/MeOH to give **8** (47%) in 21% overall yield from **4**. On the other hand, the synthesis of the *N*-methylated analog **40** of the natural product **6**, was undertaken from **22**. Thus, reduction of **22** with $LiAlH_4$/THF afforded the pyrroloindole **39**[3d] in 67% yield. The X-ray structure of **39** is shown in Figure 2 (Table 1). Reductive alkylation of **39** with CH_2O/H_2O and then with $NaBH_4$/MeOH afforded **40**[23] in 89% yield.

3. Conclusion

In summary, we have developed a general and practical protocol for the synthesis of 3-hydroxyoxindoles starting from indole or oxindole derivatives. This methodology has allowed us to achieve the syntheses of natural products **1**, **4**, **5** and of unnatural **8**.

4. Experimental

4.1. General experimental procedures

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. The 400 and 100 MHz ^1H and ^{13}C NMR spectra were obtained on a JEOL Eclipse 400 spectrometer and the 300 and 75 MHz ^1H and ^{13}C NMR spectra were obtained on a Varian Mercury-300 spectrometer, using $CDCl_3$, CD_3OD, acetone-d_6 or DMSO-d_6 as the solvent and TMS as the internal reference. For the complete assignments 2D NMR spectra, HMQC and HMBC were used. Chemical shifts are reported in ppm from TMS. Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz) and assignment. Low-resolution mass spectra were recorded at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured on a JEOL JMS-SX 102A mass spectrometer at Instituto de Química, UNAM-Mexico. Microanalytical determinations were performed on a Perkin Elmer 2400 Series PCII apparatus. Analytical thin-layer chromatography (TLC) was done on silica gel 60 F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography[24] was done using silica gel 60 (230–400 mesh) from Aldrich.

4.2. General procedure for the preparation of indole carbamates 13–15

A solution of the appropriate indole **9**–**11** (16.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) 246 μL (0.250 g, 0.1 equiv) in Me_2CO_3 (50 mL) was stirred at reflux for a specified period of time as follows: **9** (26 h), **10** (33 h) and **11** (26 h). After cooling to room temperature, EtOAc (50 mL) was added to the mixture and the organic phase was washed with a saturated solution of NH_4Cl (2×30 mL) and brine (2×30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude products **13**–**15** were purified by flash chromatography on silica gel (using EtOAc/hexane 2:3 for **13** and **14**, and EtOAc for **15**, as the eluant).

4.2.1. Methyl(1-carbomethoxy-1*H*-indol-3-yl)acetate (13). Prepared from 3.10 g of **9** as a yellow oil (3.3 g, 82%); ^1H NMR ($CDCl_3$), δ 8.17 (1H, br d, J=7.8 Hz, H7); 7.60 (1H, s, H2); 7.53 (1H, d, J=7.3 Hz, H4); 7.35 (1H, td, J=7.8, 1.1 Hz, H6); 7.27 (1H, td, J=7.9, 1.1 Hz, H5); 4.02 (3H, s, NCO_2CH_3); 3.72 (2H, s, H8); 3.71 (3H, s, CO_2CH_3). ^{13}C NMR ($CDCl_3$), δ 171.3 (CO_2Me); 151.3 (NCO_2Me); 135.4 (C7a); 130.0 (C3a); 124.9 (C6); 124.0 (C2); 123.0 (C5); 119.0 (C4); 115.2 (C7); 114.0 (C3); 53.8 (NCO_2CH_3); 52.2 (CO_2CH_3); 30.8 (C8). IR (film) ν_{max} 3029, 2954, 1738, 1612, 1455, 1259 cm^{-1}. EIMS *m/z* (relative intensity) 247 (M^+, 41), 188 (100), 144 (49). Anal. Calcd for $C_{13}H_{11}NO_4$: C 63.15; H 5.30; N 5.66. Found: C 62.77; H 5.35; N 5.75.

4.2.2. 3-(2-Carbomethoxyethoxyl)-1-carbomethoxy-1*H*-indole (14). Prepared from 2.64 g of **10** as a yellow oil (3.27 g, 72%). ^1H NMR (DMSO-d_6), δ 8.08 (1H, d, J=7.5 Hz, H7); 7.64 (1H, d, J=7.7 Hz, H4); 7.56 (1H, s, H2); 7.34 (1H, td, J=7.3, 1.5 Hz, H6); 7.26 (1H, td, J=7.7, 1.3 Hz, H5); 4.36 (2H, t, J=7.0 Hz, H9); 3.97 (3H, s, NCO_2CH_3); 3.67 (3H, s, OCO_2CH_3); 3.02 (2H, td, J=6.9, 1.1 Hz, H8). ^{13}C NMR (DMSO-d_6), δ 155.1 (OCO_2Me); 150.8 (NCO_2Me); 134.8 (C7a); 130.0 (C3a); 124.6 (C6); 123.1 (C2); 122.7 (C5); 119.2 (C4); 117.1 (C3); 114.6 (C7); 66.6 (C9); 54.5 (OCO_2CH_3); 53.9 (NCO_2CH_3); 23.8 (C8). IR (film) ν_{max} 2958, 1747, 1457, 1381, 1264 cm^{-1}. EIMS *m/z* (relative intensity) 277 (M^+, 12), 201 (100), 144 (22), 115 (39), 59 (32). Anal. Calcd for $C_{14}H_{15}NO_5$: C 60.64; H 5.45; N 5.05. Found: C 60.86; H 5.68; N 4.46.

4.2.3. Methyl(1-carbomethoxy-1*H*-indol-3-yl)acetamide (15). Prepared from 3.09 g of **11** as colorless crystals (2.55 g, 63%), mp 147–148 °C (Et_2O). ^1H NMR ($CDCl_3$), δ 8.16 (1H, br d, H7); 7.55 (1H, s, H2); 7.51 (1H, d, J=8.1 Hz, H4); 7.36 (1H, td, J=7.0, 1.1 Hz, H6); 7.27 (1H, td, J=8.0, 1.1 Hz, H5); 5.92 (1H, br s, NH), 3.98 (3H, s, CO_2CH_3); 3.63 (2H, s, H8); 2.74 (3H, d, J=5.1 Hz, NCH_3). ^{13}C NMR ($CDCl_3$), δ 170.6 (*C*ONHMe); 151.2 (NCO_2Me); 135.6 (C7a); 129.8 (C3a); 125.2 (C6); 124.4 (C2); 123.3 (C5); 119.1 (C4); 115.3 (C7); 114.9 (C3); 53.8 (NCO_2CH_3); 33.0 (C8); 26.4 (NCH_3). IR (KBr) ν_{max} 3437, 3275, 3126, 1745, 1650, 1555, 1456 cm^{-1}. EIMS *m/z* (relative intensity) 246 (M^+, 55), 188 (100), 144 (59), 102 (20), 58 (17). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C 63.40; H 5.73; N 11.38. Found: C 63.51; H 5.93; N 11.41.

4.2.4. Preparation of (1-carbomethoxy-1*H*-indol-3-yl)-acetonitrile (16). To a solution of 1.5 g of **12** (9.62 mmol) in $ClCO_2Me$ (15 mL) was added NaH (1.73 g, 72.1 mmol) and heated under reflux for 24 h. After cooling to room temperature, EtOAc (150 mL) was added. The mixture was washed with a saturated solution of NH_4Cl (4×50 mL) and brine (2×30 mL), dried over Na_2SO_4, filtrated and concentrated in vacuum. The resultant crude product was purified by crystallization with EtOAc/hexane to obtain **16** as a white solid (1.51 g, 73%), mp 121–123 °C. Lit.[13] 119–120 °C.

4.3. General procedure for the preparation of 3-hydroxyoxindoles 1, 4, 18–22 and furoindole 31

To a solution of the appropriate indole **13** (0.494 g, 2 mmol), **14** (0.195 g, 0.7 mmol), **15** (0.50 g, 2.03 mmol) or oxindole **24** (0.51 g, 2.49 mmol), **25** (0.765 g, 3.1 mmol), **27** (0.239 g, 0.72 mmol), **28** (0.20 mg, 1.16 mmol), **29** (0.153 g, 0.82 mmol) in acetone (10–15 mL) was added $NaHCO_3$ (3.5 equiv for **13**, **15**, **25**, **28** and **29**, 5.25 equiv for **27**, and 7.0 equiv for **14** and **24**). The resulting thick mixture was treated dropwise, over 10 min at room temperature, with a solution of oxone monopersulfate complex (2.5 equiv of $KHSO_5$ for **13**, **15**, **25**, **28** and **29**, 3.75 equiv for **27**, and 5.0 equiv for **14**, **24**) and 5 mg of disodium EDTA in water (5–10 mL). After addition was complete, the mixture was stirred at room temperature for additional 1.3 h for **29**, 3 h for **13**, 5 h for **14**, 8 h for **24**, 0.75 h for **25**, 30 h for **27**, 3.5 h for **28**, and under reflux for 2 h for **15**. After cooling to room temperature the acetone was evaporated under reduce pressure and the residue was dissolved in EtOAc (50 mL). The separated organic phase was washed with brine (2×20 mL), dried over $NaSO_4$ and concentrated in vacuo. The resultant crude products were purified by flash column chromatography with EtOAc/hexane 2:3 for **1**, **4**, **18** and **20**, EtOAc/hexane 1:4 for **19**, EtOAc/hexane 1:1 for **21** and **22**, and EtOAc/MeOH 97:3 for **31**.

4.3.1. Methyl(3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)-acetate (1). Prepared from **24** as colorless crystals (0.440 g, 80%), mp 132–133 °C (EtOAc/hexane). ^{1}H NMR (CD_3OD), δ 7.39 (1H, d, J=7.3 Hz, H4); 7.28 (1H, td, J=7.7, 1.1 Hz, H6); 7.05 (1H, td, J=7.7, 1.1 Hz, H5); 6.92 (1H, d, J=7.7 Hz, H7); 4.91 (2H, s, NH and OH); 3.50 (3H, s, CO_2Me); 3.12 and 3.10 (2H, AB system, J=15.3 Hz, H8). ^{13}C NMR (CD_3OD), δ 180.9 (C=O lactam); 171.0 (CO_2Me); 143.6 (C7a); 131.7 (C3a); 131.0 (C6); 125.2 (C4); 123.6 (C5); 111.3 (C7); 74.8 (C3); 52.1 (CO_2CH_3); 42.6 (C8). IR (KBr) ν_{max} 3388, 3322, 3042, 2964, 1718, 1622 cm^{-1}. EIMS m/z (relative intensity) 221 (M^+, 42), 161 (82), 148 (100), 133 (34), 120 (60), 92 (50), 65 (40). Anal. Calcd for $C_{11}H_{11}NO_4$: C 59.73; H 5.01; N 6.33. Found: C 59.58; H 4.94; N 5.91.

4.3.2. (3-Hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetonitrile (4). Prepared from **28** as pale yellow crystals (0.206 g, 94%), mp 162–164 °C (EtOAc/hexane). Lit.[1d] 162–163 °C. Although compound **4** is known,[1d] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR (acetone-d_6), δ 9.76 (1H, br s, NH); 7.62 (1H, d, J=7.3 Hz, H4); 7.36 (1H, t, J=7.7 Hz, H6); 7.13 (1H, t, J=7.7 Hz, H5); 7.02 (1H, d, J=8.1 Hz, H7); 5.88 (1H, s, OH); 3.19 and 2.98 (2H, AB system, J=16.6 Hz, H8). ^{13}C NMR (acetone-d_6) δ 178.1 (C=O lactam); 143.1 (C7a); 131.8 (C6); 130.8 (C3a); 125.9 (C4); 124.0 (C5); 117.7 (CN); 111.9 (C7); 74.0 (C3); 27.8 (C8). IR (KBr) ν_{max} 3352, 2964, 2850, 2254, 1726, 1244, 1619 cm^{-1}. EIMS m/z (relative intensity) 188 (M^+, 17), 170 (100), 148 (90), 115 (58). Anal. Calcd for $C_{10}H_8N_2O_2$: C 63.83; H 4.28; N 14.89. Found: C 63.81; H 4.35; N 14.65.

4.3.3. Methyl(1-carbomethoxy-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetate (18). Prepared from **13** as colorless crystals (0.350 g, 63%), mp 127–129 °C (EtOAc/hexane). ^{1}H NMR (DMSO-d_6), δ 7.84 (1H, d, J=8.0 Hz, H7); 7.52 (1H, dd, J=7.5, 1.1 Hz, H4); 7.41 (1H, td, J=8.0, 1.4 Hz, H6); 7.22 (1H, td, J=7.7, 1.1 Hz, H5); 6.60 (1H, s, OH); 3.94 (3H, s, NCO_2CH_3); 3.39 (3H, s, CO_2CH_3); 3.25 and 3.19 (2H, AB system, J=16.5 Hz, H8). ^{13}C NMR (DMSO-d_6), δ 174.7 (C=O lactam); 169.3 (CO_2Me); 151.0 (NCO_2Me); 139.5 (C7a); 129.8 (C3a); 129.7 (C6); 124.7 (C5); 123.9 (C4); 114.5 (C7); 72.1 (C3); 53.7 (NCO_2CH_3); 51.5 (CO_2CH_3); 41.8 (C8). IR (KBr) ν_{max} 3458, 3003, 2957, 1783, 1740, 1711, 1610 cm^{-1}. EIMS m/z (relative intensity) 279 (M^+, 15), 219 (24), 146 (100), 90 (22), 59 (15). Anal. Calcd for $C_{13}H_{13}NO_6$: C 55.92; H 4.69; N 5.02. Found: C 56.40; H 4.84; N 4.73.

4.3.4. 1-Carbomethoxy-1*H*-3-hydroxy-3-(2-carbomethoxyethoxyl)-2-indolinone (19). Prepared from **14** as a pale yellow oil (0.204 g, 94%). ^{1}H NMR ($CDCl_3$), δ 7.22 (1H, d, J=8.0 Hz, H7); 7.42 (1H, dd, J=6.6, 1.0 Hz, H4); 7.40 (1H, td, J=6.2, 1.5 Hz, H6); 7.24 (1H, td, J=7.7, 1.1 Hz, H5); 4.24 (1H, ddd, J=11.3, 6.3, 4.8 Hz, H9A), 3.40 (1H, ddd, J=11.3, 8.8, 5.9 Hz, H9B), 3.99 (3H, s, NCO_2CH_3), 3.69 (3H, s, CO_2CH_3); 3.57 (1H, br s, OH); 2.48 (1H, ddd, J=14.3, 8.4, 6.3 Hz, H8A); 2.28 (1H, ddd, J=14.3, 5.9, 5.1 Hz, H8B). ^{13}C NMR ($CDCl_3$), δ 176.2 (C=O lactam); 155.3 (OCO_2Me); 151.3 (NCO_2Me); 139.0 (C7a); 130.5 (C3a); 128.3 (C6); 125.5 (C5); 124.1 (C4); 115.6 (C7); 74.8 (C3); 63.2 (C9); 55.0 (OCO_2CH_3); 54.1 (NCO_2CH_3); 37.7 (C8). IR ($CHCl_3$) ν_{max} 3550, 3030, 3022, 3010, 2356, 1802, 1748, 1440, 1276 cm^{-1}. EIMS m/z (relative intensity) 309 (M^+, 25), 281 (7), 205 (40), 178 (26), 146 (100), 83 (11). Anal. Calcd for $C_{14}H_{15}NO_7$: C 54.37; H 4.89; N 4.53. Found: C 54.69; H 4.69; N 4.55.

4.3.5. Methyl(1-acetyl-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetate (20). Prepared from **25** as a white solid (0.562 g, 69%), mp 111–112 °C (AcOEt/hexane). ^{1}H NMR ($CDCl_3$), δ 8.21 (1H, d, J=8.0 Hz, H7); 7.42 (1H, d, J=7.4 Hz, H4); 7.39 (1H, td, J=8.5, 1.1 Hz, H6); 7.24 (1H, t, J=7.3 Hz, H5); 4.41 (1H, br s, OH); 3.61 (3H, s, CO_2CH_3); 3.12 and 2.99 (2H, AB system, J=16.2 Hz, H8); 2.61 (3H, s, $NCOCH_3$). ^{13}C NMR ($CDCl_3$), δ 177.5 (C=O lactam); 171.1 (C=O amide); 170.5 (CO_2Me); 140.4 (C7a); 131.0 (C6); 128.4 (C3a); 126.0 (C5); 123.7 (C4); 117.2 (C7); 73.6 (C3); 52.5 (CO_2CH_3); 42.0 (C8); 26.7 ($NCOCH_3$). IR (KBr) ν_{max} 3429, 2958, 2939, 1776, 1731, 1683, 1607, 1479 cm^{-1}. EIMS m/z (relative intensity) 263 (M^+, 35), 221 (94), 161 (100), 146 (96), 120 (23), 90 (38). Anal. Calcd for $C_{13}H_{13}NO_5$: C 59.31; H 4.98; N 5.32. Found: C 59.40; H 5.00; N 5.23.

4.3.6. 3-Hydroxy-3-[2-(tosyloxy)ethyl]-2-indolinone (21). Prepared from **27** as a white solid (0.162 g, 65%), mp 142–143 °C (decomp.) (EtOAc/hexane). Lit.[2b] 144–145 °C. The later referred work contains ^{1}H NMR data where the H5 and H6 signals are reversed, while the ^{13}C NMR signals are unassigned. ^{13}C NMR (acetone-d_6), δ 179.1 (C=O lactam); 145.7 (C4′); 142.2 (C7a); 133.8 (C1′); 131.5 (C3a); 130.8 (C3′, C5′); 130.2 (C6); 128.5 (C2′, C6′); 124.9 (C4); 122.9 (C5); 110.8 (C7); 74.8 (C3); 67.0 (C9); 37.4 (C8); 21.5 (CH_3).

4.3.7. (1-Methyl-3-hydroxy-2-oxo-2,3-dihydroindol-3-yl)acetonitrile (22). Prepared from **29** as colorless crystals (0.138 g, 83%), mp 130–131 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz), δ 7.64 (1H, ddd, J=7.5, 1.3, 0.7 Hz,

H4), 7.41 (1H, td, J=7.5, 1.3 Hz, H6); 7.17 (1H, td, J=7.5, 0.9 Hz, H5); 6.91 (1H, br d, J=7.7 Hz, H7); 4.62 (1H, s, OH); 3.20 (3H, s, CH_3); 2.97 and 2.65 (2H, AB system, J=16.5 Hz, H8). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 175.5 (C=O lactam); 142.6 (C7a); 130.8 (C6); 127.6 (C3a); 124.1 (C4); 123.8 (C5); 115.4 (CN); 109.1 (C7); 72.6 (C3); 27.3 (C8); 26.6 (CH_3). IR ($CHCl_3$) ν_{max} 3362, 2258, 1724 cm^{-1}. EIMS m/z (relative intensity) 202 (M^+, 23), 162 (100). FABHRMS m/z 202.0744 (M^+, $C_{11}H_{10}N_2O_2$ requires 202.0742).

4.3.8. Methyl(3a-hydroxy-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo-[2,3-*b*]indole)-8-carboxylate (31). Prepared from **15** as a white solid (0.486 g, 96%), mp 150–152 °C (Et_2O). ^{1}H NMR (DMSO-d_6), δ 7.74 (1H, br s, H7); 7.54 (1H, d, J=7.7 Hz, H4); 7.43 (1H, t, J=7.8 Hz, H6); 7.19 (1H, t, J=7.3 Hz, H5); 6.56 (1H, s, OH); 6.17 (1H, s, H8a); 3.86 (3H, s, OMe); 3.29 and 3.23 (2H, AB system, J=18 Hz, H3). ^{13}C NMR (DMSO-d_6), δ 172.6 (C=O lactone); 152.3 (NCO_2Me); 140.2 (C7a); 132.6 (C3b); 130.6 (C6); 125.3 (C4); 124.3 (C5); 114.9 (C7); 96.2 (C8a); 79.8 (C3a); 35.4 (OMe); 40.6 (C3). IR (KBr) ν_{max} 3408, 3018, 1792, 1706, 1604, 1488, 1450, 1396 cm^{-1}. EIMS m/z (relative intensity) 249 (M^+, 82), 221 (18), 204 (30), 193 (32), 176 (30), 161 (26), 146 (100), 132 (33), 77 (52), 59 (56). Anal. Calcd for $C_{12}H_{11}NO_5$: C 57.83; H 4.45; N 5.62. Found: C 58.02; H 4.44; N 5.27.

4.3.9. Methyl oxindole-3-acetate (24). To a stirred solution of **23** (1.45 g, 7.58 mmol) in MeOH (20 mL) was added *p*-toluensulfonic acid (43 mg) and heated under reflux for 7 h. After cooling to room temperature, the MeOH was evaporated under reduced pressure and the residue was dissolved with EtOAc (50 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (2×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was purified by flash column chromatography eluting with EtOAc/hexane 2:3 to give **24** as colorless crystals (1.20 g, 77%), mp 168–170 °C (EtOAc/hexane). Lit.[1a] 170–172 °C. Lit.[15a] 164–167 °C. Although **24** is known,[1a,15a] it is spectroscopically not yet fully characterized. Thus, NMR data follow: ^{1}H NMR (DMSO-d_6), δ 10.44 (1H, br s, NH); 7.19 (1H, d, J=7.7 Hz, H4); 7.16 (1H, t, J=7.7 Hz, H6); 6.91 (1H, t, J=7.3 Hz, H5); 6.83 (1H, d, J=7.7 Hz, H7); 3.67 (1H, t, J=5.9 Hz, H3); 3.55 (3H, s, CO_2CH_3); 2.98 (1H, dd, J=16.9, 5.1 Hz, H8A); 2.82 (1H, dd, J=16.8, 7.0 Hz, H8B). ^{13}C NMR (DMSO-d_6), δ 178.0 (C=O lactam); 171.2 (CO_2Me); 142.9 (C7a); 129.0 (C3a); 127.9 (C6); 123.6 (C4); 121.3 (C5); 109.3 (C7); 51.6 (CO_2CH_3); 41.8 (C3); 33.6 (C8). IR (KBr) ν_{max} 3150, 3026, 2947, 2880, 2821, 2731, 1726, 1702, 1622, 1488 cm^{-1}. EIMS m/z (relative intensity) 205 (M^+, 30), 173 (34), 145 (100), 128 (35), 117 (52), 90 (26), 77 (26). FABHRMS m/z 206.0822 (MH^+, $C_{11}H_{11}NO_3$ requires 206.0817).

4.3.10. Methyl(1-acetyl-2-oxo-2,3-dihydroindol-3-yl)-acetate (25). To a stirred solution of **24** (0.239 g, 1.16 mmol) in Ac_2O (20 mL) was added pyridine (2 mL), heated at reflux for 9 h, cooled to room temperature and diluted with EtOAc (30 mL). The organic phase was washed with 10% aqueous HCl (2×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 3:1 to give **24** as a yellow oil (0.264 g, 92%). ^{1}H NMR ($CDCl_3$), δ 8.22 (1H, d, J=7.7 Hz, H7); 7.31 (1H, t, J=6.9 Hz, H6); 7.23 (1H, d, J=7.4 Hz, H4); 7.17 (1H, td, J=7.3, 1.1 Hz, H5); 3.91 (1H, t, J=5.5 Hz, H3); 3.64 (3H, s, CO_2CH_3); 3.09 (1H, dd, J=17.2, 4.8 Hz, H8A); 3.00 (1H, dd, J=17.2, 6.5 Hz, H8B); 2.67 (3H, s, $NCOCH_3$). ^{13}C NMR ($CDCl_3$), δ 178.2 (C=O lactam); 171.0 (C=O amide); 170.9 (CO_2Me); 140.9 (C7a); 128.4 (C6); 127.2 (C3a); 125.2 (C5); 123.2 (C4); 116.8 (C7); 52.3 (CO_2CH_3); 42.7 (C3); 35.1 (C5); 26.7 ($NCOCH_3$). IR (KBr) ν_{max} 2958, 2939, 1776, 1732, 1684, 1569, cm^{-1}. EIMS m/z (relative intensity) 247 (M^+, 23), 205 (29), 173 (19), 145 (100), 117 (34), 90 (12). Anal. Calcd for $C_{13}H_{13}NO_4$: C 63.15; H 5.30; N 5.66. Found: C 63.26; H 5.49; N 5.24.

4.3.11. 3-(2-Hydroxyethyl)-2-indolinone (26). To a solution of **10** (0.250 g, 1.55 mmol) in dimethyl sulfoxide (DMSO) (0.120 mL, 1.55 mmol) were added 0.31 mL (3.1 mmol) of 36% aqueous HCl and the mixture was stirred at room temperature for 6 h, diluted with EtOAc (30 mL) and neutralized with saturated solution of $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc (2×30 mL), the combined organic layers were washed with brine (2×30 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 1:4 to give **26** as white crystals (0.197 g, 72%), mp 109–111 °C (EtOAc/hexane). Lit.[2a] 111–112. Lit.[2b] 112–114 °C.

4.3.12. 3-[2-(Tosyloxy)ethyl]-2-indolinone (27). To a solution of **26** (0.322 g, 1.8 mmol) in pyridine (7 mL) was added *p*-toluenesulfonyl chloride (0.416 g, 2.2 mmol) and the mixture stirred for 3 h at room temperature. The reaction mixture was poured onto a cold 10% aqueous HCl solution and extracted with EtOAc (4×30 mL). The combined organic layers were washed with brine (2×30 mL), dried and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 1:1 to give **27** as colorless crystals (0.516 g, 86%), mp 111–114 °C (EtOAc/hexane). Lit.[16] 115–116 °C. ^{1}H NMR ($CDCl_3$), δ 9.40 (1H, br s, NH); 7.73 (2H, d, J=8.0 Hz, H2′, H6′); 7.31 (2H, d, J=8.1 Hz, H3′, H5′); 7.18 (1H, t, J=7.6, Hz, H6); 7.09 (1H, d, J=7.3 Hz, H4); 6.97 (1H, t, J=7.7 Hz, H5); 6.89 (1H, d, J=7.7 Hz, H7); 4.26 (2H, t, J=6.6 Hz, H9); 3.50 (1H, t, J=6.6 Hz, H3); 2.41 (3H, s, CH_3); 2.24 (2H, m, H8). ^{13}C NMR ($CDCl_3$), δ 179.9 (C=O lactam); 144.9 (C4′); 141.7 (C7a); 132.6 (C1′); 129.9 (C3′, C5′); 128.3 (C6); 128.1 (C3a); 127.8 (C2′, C6′); 124.1 (C4); 122.4 (C5); 110.2 (C7); 67.3 (C9); 42.3 (C3); 29.7 (C8); 21.6 (CH_3). IR ($CHCl_3$) ν_{max} 3185, 3084, 1702, 1622, 1430, 1358, 1227 cm^{-1}. EIMS m/z (relative intensity) 160 ($M^+ - C_7H_7SO_3$, 14), 159 (100), 144 (99), 130 (74), 77 (21), 51 (14).

4.3.13. (2-Oxo-2,3-dihydroindol-3-yl)acetonitrile (28). To a solution of **12** (1.5 g, 9.6 mmol) in neat DMSO (0.687 mL, 9.6 mmol) were added 1.9 mL (19.2 mmol) of 36% aqueous HCl and the mixture was stirred for 10 h at room temperature, diluted with water (100 mL), neutralized with $NaHCO_3$, and extracted with EtOAc (4×25 mL). The organic layer was washed with brine (2×20 mL), dried

and evaporated to dryness in vacuo. The resultant crude product was crystallized to give **28** as pale yellow crystals (1.3 g, 78%), mp 163–165 °C (EtOAc/hexane). ^{1}H NMR (DMSO-d_6), δ 10.62 (1H, s, NH); 7.39 (1H, d, J=7.4 Hz, H4); 7.24 (1H, t, J=7.7 Hz, H6); 7.01 (1H, t, J=7.5 Hz, H5); 6.88 (1H, d, J=7.7 Hz, H7); 3.82 (1H, t, J=5.9 Hz, H3), 3.20 (1H, dd, J=17.2, 5.8 Hz, H8A), 3.06 (1H, dd, J=17.2, 5.9 Hz, H8B). ^{13}C NMR (DMSO-d_6), δ 176.4 (C=O lactam); 142.8 (C7a); 128.6 (C6), 127.1 (C3a), 124.2 (C4), 121.6 (C5); 118.2 (CN); 109.6 (C7); 41.3 (C3); 17.6 (C8). IR (KBr) ν_{max} 3137, 2966, 2897, 2249, 1708, 1247 cm^{-1}. EIMS *m/z* (relative intensity) 172 (M^+, 65), 132 (100), 77 (33), 51 (37). Anal. Calcd for $C_{10}H_8N_2O$: C 69.76; H 4.68; N 16.27. Found: C 69.87; H 4.74; N 15.91.

4.3.14. Methyl 3-isatylideneacetate (32). To a stirred solution of **18** (0.250 g, 0.895 mmol) in MeOH (20 mL) was added NaH (5.4 mg, 0.23 mmol) and heated under reflux for 15 min. After cooling to room temperature the MeOH was evaporated under reduced pressure and the residue was dissolved with EtOAc (30 mL). The organic phase was washed with saturated solution of NH_4Cl (2×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography eluting with EtOAc/hexane 2:3 to give **1** (82 mg, 42%) and **32** as an orange solid (0.086 g, 47%), mp 181–182 °C (EtOAc/hexane). Lit.[20b] 178–180 °C. ^{13}C NMR ($CDCl_3$), δ 169.4 (C=O lactam); 166.2 (CO_2Me); 143.5 (C7a); 138.6 (C3); 132.9 (C6); 129.2 (C4); 123.1 (C5); 122.2 (C8); 120.5 (C3a); 110.4 (C7); 52.4 (CO_2CH_3).

4.3.15. 3a-Hydroxy-8-methyl-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole (33). To a cooled solution of **18** (0.2 g, 0.72 mmol) in dry THF (20 mL) was added $LiAlH_4$ (0.2 g, 5.26 mmol). The resulting mixture was stirred under reflux for 3 h, then quenched with EtOAc (25 mL) and with cold water (40 mL). The solids were filtered off and the organic layer was separated. The aqueous phase was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine (3×20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc/hexane 2:3 to give **33** as a brown oil (0.029 g, 21%). ^{1}H NMR ($CDCl_3$), δ 7.25 (1H, dd, J=7.3, 1.1 Hz, H4); 7.19 (1H, td, J=7.6, 1.1 Hz, H6); 6.72 (1H, td, J=7.5, 1.1 Hz, H5); 6.41 (1H, d, J=8.1 Hz, H7); 5.11 (1H, s, H8a); 4.01 (1H, ddd, J=9.2, 7.7, 2.2 Hz, H2A); 3.56 (1H, ddd, J=11.0, 9.2, 5.5 Hz, H2B); 2.88 (3H, s, CH_3); 2.60 (1H, br s, OH); 2.39 (1H, ddd, J=12.1, 11.0, 7.7 Hz, H3A); 2.27 (1H, ddd, J=5.5, 2.2 Hz, H3B). ^{13}C NMR ($CDCl_3$), δ 151.1 (C7a); 130.5 (C6); 130.4 (C3b); 123.7 (C4); 117.9 (C5); 106.1 (C7); 105.0 (C8a); 88.0 (C3a); 67.5 (C2); 41.3 (C3); 31.4 (CH_3). IR (KBr) ν_{max} 3399, 3052, 2929, 1610, 1481 cm^{-1}. EIMS *m/z* (relative intensity) 191 (M^+, 100), 160 (82), 146 (32), 118 (26), 106 (29), 91 (26), 77 (41), 51 (20). FABHRMS *m/z* 190.0867 (M−1, $C_{11}H_{13}NO_2$ requires 190.0868).

4.3.16. Methyl(3-hydroxy-1-carbomethylamin-2-oxo-2,3-dihydroindol-3-yl)acetamide (34). Excess methylamine (4 mL) was condensed at −78 °C in a flask containing **18** (0.2 g, 0.72 mmol). The cooling bath was removed and the reaction mixture was stirred until the excess methylamine was evaporated. The solid residue was washed with Et_2O to afford **34** as a white solid (0.195 g, 98%), mp 217–218 °C (decomp.). ^{1}H NMR ($CDCl_3$), δ 10.08 (1H, br s, OH); 7.97, 7.76 (2H, 2c, J=4.4 Hz, 2N*H*Me); 7.35 (1H, dd, J=7.7, 1.1 Hz, H7); 7.21 (1H, td, J=7.7, 1.1 Hz, H5); 6.95 (1H, td, J=7.1, 1.1 Hz, H6); 6.81 (1H, dd, J=7.6, 0.6 Hz, H4); 3.00 (2H, s, H8); 2.59, 2.48 (6H, 2d, J=4.8 Hz, NHCH_3). ^{13}C NMR ($CDCl_3$), δ 169.3 (C=O urea); 167.3 (C=O amide); 148.7 (C=O lactam); 134.9 (C7a); 129.1 (C5); 124.7 (C7); 122.2 (C6); 119.6 (C3a); 113.9 (C4); 84.1 (C3); 43.6 (C8); 26.2, 25.3 (2NHCH_3). IR (KBr) ν_{max} 3358, 3313, 2999, 2945, 1745, 1649, 1600 cm^{-1}. EIMS *m/z* (relative intensity) 277 (M^+, 3.4), 220 (100), 202 (62), 162 (54), 144 (71), 118 (40), 58 (40), 44 (60). FABHRMS *m/z* 278.1140 (MH^+, $C_{13}H_{15}N_3O_4$ requires 278.1141).

4.4. General procedure for the prenylation of 35 and 36

To a solution of **1** (0.205 g, 0.93 mmol) or **4** (0.100 g, 0.57 mmol) in acetone (15 mL) were added 268 μL of prenyl bromide (2.3 mmol) and 321 mg of K_2CO_3 (2.3 mmol) or 193 μL (1.44 mmol) and 199 mg of K_2CO_3 (1.44 mmol), respectively, and the mixture was heated under reflux for 4 h. After cooling to room temperature, the solid was filtered off and washed with acetone (2×10 mL), the volatiles were evaporated under reduced pressure and the residue was dissolved with EtOAc (100 mL). The organic layer was washed with brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc/hexane 2:3.

4.4.1. Methyl[3-hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl]acetate (35). Prepared from **1** as colorless crystals (0.261 g, 97%), mp 172–174 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$), δ 7.39 (1H, dd, J=7.2, 0.7 Hz, H4); 7.30 (1H, td, J=7.6, 1.1 Hz, H6); 7.06 (1H, td, J=7.7, 0.7 Hz, H5); 6.80 (1H, d, J=7.2 Hz, H7); 5.18 (1H, br t, J=6.6 Hz, H9); 4.55 (1H, br s, OH); 4.32 (1H, dd, J=16.9, 6.6 Hz, H8A); 4.27 (1H, dd, J=16.5, 6.6 Hz, H8B); 3.64 (3H, s, OCH_3); 2.99 and 2.93 (2H, AB system, J=16.1 Hz, H13); 1.82, 1.72 (6H, 2s, Me11, Me12). ^{13}C NMR ($CDCl_3$), δ 175.8 (C=O lactam); 170.7 (CO_2CH_3); 142.9 (C7a); 136.9 (C10); 130.0 (C6); 129.3 (C3a); 123.9 (C4); 123.0 (C5); 118.0 (C9); 109.3 (C7); 73.5 (C3); 52.0 (OMe); 41.4 (C13); 38.2 (C8); 25.6, 18.2 (Me11, Me12). IR ($CHCl_3$) ν_{max} 3278, 3010, 2918, 1737, 1694, 1616, 1433, 1407 cm^{-1}. EIMS *m/z* (relative intensity) 289 (M^+, 43), 271 (21), 221 (28), 212 (30), 161 (81), 146 (100), 69 (38). Anal. Calcd for $C_{16}H_{19}NO_4$: C 66.42; H 6.62; N 4.84. Found: C 66.39; H 6.67; N 4.44.

4.4.2. [3-Hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl]acetonitrile (36). Prepared from **4** as colorless crystals (0.141 g, 96%), mp 116–118 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$), δ 7.64 (1H, d, J=7.3 Hz, H4); 7.37 (1H, td, J=7.7, 1.1 Hz, H6); 7.15 (1H, td, J=7.7, 0.8 Hz, H5); 6.86 (1H, d, J=8.0 Hz, H7); 5.13 (1H, br t, J=6.9 Hz, H9), 4.82 (1H, s, OH); 4.33 (1H, dd, J=15.4, 6.6 Hz, H8A) 4.23 (1H, dd, J=15.4, 6.6 Hz, H8B) 3.02 and 2.68 (2H, AB system, J=16.8, 16.4 Hz, H13); 1.80, 1.71 (6H, s, Me11, Me12); 1.71 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$),

δ 175.3 (s, C=O lactam); 142.1 (C7a); 137.7 (C10); 130.7 (C6); 127.9 (C3a); 124.3 (C4); 123.8 (C5); 117.3 (C9); 115.5 (CN); 109.9 (C7); 72.7 (C3); 38.3 (C8); 27.4 (C13); 25.6, 18.2 (Me11, Me12). IR (KBr) ν_{max} cm^{-1} 3282, 2968, 2850, 2251, 1702, 1243, 1617, 1107, 825. EIMS *m/z* (relative intensity) 256 (M^+, 26), 238 (7), 188 (29), 170 (20), 148 (85), 69 (100). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C 70.29; H 6.29; N 10.93. Found: C 69.88; H 6.28; N 10.55.

4.4.3. Methyl(3-hydroxy-1-(3-methyl-2-buten-1-yl)-2-oxo-2,3-dihydroindol-3-yl)acetamide (37). To a solution of **35** (0.5 g, 1.73 mmol) in MeOH (10 mL) was added 40% aqueous $MeNH_2$ (3.3 mL). The mixture was stirred at room temperature for 16 h, then diluted with EtOAc (100 mL) and washed with saturated solution of NH_4Cl (3×20 mL) and brine (2×20 mL), dried over Na_2SO_4 and evaporated to dryness in vacuo. The resultant crude product was purified by flash column chromatography with EtOAc/hexane 4:1 to give **37** as a yellow oil (0.490 g, 98%). ^1H NMR ($CDCl_3$), δ 7.39 (1H, dd, *J*=7.7, 1.1 Hz, H4); 7.28 (1H, td, *J*=7.7, 1.1 Hz, H6); 7.05 (1H, td, *J*=7.3, 0.7 Hz, H5); 6.78 (1H, d, *J*=8.0 Hz, H7); 6.22 (1H, br s, NH); 5.82 (1H, br s, OH); 5.13 (1H, br t, *J*=6.6 Hz, H9); 4.28 (1H, dd, *J*=16.4, 6.9 Hz, H8A); 4.23 (1H, dd, *J*=16.9, 6.6 Hz, H8B); 2.85 (3H, d, *J*=5.1 Hz, NMe); 2.74, 2.50 (2H, AB system, *J*=15.0 Hz, H13); 1.80, 1.70 (6H, 2s, Me11, Me12). ^{13}C NMR ($CDCl_3$), δ 176.1 (C=O lactam); 170.9 (C=O amide); 142.2 (C7a); 137.1 (C10); 130.2 (C3a); 129.7 (C6); 124.1 (C4); 123.2 (C5); 118.0 (C9); 109.3 (C7); 74.4 (C3); 41.9 (C13); 38.2 (C8); 26.3 (NMe); 25.6, 18.15 (Me11, Me12). IR (KBr) ν_{max} 3330, 2972, 2933, 1714, 1650, 1614, 1557, 1488, 1469 cm^{-1}. EIMS *m/z* (relative intensity) 288 (M^+, 50), 270 (63), 212 (95), 192 (24), 161 (100), 146 (53), 69 (29). FABHRMS *m/z* 289.1537 (MH^+, $C_{16}H_{20}N_2O_3$ requires 289.1552).

4.5. General procedure for the $LiAlH_4$ reduction of 36 and 22

To a solution of **36** (0.5 g, 1.95 mmol) or **22** (0.48 g, 2.37 mmol) in anhydrous THF (20 mL), cooled at 5 °C, was added $LiAlH_4$ (0.297 g, 7.8 mmol for **36** and 0.087 g, 2.30 mmol for **22**). The resulting mixture was stirred under reflux for 0.25 h for **36** and at room temperature for 3 h for **22**, cooled and quenched dropwise with cold H_2O (25 mL) and EtOAc (25 mL). The solids were filtered off through a Celite pad, washed with EtOAc (80 mL) and the organic phase was washed with brine (2×20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant crude product **38** was crystallized from EtOAc/hexane and **39** was purified by flash chromatography eluting with CH_2Cl_2/MeOH 19:1.

4.5.1. 3a-Hydroxy-8-(3-methyl-2-buten-1-yl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (38). Prepared from **36** as colorless crystals (0.222 g, 47%), mp 164–166 °C. ^1H NMR ($CDCl_3$), δ 7.23 (1H, dd, *J*=7.3, 1.1 Hz, H4); 7.12 (1H, td, *J*=7.7, 1.1 Hz, H6); 6.68 (1H, t, *J*=7.3 Hz, H5); 6.41 (1H, d, *J*=8.0 Hz, H7); 5.19 (1H, br t, H10); 4.63 (1H, s, H8a); 3.82 (1H, dd, *J*=15.7, 7.3 Hz, H9A); 3.75 (1H, dd, *J*=15.8, 6.2 Hz, H9B); 3.07 (2H, br s, OH, NH); 3.03 (1H, ddd, *J*=13.6, 7.0, 2.6 Hz, H2A); 2.76 (1H, ddd, *J*=14.6, 10.6, 6.3 Hz, H2B); 2.14 (2H, m, H3); 1.73, 1.70 (6H, 2s, Me12, Me13). ^{13}C NMR ($CDCl_3$), δ 150.6 (C7a); 135.7 (C11); 131.8 (C3b); 129.9 (C6); 123.8 (C4); 120.1 (C10); 117.6 (C5); 106.8 (C7); 90.6 (C8a); 88.4 (C3a); 45.7 (C3); 43.4 (C9); 42.4 (C2); 29.9, 18.2 (Me12, Me13). IR (KBr) ν_{max} 3435, 3245, 3052, 3029, 2971, 2929, 2902, 2636, 1610, 1489, 1467 cm^{-1}. EIMS *m/z* (relative intensity) 244 (M^+, 50), 226 (22), 224 (22), 211 (26), 158 (100), 157 (96), 130 (39), 129 (24), 69 (43). Anal. Calcd for $C_{15}H_{20}N_2O$: C 73.74; H 8.25; N 11.47. Found: C 73.65; H 8.58; N 11.13.

4.5.2. 3a-Hydroxy-8-methyl-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (39). Prepared from **22** as colorless crystals (0.226 g, 50%), mp 127–128 °C (acetone/CH_2Cl_2). Lit., [3d] mp 126–128 °C. Although compound **39** is known,[3d] no spectral characterization has been given. Thus, NMR data follow. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25 (1H, dd, *J*=7.4, 1.4 Hz, H4); 7.17 (1H, td, *J*=7.4, 1.4 Hz, H6); 6.70 (1H, td, *J*=7.4, 1.1 Hz, H5); 6.41 (1H, br d, *J*=8.0 Hz, H7); 4.59 (1H, s, H8a); 3.17 (1H, m, H2A); 2.83 (3H, s, NCH_3); 2.82 (1H, m, H2B), 2.20 (2H, m, H3A, H3B); ^{13}C NMR ($CDCl_3$) δ 151.0 (C7a); 131.3 (C3b); 129.7 (C6); 123.4 (C4); 117.4 (C5); 106.2 (C7); 92.8 (C8a); 88.3 (C3a); 45.9 (C2); 42.2 (C3); 32.3 (NCH_3).

4.5.3. 3a-Hydroxy-1,8-dimethyl-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (40). To a solution of pyrroloindole **39** (0.30 g, 1.8 mmol) in MeOH (11 mL) at room temperature was added 37% aqueous CH_2O (1 mL, 12.3 mmol). The resulting mixture was stirred at this temperature for 3 h, then cooled to 0 °C, and $NaBH_4$ (0.261 g, 6.9 mmol) was added portionwise over 5 min. After stirring the mixture for 1 h at room temperature, the solvent was removed under reduced pressure, the residue was treated dropwise with H_2O (18 mL) and Et_2O (40 mL). The aqueous layer was extracted with Et_2O (2×40 mL) and the combined organic layers were washed with brine (1×60 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with acetone/EtOAc 9:1, yielding 0.287 g (89%) of the title compound as colorless crystals, mp 68–69 °C (CH_2Cl_2/MeOH 4:1). Although compound **40** is known,[23] it is spectroscopically not yet fully characterized. Thus, NMR data follows: ^1H NMR ($CDCl_3$, 300 MHz), δ 7.23 (1H, dd, *J*=7.5, 1.3 Hz, H4); 7.19 (1H, td, *J*=7.5, 1.3 Hz, H6); 6.74 (1H, td, *J*=7.5, 0.7 Hz, H5); 6.49 (1H, br d, *J*=7.9 Hz, H7); 4.21 (1H, s, H8a); 2.94 (3H, s, CH_3); 2.82 (1H, m, H2A); 2.63 (1H, m, H2B); 2.55 (3H, s, CH_3); 2.29 (1H, m, H3A); 2.16 (1H, m, H3B). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 152.0 (C7a); 131.8 (C3b); 130.0 (C6); 123.3 (C4); 118.5 (C5); 108.0 (C7); 97.9 (C8a); 88.2 (C3a); 53.1 (C2); 40.2 (C3); 38.3 (N1 CH_3); 36.9 (N8 CH_3).

4.5.4. 3a-Hydroxy-1-methyl-8-(3-methyl-2-buten-1-yl)-1,2,3,3a,8a-hexahydropyrrolo[2,3-*b*]indole (8). *Method A*. To a cool solution of **37** (0.362 g, 1.3 mmol) in dry THF (20 mL) was added $LiAlH_4$ (0.143 mg, 3.8 mmol). The resulting mixture was stirred under reflux for 5 h, quenched with EtOAc (50 mL) and with cold water (120 mL). The mixture was filtrated and the organic layer was separated and washed with saturated solution of NH_4Cl (3×30 mL) and brine (2×20 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column

chromatography eluting with EtOAc/hexane 4:1 to give **8** (0.179 mg, 55%) as a pale yellow oil.

Method B. To a solution of **38** (0.255 g, 1.0 mmol) in MeOH (10 mL) was added CH_2O (0.665 mL, 8.8 mmol) and the mixture was stirred at room temperature for 5 h. The mixture was cooled and $NaBH_4$ (173.0 mg, 4.54 mmol) was added, then warmed to room temperature and stirred for 2 h. The volatiles were evaporated, water (50 mL) was added and extracted with Et_2O (4×20 mL). The organic phase was washed with brine (2×25 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc/hexane 4:1 to give **8** (0.127 g, 47%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$), δ 7.24 (1H, dd, J=7.3, 0.7 Hz, H4); 7.14 (1H, td, J=8.1, 1.5 Hz, H6); 6.73 (1H, td, J=7.3, 0.7 Hz, H5); 6.51 (1H, d, J=8.0 Hz, H7); 5.22 (1H, br t, J=6.0 Hz, H10); 4.32 (1H, s, H8a); 3.88 (1H, dd, J=16.0, 8.4 Hz, H9A); 3.82 (1H, dd, J=16.1, 8.4 Hz, H9B); 3.02 (1H, br s, OH); 2.79 (1H, ddd, J=9.2, 6.8, 4.8 Hz, H2A); 2.62 (1H, ddd, J=8.6, 8.5, 6.9 Hz, H2B); 2.50 (3H, s, NCH_3); 2.28 (1H, ddd, J=12.4, 8.1, 6.9 Hz, H3A); 2.16 (1H, ddd, J=12.4, 5.9, 4.8 Hz, H3B); 1.72, 1.70 (6H, 2s, Me12, Me13). ^{13}C NMR ($CDCl_3$), δ 151.4 (C7a); 134.7 (C11); 132.5 (C3b); 129.7 (C6); 123.3 (C4); 120.7 (C10); 118.2 (C5); 108.5 (C7); 95.5 (C8a); 88.3 (C3a); 53.0 (C2); 47.1 (C9); 40.4 (C3); 38.5 (NCH_3); 25.7, 18.2 (Me12, Me13). IR (KBr) ν_{max} 3354, 3050, 2964, 2928, 2856, 1673, 1608, 1488, 1465 cm^{-1}. EIMS *m/z* (relative intensity) 258 (M^+, 25), 238 (41), 169 (100), 146 (20), 69 (34). FABHRMS *m/z* 259.1816 (MH^+, $C_{16}H_{22}N_2O$ requires 259.1810).

4.6. X-ray diffraction analysis of 4, 18, 22, 28, 35 and 39

Single crystal X-ray diffraction studies were done on a Bruker Smart 6000 CCD diffractometer for **4**, **18**, **28** and **35** using Mo radiation (λ=0.7073 Å). A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. These data were processed with the SAINT software package, provided by the diffractometer manufacturer, by using a narrow-frame integration algorithm. An empirical absorption correction was applied. Data collections for **22** and **39** were done on a Bruker-Nonius CAD4 diffractometer using Cu radiation (λ=1.5418 Å). The structures were solved by direct methods using the SHELXS-97[25] program included in the WINGX VI.6.[26] The structural refinement was carried out by full-matrix least squares on F^2. The non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, hydrogen coordinates, calculated and observed structure factors and torsion angles are in deposit at the Cambridge Crystallographic Data Center.

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Synthesis of the 11β-hydroxymethyl-androst-4-en-3,17-dione

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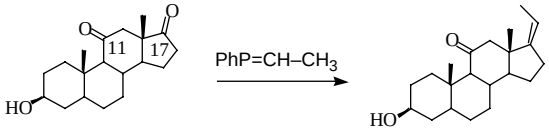
Abstract—The 11β-hydroxymethyl-androst-4-en-3,17-dione **5** was prepared within five synthetic steps starting from the commercially available adrenosterone with an overall yield of 24%. The 11-ketosteroid **1** was subjected to a Peterson methylenation. The subsequent hydroboration/oxidation sequence in position 11 was regio- and stereoselectively conducted using the borane–methyl sulfide complex at 0 °C. The target molecule was then obtained by deprotection using in situ generated TMSI.

1. Introduction

Several differently substituted androstenediones have been described in the literature as aromatase inhibitors or testosterone precursors.[1–5] However, only one example of C-11β modified androstenedione bearing a lateral carbon chain has been reported to date: the 11β-(4-methoxy-phenyl)-androstenedione, which was prepared within 11 synthetic steps in low yield.[5] The access to C-11 substituted steroids in androstane and androstene series is rather limited by the low reactivity at that position. As an example, a 100% regioselective Wittig olefination was done at C-17 on 3β-hydroxy-androstan-11,17-dione (Scheme 1).[6]



Scheme 1.

However, our group has recently shown that some organometallic reagents could be efficiently added to 11-keto androstenes.[7–9] After those encouraging results, we have thus turned our attention to the methylenation reaction of that position, the 11-methylene androstene **3** obtained could then be transformed into the corresponding 11β-hydroxymethyl derivative **4**, which in turn could lead to the androstenedione **5** expected.

2. Results and discussion

Scheme 2 describes the synthetic route chosen to the 11β-hydroxymethyl-androstenedione **5**. The ketosteroid **1** was prepared by protection of the C-3 and C-17 ketones of the commercially available adrenosterone using standard procedure.[10]

Various methylenation conditions were tested. Although the Tebbe reagent,[11] the CH_2Br_2–Zn–$TiCl_4$ system,[12] and the Olah conditions[13] are usually efficient on hindered ketones, when working on the steroid **1**, no methylenation product could be observed. The Peterson procedure,[14] already used in the nor-pregnene series,[15] was more suitable to our case (Scheme 3).

Table 1 presents the results obtained for the addition of Me_3SiCH_2M (M = MgCl, Li) to the 11-keto androstene **1**.

No addition was observed when the (trimethylsilyl)methyl magnesium chloride (1 M solution in diethylether) was used in THF at room temperature or at 50 °C (Table 1, entries 1 and 2). In toluene, increasing the temperature from room temperature to reflux allowed to get 23% addition (Table 1, entries 1 and 3). The use of (trimethylsilyl)methyl lithium (1 M solution in pentane) in THF or toluene gave about 50% addition at room temperature, and the addition was almost quantitative in refluxing toluene within 1 h (Table 1, entries 4 and 5).

The elimination reaction of the β-hydroxysilyl derivative **2** did not proceed under the addition conditions. The 11-methylene steroid **3** was thus prepared using potassium hydride in refluxing THF (78% yield).

Keywords: 11-Ketosteroids; Methylenation; Stereoselection.
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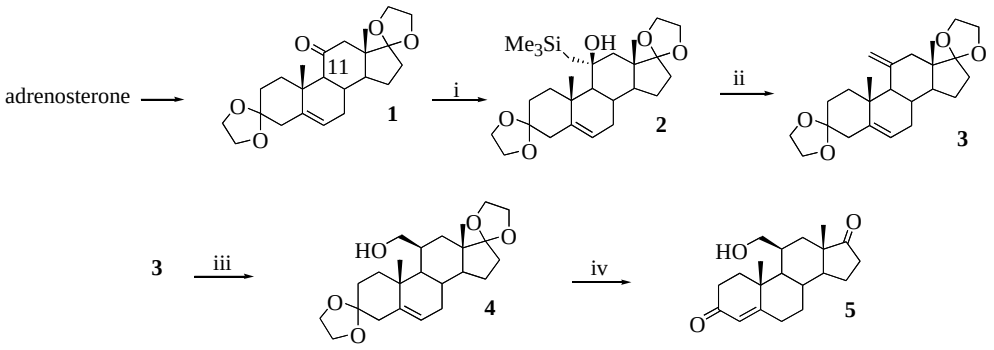
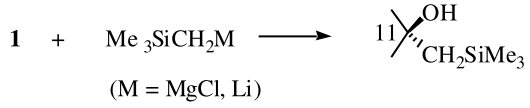


Scheme 2. Reagents and conditions: (i) Me_3SiCH_2Li/toluene, reflux; (ii) KH/THF, reflux; (iii) a. $BH_3 \cdot SMe_2$/THF, 0 °C; b. H_2O_2/NaOH; (iv) TMSCl, NaI/CH_3CN.



Scheme 3.

The hydroboration reaction of the steroid **3** was initially performed using 9-BBN or catechol borane to induce high selectivity, but no reaction was observed with these reagents. The more reactive borane BH_3 (used as a complex with dimethylsulfide (BMS) or with THF), was thus employed at different temperatures, reaction times and concentrations (Table 2). After oxidation, both the hydroxy compound **4** and the dihydroxy compound **9**, were obtained (Scheme 4), and their configuration was determined by NMR.

The NOESY spectrum of **4** presented cross-peaks between protons of the hydroxymethyl moiety and those of the angular methyls CH_3-18 and 19, thus indicating the C-11β configuration. Concerning **9**, using the shape of its ^{1}H NMR signal, the configuration C-6α was attributed.[16]

The selectivity was low at room temperature (Table 2, entries 1 and 2), but was improved when working at lower temperature (Table 2, entries 3–6). The best result was obtained after 24 h at 0 °C using 2.5 equiv of BMS (Table 2, entry 5), allowing us to prepare the alcohol **4** with 45% isolated yield.

The double bond in position 11 was more reactive than the one in position 5,6 (Table 2, entries 3, 4 and 6). Thus, once formed, the alkyl borane **7**, could react with remaining BH_3 to give the diborane compound **8**. Both additions proceeded through the least hindered α face of the steroid, at C-11 or C-5,6. An opposite result was observed for the hydroboration by BH_3 of the 3,3;17,17-bisethylenedioxy-androst-5-ene, which occurred predominently through the β face (β/α 4/1).[17] The first hydroboration reaction, producing **7**, thus prevents the second hydroboration (from **7** to **8**) occuring from the β face.

Using in situ generated TMSI, from TMSCl and NaI, the protecting groups in position 3 and 17 of the 11β-hydroxymethyl-androst-4ene-3,17-dione **5** were quantitatively removed in acetonitrile at room temperature. Under such conditions, alcohols may be converted into halogenated species.[18] That reaction was likely to be slowed down

Table 1. Addition of Me_3SiCH_2M (3 equiv) to steroid **1**

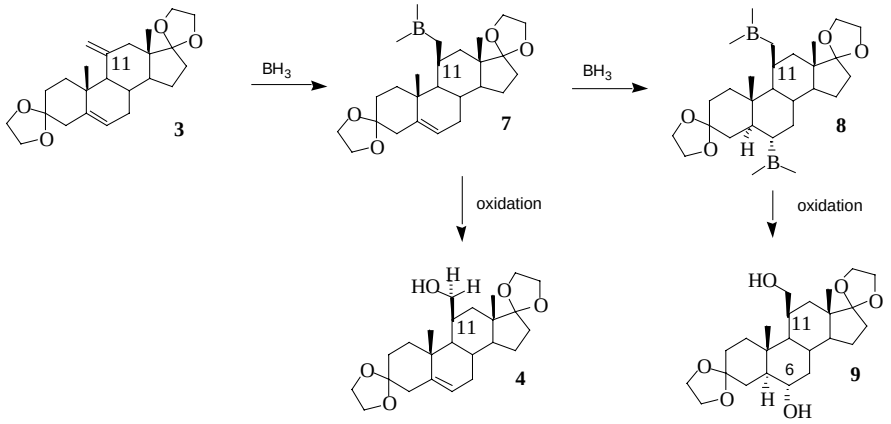
Entry	M	Solvent	*T* (°C)	*t* (h)	Conversion (%) **2**[a]
1	MgCl	THF or toluene	rt	2	0
2	MgCl	THF	50	1.5	0
3	MgCl	Toluene	Reflux	2	23
4	Li	THF or toluene	rt	3	45–50
5	Li	Toluene	Reflux	1	90–95 (76% yield)

[a] Determined by ^{1}H NMR.

Table 2. Hydroboration/oxidation of steroid **3** (in THF, with nBH_3)

Entry	Borane[a]	*n* (equiv)	*T* (°C)	*t* (h)[b]	% **3**[c]	% **4**[c]	% **9**[c]
1	BMS	1	rt	1	37	50	13
2	$BH_3 \cdot THF$	1.1	rt	4	33	41	26
3	BMS	1	0	1	90	10	0
4	BMS	1	0	24	70	30	0
5	BMS	2.5	0	24	15	70	15
6	BMS	3	−10	24	40	60	0

[a] Commercially avalaible borane–dimethyl sulfide complex (BMS) or borane·THF 1 M in THF.
[b] Time for hydroboration step.
[c] Determined by ^{1}H NMR.



Scheme 4.

by the steric hindrance of the position 11β and was not observed in our case.

3. Conclusion

The new 11β-hydroxymethyl-androst-4-en-3,17-dione **5** was prepared within 5 synthetic steps starting from the commercially available adrenosterone with an overall yield of 24%. This synthesis involves the preparation of several intermediates, such as the 11-methylene androstene **3** or the 11β-hydroxymethyl steroid **4**. Those steroids may be used for the preparation of new androstenediones or substituted testosterones bearing subtituents in C-11. This work is currently under investigation in our laboratory.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AC 300 spectrometer. Chemical shifts are reported in ppm and referenced to the residual proton resonances of the solvent used. Infrared (IR) spectra were recorded by using a BOMEN MB spectrometer. Mass spectra were obtained on NERMAG R 1010C apparatus. Optical rotations were measured on a Jasco P-1010 polarimeter at 589 nm and room temperature. Melting points were measured on a Kofler apparatus. Silica gel Merck Gerudan SI (40–60 μm) was used for column chromatography. Elemental analysis were measured at the microanalysis laboratory of the Pierre et Marie Curie University (Paris, France). All solvents and reagents were purified when necessary using standard procedures.

4.1.1. 3,3,17,17-(Ethylenedioxy)-androst-5-ene-11-one (1). This ketosteroid was prepared, as described by Bernstein,[10] using toluene instead of benzene as solvent, from the adrenosterone (Aldrich). Yields of 80–90% are obtained after crystallization in ether.

4.1.2. 3,3,17,17-(Ethylenedioxy)-11β-hydroxy-11α-(methyltrimethylsilyl)-androst-5-ene (2). 12.8 g (33 mmol) of the ketosteroid **1** and dry toluene (120 mL) were introduced into a three-necked flask under argon. (Trimethylsilylmethyl)lithium (100 mL, 1 M in pentane, 100 mmol) was then slowly added and the mixture was stirred at reflux for 2 h, after which water was added. The organic layer was separated, washed with water, dried on magnesium sulfate and evaporated. The crude product was purified by chromatographic column on silica gel (dichloromethane then diethylether) to give 12 g (76% yield) of steroid **2**, white powder: mp 124 °C; $[\alpha]_D$ −47.8 (*c* 1.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (m, 9H, $Si(CH_3)_3$) 1.03 and 1.37 (s, 3H, CH_3-18 and CH_3-19) 3.85–3.95 (m, 8H, CH_2-ketal) 5.28 (m, 1H, H-6) ppm; ^{13}C (75 MHz, $CDCl_3$) δ 0.0, 14.0, 20.3, 22.5, 30.1, 31.9, 32.2, 33.0, 37.2, 38.9, 40.1, 40.6, 43.7, 48.5, 48.9, 56.6, 63.1, 63.3, 63.4, 64.2, 77.4, 107.8, 118.6, 120.4, 141.2 ppm; MS (EI 70 eV) *m/z* 476 ($M^{+\cdot}$), 458 ($[M-H_2O]^{+\cdot}$), 346, 140, 115, 99, 73, 55, 42; IR (KBr) ν_{OH}=3509 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O_5Si$ (476.3): C 68.02, H 9.30. Found C 67.72, H 9.63.

4.1.3. 3,3,17,17-(Ethylenedioxy)-11-methylidene-androst-5-ene (3). Nine grams (18.9 mmol) of the steroid **2**, dry THF (100 mL) and 2.6 g (19.4 mmol) of KH (30 wt% dispersion in mineral oil) were introduced into a flask under argon. The mixture was stirred under reflux for 2 h. Ethyl acetate and water were then added. The organic layer was separated, washed with water, dried on magnesium sulfate and evaporated. The crude product was crystallized in pentane to give 5.7 g (78% yield) of steroid **3** mp 234 °C. The spectra of this steroid are in good accordance with our previous description.[19]

4.1.4. 3,3,17,17-(Ethylenedioxy)-11β-hydroxymethyl-androst-5-ene (4). 1.1 g (2.8 mmol) of the steroid **3** was dissolved in dry THF (15 mL) under argon and this solution was cooled at 0 °C. 0.7 mL (7 mmol) of borane–methyl sulfide complex was then added and the mixture was stirred at 0 °C for 24 h. The reaction mixture was oxidized by the addition of 1 mL of methanol, 1 mL of 3 M NaOH and 0.9 mL of 30% aqueous H_2O_2. After stirring for 3 h at room temperature, water was added. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried on magnesium sulfate and evaporated. The crude product was purified on silica gel chromatographic column (diethylether) to give unreacted steroid **3** followed by 0.51 g (45% yield) of steroid **4**, white powder: mp 76 °C; $[\alpha]_D$ −40 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 and 1.13 (s, 3H, CH_3-18 and CH_3-19), 2.32 (m, 1H, H-11), 3.68

(dd, 1H, $J=10.5$, 8.7 Hz), 3.82–3.94 (m, 8H, CH_2-ketal), 3.99 (dd, 1H, $J=10.5$, 6.5 Hz), 5.19 (m, 1H, H-6) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 20.5, 22.8, 29.4, 30.8, 31.5, 32.9, 34.2, 34.7, 36.8, 37.9, 40.8, 45.1, 51.9, 53.3, 64.2, 64.4, 64.6, 64.8, 65.1, 109.0, 119.6, 120.8, 141.1 ppm; MS (EI 70 eV) *m/z* 404 ($M^{+\cdot}$), 99, 86, 55; IR (KBr) $\nu_{OH}=3459\ cm^{-1}$. Anal. Calcd for $C_{24}H_{36}O_5$ (404.2): C 71.26, H 8.97. Found C 71.61, H 9.40.

4.1.5. 3,3,17,17-(Ethylenedioxy)-6α-hydroxy-11β-hydroxymethyl-androstane (9). Steroid **3** (390 mg, 1 mmol) was dissolved in dry THF (5 mL) under argon and 0.5 mL of BMS (5 mmol) was added at room temperature. The mixture was stirred for 2 h and then oxidized by the addition of 0.3 mL of MeOH, 0.3 mL of 3 M NaOH and 0.3 mL of 30% aqueous H_2O_2. After stirring for 3 h at room temperature water was added. After usual work-up, using dichloromethane as solvent, the crude product was crystallized in ether to afford 250 mg (59% yield) of a white solid: mp 250 °C; $[\alpha]_D$ +8.7 (*c* 1.83, $CHCl_3$). An analytical sample was obtained by silica gel chromatography (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 and 0.92 (s, 3H, CH_3-18 and CH_3-19), 2.32 (m, 1H, H-11), 3.37 (dt, $J=$ 4.5, 10.8 Hz, 1H, H-6), 3.56 (dd, 1H, $J=18$, 8.7 Hz), 3.84–4.00 (m, 9H, CH_2 -ketals and 1H) ppm; ^{13}C (75 MHz, $CDCl_3$) δ 14.6, 16.3, 22.7, 25.6, 30.8, 32.1, 34.3, 35.7, 36.5, 37.6, 41.8, 45.4, 51.9, 52.9, 56.1, 56.6, 64.1, 64.2, 64.7, 65.1, 67.9, 68.9, 108.8 et 119.7 ppm; MS (ICP/NH_3) *m/z* 440 $[MNH_4]^+$ 423 $[MH]^+$; IR (KBr) $\nu_{OH}=3449\ cm^{-1}$. Anal. Calcd for $C_{24}H_{38}O_6$ (422.2): C 68.22, H 9.06. Found C 68.14, H 9.05.

4.1.6. 11β-Hydroxymethyl-androst-4-ene-3,17-dione (5). One millilitre of acetonitrile was added under argon to a mixture of 100 mg (0.25 mmol) of the steroid **4** and 35 mg (0.25 mmol) of NaI. 30 μL of TMSCl (0.25 mmol) were then added under stirring at room temperature and the resulting mixture was stirred for 0.33 h. Water was then added, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, washed with aqueous sodium thiosulfate followed by water, dried on magnesium sulfate and evaporated. The crude product was purified on silica gel (diethylether/ethylacetate; 80:20) to give 80 mg (100%) of a white solid: mp 209 °C; $[\alpha]_D$ +131 (*c* 1.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 and 1.38 (s, 3H, CH_3-18 and CH_3-19), 3.64 and 3.98 (dd, 1H, $J=10.8$, 6.3 Hz), 5.68 (s, 1H, H-4) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 20.2, 21.5, 31.6, 31.7, 32.1, 33.7, 34.2, 35.1, 35.4, 38.7, 39.3, 46.6, 53.6, 55.5, 64.6, 122.0, 171.8, 199.2 and 218.4 ppm; MS (EI 70 eV) *m/z* 316 ($M^{+\cdot}$), 298 ($[M-H_2O]^{+\cdot}$), 285, 256, 241, 180, 133, 124, 105, 91, 79, 67, 55, 41; IR (KBr) 1736 (17-C=O), 1647 (3-C=O), 3391 (OH) cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_3$ (316.2) C 75.91, H 8.92. Found C 75.51, H 9.21.

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Novel crowned-porphyrin ligands. Synthesis and conformational studies

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Abstract—Three new macromolecules—a cryptand, a bis-macrocycle, and a tris-macrocycle—have been synthesized as chelating ligands for cation binding. They result from the surprisingly simple reaction of various bis-functionalized *meso*-aryl porphyrins with a diaza-crown ether coupled one to each other through either one or several urea linkage(s). Indeed, the latter induces some additional rigidity in comparison with the usual amide linkage found in such macromolecules. Various strategies are reported to optimize the yield of the reaction towards the formation of a cofacial singly-linked crown-porphyrin, which is the most promising ligand to stabilize large cations such as bismuth(III) as the angle between the two macrocycles can vary.

1. Introduction

In our on-going research program dedicated to the coordination of various cations of medical interests, we have been studying for almost a decade different types of macromolecular architectures.[1] Among these cations, one can cite gadolinium, yttrium, bismuth, or europium. The first one is obviously known to be efficient in the design of new imaging agents[2] where the last one is commonly employed for the preparation of luminescent molecules.[3] The second and third elements are either already clinically used in β-radiotherapy[4] or evaluated for α-radiotherapy,[5] respectively. An example of these chelating molecules is the cofacial cyclam-strapped porphyrins, which have proved to be efficient for the coordination of two transition metals as iron and cobalt.[6] However, such edifices are likely too rigid to be efficient chelators of larger cations such as gadolinium, europium or bismuth. Indeed, neither the former nor the latter are stabilized in single-crowned[7] or bis-crowned porphyrins,[8] respectively. In the first case, we have explained this non coordination of gadolinium presumably because of a *para*-pyridyl residue on two *meso* positions of the porphyrin, which can directly interact with the lanthanide cation, a competitive interaction to the metallation process. In the second example, the bis-crowned porphyrin was not flexible enough to be distorted and hence to allow the entry of the bismuth cation inside the cavity. However, as these three elements exhibit different radii,[9] our goal was to design a rigid but still flexible family of molecules, which could adapt its size to the desired cation.[10] This is the reason why we have investigated the synthesis of singly-linked crown porphyrins.

2. Results and discussion

The reaction of 1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane (Kryptofix-2,2 or diaza-18-crown-6 ether) on a 5,15-*o*-diamido picket porphyrin or on a 5,15-*o*-diaminophenyl porphyrin usually leads to the formation of a macromolecule in which the two different macrocycles appear to be in a cofacial geometry as in macrotricycle **1**.[11] Indeed, in the latter, the diaza-crown ether being bis-linked on the porphyrin, cannot escape from its apical position, as it can in compound **2**. However, when the bonds between the two

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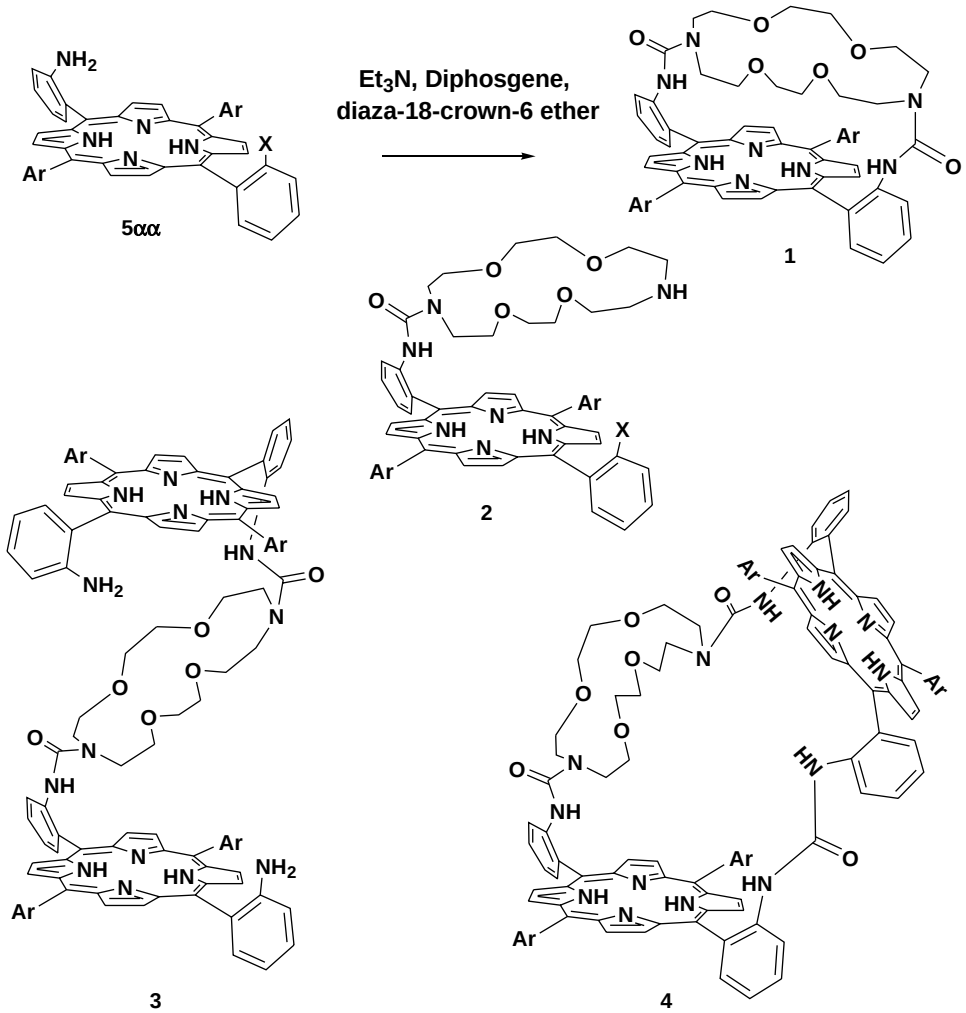
macrocyles are very short as in the case of a urea bond,[12] we noticed that the system was not sufficiently flexible to coordinate metal cations bulkier than zinc for instance. To obtain flexible systems, we required the crown-ether motif to be able—more or less—to move away from the porphyrin according to the cation to stabilize, hence the target molecule **2**. Such a compound should exist as two different isomers (*endo* and *exo*) but owing to the urea bond, the cofacial geometry is expected to be favored. Moreover, if one considers that the crown-ether is attached by the *meso* positions 5 and 15, it is obvious that the steric hindrance induced by the two other *meso* positions, namely 10 and 20 can influence the approach of the cage by the cation and also the position of the strapped crown-ether. Accordingly, we studied various aromatic groups (Scheme 1) such as 2,4,6-trimethylphenyl (mesityl, compounds labeled **a**) or 3,5-dimethoxyphenyl (compounds labeled **b**). Indeed, in the case of the dimesityl porphyrin, the two *ortho* positions of the aromatic rings in the positions 10 and 20 being substituted by a methyl group, the crown ether is expected to be less mobile than in the other series with methoxy groups in *meta* positions. This detail will be discussed vide infra. Actually, by choosing the experimental conditions, we could optimize the reaction towards the preparation of **1** or **2**, concomitantly with the synthesis of the tris-macrocycle **3** and the macrotetracycle **4**. Obviously, to avoid unambiguously the synthesis of the macrotricyclic crown-porphyrin **1**, the unique procedure would consist in protecting one amino function of both the porphyrin and the crown-ether. But in regard with the facility of the synthetic path of Scheme 1, we preferred to vary the experimental procedure (method B vs method A, see Section 4.2) to obtain compound **2**. Additionally, in the mesityl series **a**, we have also investigated an alternative procedure that consists in working with a singly reduced porphyrin such as **5aNO$_2$**. In literature, this type of selectivity has already been achieved either by reducing[13] only one nitro group of a 2,6-dinitro-*meso*phenyl group or by acylating only one amino function after reduction of the two nitro functions.[14] Theoretically, in a typical synthesis, **1** should be the single product of the reaction but is also the less attractive. Practically, the three other compounds exhibit more sophisticated structures. For instance, in compound **2**, two structural criterions have to be considered. The first deals with the 'face-to-face' spatial arrangement of the two macrocycles. As already mentioned, the urea bond itself should maintain this cofacial geometry. Moreover, this is verified by proton NMR spectroscopy, since we can carry



Scheme 1. General synthesis of crowned porphyrins from an α-5,15-bis-(2-amino-phenyl)porphyrin or from an α-5-(2-amino-phenyl)-α-15-(2-nitro-phenyl)porphyrin. Compounds are labelled as follow: series **a**: Ar=2,4,6-trimethyl-phenyl, series **b**: Ar=3,5-dimethoxy-phenyl. When X=NO_2, NO_2 is added at the end of the name. Note that two methods can be used for this reaction.

out a reliable comparison with compound **1** for which we know precisely the conformation. For instance, in **1b**, the fingerprint of the crown-ether is composed of 3 singlets integrating for 8 protons each at 2.56, 1.94 and 0.49 ppm. In the case of **2b**, the NMR signature becomes 6 broad singlets of 4 protons in the range 2.68–1.43 ppm. In the latter compound, signals upfield shifted as in compound **1b** do not exist anymore, which testifies well to the larger distance —at least for some protons— of the crown-ether to the cone of anisotropy of the porphyrin. However, it is difficult to investigate if the crown-ether motif is still above the porphyrin or presumably slightly off-centered. In the 2,4,6-trimethyl-phenyl series **a**, a similar conclusion is drawn with signals at 2.60, 2.07 and 1.56 ppm for **1a** and signals between 2.88 and 1.97 ppm for **2aNO$_2$**.

But the most intriguing observation resulting from the comparison of the various NMR data consists in the signature of the crown-ether obtained in the case of the bis-porphyrin compound **3b**. Indeed, one can easily conceive various spatial arrangements in solution for this type of compound (Fig. 1). The most probable is depicted in representation (c1) with no specific conformation of the crown-ether moiety and the two porphyrin units most distant one from the other. Yet, this conformation is not consistent at all with the chemical shifts of the protons from the crown-ether, which resonate as broad singlets of 8 protons each at 1.82, 1.13, and −0.46 ppm. Theses chemical shifts show that all the protons of the crown-ether in **3b** are more shielded than they are in **1b**. More particularly, 8 of them are more upfield-shifted of 1 ppm (−0.46 ppm) relatively to the 8 most shielded protons in **1b** (0.49 ppm). This observation implies that **3b** has to exist in a conformation in which the crown-ether motif undergoes the additive effect of the two porphyrin rings. Such possible conformations are represented in (c2) and (c3) (Fig. 1). However, the conformation (c2) is difficult to explain as there is no argument to justify a 'curved' conformation of the crown-ether. Conversely, in conformation (c3), the fact that the crown-ether is pinched between the two porphyrins could be induced by the urea linkage itself, as in compound **2b** in which a relaxed face-to-face conformation is observed. Hence, we propose this 'Z-shape' structure in solution for compound **3b**.

Finally, the fourth isolated compound is the macrotetracycle **4b**. Although related somehow to the coreceptor molecules reported by Lehn and co-workers,[15] **4b** is different as the two porphyrin units are not expected to be cofacial. Indeed, in this compound, the two porphyrinic units are attached via a urea linkage, which act as a hinge, and the angle between the two porphyrins is actually imposed by the crown-ether, which acts as a spacer. The chemical shifts of the protons from the crown-ether are 3.80, 2.15, and 0.89 ppm. In light of the structure of **4b**, these chemical shifts are expected as they are more down-field shifted than in **2b**, one of them being almost the same (0.89 ppm in **4b** vs 0.49 ppm in **2b**). According to these data, it can be predicted that the angle between the porphyrin(s) and the crown-ether is larger in **4b** than it is in **2b**. But obviously, **4b** should be more flexible than **2b**.

As already mentioned, to optimise the formation of compounds **2** relatively to compounds **1**, we have employed two different approaches. The first one that we have described consists in modifying the experimental procedure. For instance, when method B (see Section 4) is applied instead of method A, the yield of isolated compound **2b** rises up from 5 to 48% yield, mostly at the expense of compounds **1b** and **3b**, the yield of compound **4b** increasing from 3 to 11%. Actually, these two experimental procedures differ mainly by the fact that in method B, both reagents, the activated porphyrin and the crown-ether are added together. The second approach, increasing the yield of **2a** consists in

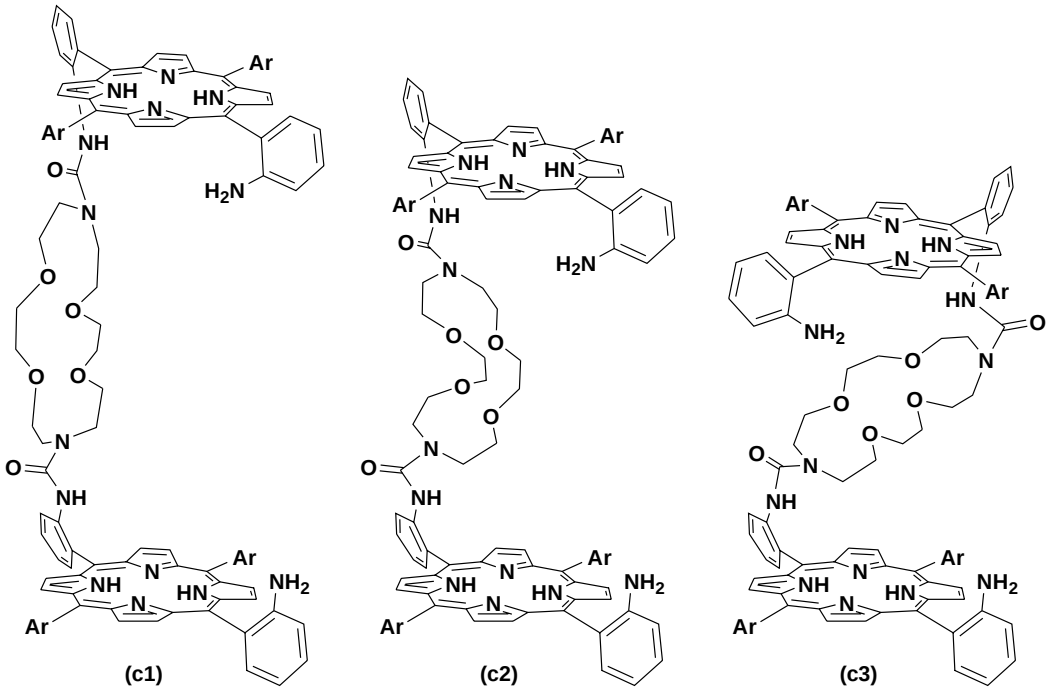
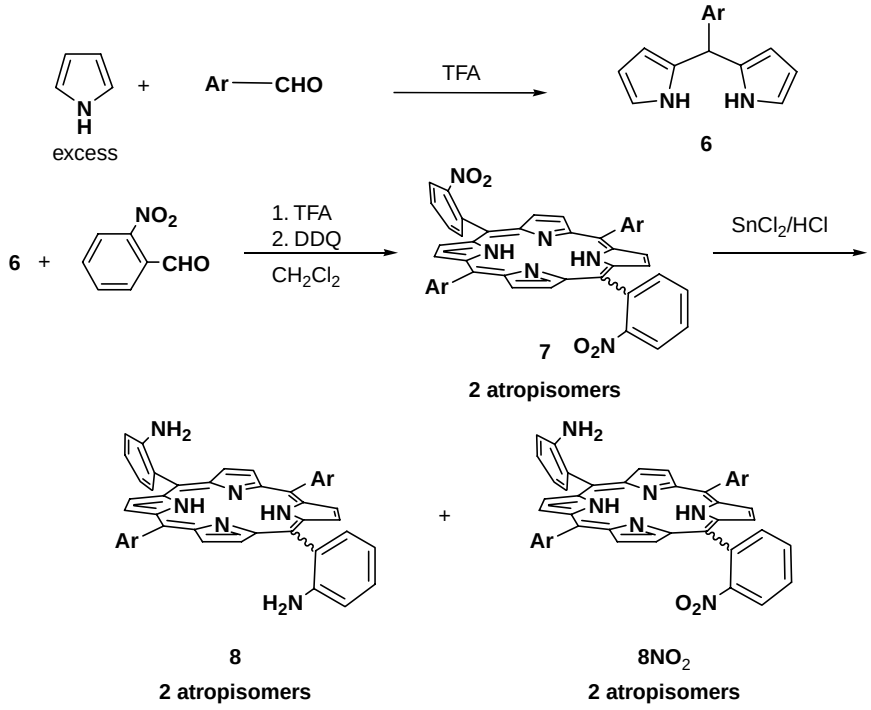


Figure 1. Various possible conformations (c1–c3) of tris-macrocycle **3**.



Scheme 2. Synthesis of the two porphyrinic building-blocks. For compounds labelling, use convention of Scheme 1. When Ar=2,4,6-trimethyl-phenyl, the reduction step leading to **8** was performed at 0 °C.

inhibiting the reactivity of one of the anilines of the porphyrin. Therefore, we have performed a partial reduction of the nitro groups of **7a** to obtain **8aNO$_2$** (Scheme 2), and then, after a separation of the two atropisomers, obtained the **5aNO$_2$**$\alpha\alpha$ atropisomer (Scheme 1). Hence, following the same procedure applied for the diamino counterparts, it is obvious that the formation of either **1a** or **4a** becomes impossible, thereby controlling the reaction towards the exclusive formation of **2a** and **3a**. However, when the reaction was performed with **5aNO$_2$**$\alpha\alpha$, it should be noted that compound **3a** was not obtained either, or only as negligible traces. This observation demonstrates that working with a mono-nitro mono-amino tetraaryl porphyrin represents an efficient alternative for the almost exclusive synthesis of bis-macrocycles **2**.

Incidentally, in compounds **2**, if one considers that the 2-amino (or nitro) aryl groups are on the 5 and 15 *meso* positions, the substitution of the two other *meso* aryl groups may have some influence on the conformation of the compound. For example, in the mesityl series (compounds **a**), it could be probed if the two methyl groups in *ortho* position generate a steric hindrance with the crown-ether or not. Again, this is confirmed by comparing the proton NMR data of **2a** with **2b**. For instance, the chemical shifts of the protons from the crown-ether in **2a** are slightly larger than their analogues in **2b** but the difference is not really significant. Therefore, we can assume that the conformation is not strongly affected by the nature of the two *meso* aryl groups in positions 10 and 20. Additionally, it should be pointed out that any possible distortion of the porphyrin could influence the geometry of the various compounds. Actually, consideration of the X-ray structure of **7a**$\alpha\alpha$, that could be determined (Fig. 2), reveals that there is indeed a slight distortion of the porphyrin cycle, presumably due to the steric hindrance of the two *ortho* positions (Fig. 2b). According to the distances of atoms from the mean porphyrin plane, the distortion may be chiefly described in terms of a saddled conformation, in view of the alternate

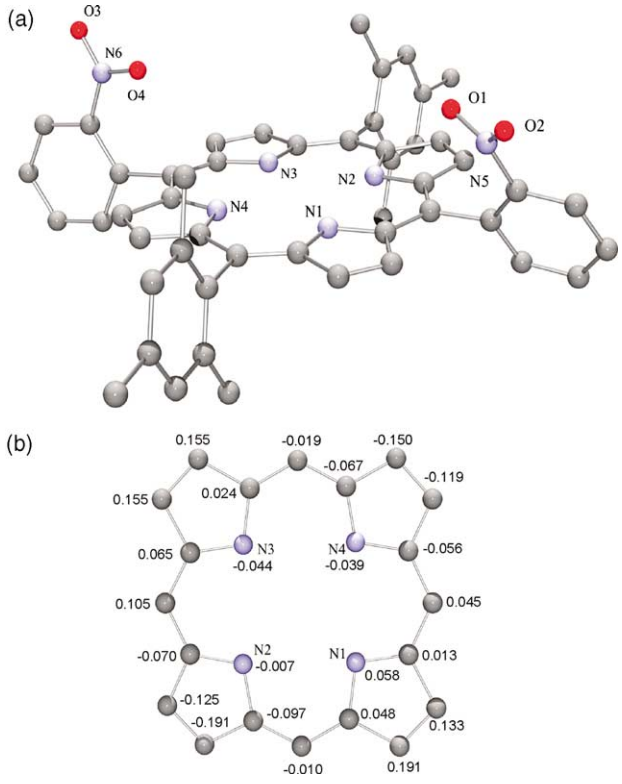


Figure 2. Ball and stick representation of the X-ray structure of the atropisomer $\alpha\alpha$ of **7a**; (a) perspective view, (b) apical view with distances in Å of each atom to the mean plane of the porphyrin.

tilting of adjacent pyrrolic units and *meso* carbons. However, the distortion is not purely saddled as it also exhibits some ruffling, since the Cα–N–N–Cα torsion angles between two diametrically opposed pyrroles are equal to 2.41 and 8.61°.

3. Conclusion

According to two different approaches, we have shown that with a simple and unique reaction, we can synthesize four macromolecules, all of them incorporating at least one porphyrin unit as well as one crown-ether moiety. Whereas one of the two described methods allows the preponderant formation of both the bis-macrocycle and the macrotetracycle, an alternative approach is also proposed to optimize the synthesis of the bis-macrocycle versus the macrotetracycle. Among these four ligands, three of them should exhibit very different properties towards the binding of various cations from groups 13 and 15 or lanthanides. These three macromolecules differ both by the shape and the size of the cavity resulting from the assembly of several macrocycles either by one or two link(s). Coordination studies of these novel bis-macrocycle, tris-macrocycle, and macrotetracycle will be reported elsewhere.

4. Experimental

4.1. General considerations

^{1}H (500.13, 300.13 MHz) NMR spectra were recorded on Bruker Avance spectrometers and referenced to the residual protonated solvent. Mass spectra were performed on a MS/MS ZABSpec TOF spectrometer at the University of Rennes I (C.R.M.P.O.). UV–vis spectra were recorded on a Varian Cary 1E and an Uvikon XL spectrometers. Infrared spectra were recorded on Bruker IFS 66 and 28 spectrometers. All solvents (ACS for analysis) were purchased from Carlo Erba. THF was distilled from potassium metal whereas methanol was distilled from magnesium turnings. CH_2Cl_2 was used as received. Triethylamine was distilled from CaH_2. The starting materials were generally used as received (Acros, Aldrich) without any further purification. All reactions were performed under an argon atmosphere and monitored by TLC (silica, CH_2Cl_2/MeOH). Column flash chromatography was performed on silica gel (Merck TLC-Kieselgel 60H, 15 μm). Elemental analyses were obtained on an EA 1108 Fisons Instruments.

4.2. General synthetic paths

The two following procedures were performed to graft a crown ether on the porphyrin: method A optimises the yield of **1b** and method B, the yield of **2b**.

Method A. In a two neck round bottom flask equipped with a stir bar and a gas inlet, **5bαα** (120 mg, 0.16 mmol) was charged with dry THF (10 mL) and Et_3N (0.1 mL). The mixture was cooled to 0 °C then, diphosgene (9.6 μL, 79 μmol) was added. After 1 h, diaza-18-crown-6 ether (46 mg, 0.18 mmol) in 10 mL of dry CH_2Cl_2 was added dropwise over 30 min and the mixture was stirred for an additional 1 h. The solvent was removed under vacuum and the residue was purified by silica gel chromatography. The compound **4b** was eluted with CH_2Cl_2 and obtained in 3% yield (9 mg), compound **3b** was eluted with 0.2% methanol/CH_2Cl_2 and obtained in 15% yield (22 mg), compound **1b** was eluted with 0.8% methanol/ CH_2Cl_2 and obtained in 55% yield (97 mg) and compound **2b** was eluted with 2% methanol/CH_2Cl_2 and obtained in 5% yield (8.4 mg).

Method B. In a two neck round bottom flask equipped with a stir bar and a gas inlet, **5bαα** (120 mg, 0.16 mmol) was charged with dry THF (10 mL) and Et_3N (0.1 mL). The reaction mixture was cooled to 0 °C then diphosgene (7.2 μL, 59 μmol) was added. After 1 h, the resulting reaction mixture of activated porphyrin was charged in a 10 mL syringe as well as a solution of diaza-18-crown-6 ether (46 mg, 0.18 mmol) in dichloromethane (10 mL). These two solutions were added dropwise over 2 h with a syringe pump to a solution of THF (400 mL) and NEt_3 (0.1 mL). The mixture was stirred for an additional 1 h. The solvent was removed under vacuum and the residue was purified by chromatography column. Compound **4b** was eluted with CH_2Cl_2 and obtained in 11% yield (33 mg), compound **3b** was eluted with 0.2% methanol/CH_2Cl_2 and obtained in 13% yield (19 mg), compound **1b** was eluted with 0.8% methanol/CH_2Cl_2 and obtained in 20% yield (35 mg), and compound **2b** was eluted with 2% methanol/ CH_2Cl_2 and obtained in 46% yield (77 mg). As far as concern the series of **a** derivatives, the yields are identical via method A or B with those of series **b**.

4.2.1. 1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7,16-dicarboxylic acid {2,2′-[10,20-bis-(2,4,6-trimethylphenyl)-porphyrin-α-5,15-diyl]-diphenyl}-diamide 1a. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.82$ (d, $J=4.5$ Hz, 4H, βpyr), 8.69 (d, $J=4.5$ Hz, 4H, βpyr), 8.60 (d, $J=7$ Hz, 2H, aro), 8.04 (d, $J=7.5$ Hz, 2H, aro), 7.73 (t, $J=7.5$ Hz, 2H, aro), 7.52 (t, $J_1=7$ Hz, 2H, aro), 7.37 (s, 2H, aro), 7.24 (s, 2H, aro), 5.96 (s, 2H, NHCO), 2.65 (s, 6H, –CH_3), 2.60 (s, 8H, –CH_2–), 2.11 (s, 6H, –CH_3), 2.07 (s, 8H, –CH_2–), 1.64 (s, 6H, –CH_3), 1.56 (s, 8H, –CH_2–), −2.23 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=157.0$, 141.5, 140.1, 138.9, 138.3, 138.1, 133.9, 130.3, 129.7, 128.4, 128.2, 120.8, 120.0, 118.6, 114.0, 69.2, 50.3, 30.1, 22.1, 22.0, 21.8. HRMS (ES^+) Calcd for $C_{64}H_{66}N_8O_6Na$ $(M+Na)^+$ 1065.5003. Found, 1065.5006. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\,mol^{-1}\,cm^{-1}$): 420 (329.3), 516 (23.6), 550 (7.4), 591 (7.2), 647 (3.9).

4.2.2. 1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7,16-dicarboxylic acid {2,2′-[10,20-bis-(3,5-dimethoxyphenyl)-porphyrin-α-5,15-diyl]-diphenyl}-diamide 1b. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.98$ (d, $J=4.5$ Hz, 4H, βpyr), 8.88 (d, $J=4.5$ Hz, 4H, βpyr), 8.54 (dd, $J_1=7.5$ Hz, $J_2=1.5$ Hz, 2H, aro), 7.96 (d, $J=8$ Hz, 2H, aro), 7.80 (td, $J_1=8$ Hz, $J_2=1$ Hz, 2H, aro), 7.60 (td, $J_1=7.5$ Hz, $J_2=$ 1 Hz, 2H, aro), 7.53 (s, 2H, aro), 7.15 (s, 2H, aro), 6.92 (t, $J=2$ Hz, 2H, aro), 5.80 (s, 2H, NHCO), 4.12 (s, 6H, –OCH_3), 3.92 (s, 6H, –OCH_3), 2.56 (s, 8H, –CH_2–), 1.94 (s, 8H, –CH_2–), 0.49 (br s, 8H, –CH_2–), −2.51 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=159.1$, 156.5, 155.4, 148.6, 147.5, 146.4, 142.2, 140.9, 133.5, 131.3, 129.4, 122.2, 121.7, 114.3, 113.8, 99.9, 69.3, 55.6, 49.7. HRMS

(ES$^+$) Calcd for $C_{62}H_{62}N_8O_{10}Na$ $(M+Na)^+$ 1101.4486. Found, 1101.4495. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\,mol^{-1}\,cm^{-1}$): 418 (301.3), 516 (17.1), 551 (5.5), 589 (5.4), 646 (2.6).

4.2.3. 1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7-carboxylic acid {2-[α-15-(2-nitro-phenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin-α-5-yl]-phenyl}-amide 2aNO_2. A mixture of porphyrin **5aNO_2**αα (31 mg, 41 μmol), triethylamine (11 μL, 82μmol) and carbonic acid ditrichloromethyl ester (triphosgene) (4 mg, 13.6 μmol) in dry CH_2Cl_2 (20 mL) was stirred for 1 h under argon at room temperature. This mixture was added dropwise, over 2 h with a syringe pump to a solution of diaza-18-crown-6 ether (11 mg, 41 μmol) in dry CH_2Cl_2 (10 mL). The mixture was stirred for an additional 1 h. The solvent was removed under vacuum and the residue was purified by chromatography column. The desired compound **2aNO_2** was eluted with 1% methanol/CH_2Cl_2 and obtained in 88% yield (38 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.83 (d, J=4.5 Hz, 2H, βpyr), 8.69–8.62 (m, 4H, βpyr and 1H, aro), 8.59 (d, J=4.5 Hz, 2H, βpyr), 8.43 (dd, J_1=8 Hz, J_2=1.5 Hz, 1H, aro), 8.23 (dd, J_1=7 Hz, J_2=1.5 Hz, 1H, aro), 7.99–7.92 (m, 3H, aro), 7.74 (td, J_1=8 Hz, J_2=1.5 Hz, 1H, aro), 7.69 (s, 1H, NHCO), 7.34 (td, J_1=7.5 Hz, J_2=1 Hz, 1H, aro), 7.30 (s, 2H, aro), 7.28 (s, 2H, aro), 5.00 (br s, 1H, NH), 2.88 (br s, 4H, –CH_2–), 2.63 (s, 6H, –CH_3), 2.38 (br s, 12H, –CH_2–), 1.97 (br s, 8H, –CH_2–), 1.85 (s, 6H, –CH_3), 1.82 (s, 6H, –CH_3), −2.51 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=157.3, 152.2, 141.6, 139.7, 139.2, 138.5, 138.2, 137.4, 136.6, 135.5, 131.5, 130.1, 129.9, 129.8, 128.4, 128.3, 124.3, 120.8, 119.4, 119.2, 116.0, 114.0, 71.5, 69.8, 68.7, 49.1, 47.0, 22.2, 22.0, 21.9. HRMS (ES$^+$) Calcd for $C_{63}H_{67}N_8O_7$ $(M+H)^+$ 1047.5132. Found, 1047.5131. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\,mol^{-1}\,cm^{-1}$): 420 (261.8), 516 (15.6), 549 (5.4), 592 (4.9), 648 (2.6).

4.2.4. 1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7-carboxylic acid {2-[α-15-(2-amino-phenyl)-10,20-bis-(3,5-dimethoxy-phenyl)-porphyrin-α-5-yl]-phenyl}-amide 2b. ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.06 (d, J=4.5 Hz, 2H, βpyr), 9.04 (d, J=4.5 Hz, 2H, βpyr), 8.98 (d, J=5 Hz, 2H, βpyr), 8.93 (d, J=5 Hz, 2H, βpyr), 8.59 (d, J=9 Hz, 1H, aro), 7.99 (d, J=7.5 Hz, 1H, aro), 7.87 (d, J=7.5 Hz, 1H, aro), 7.78 (t, J=6.5 Hz, 1H, aro), 7.64 (t, J=7.5 Hz, 1H, aro), 7.38 (m, 5H, aro), 7.19 (m, 3H, aro and NHCO), 6.93 (t, J=2.5 Hz, 2H, aro), 4.03 (s, 6H, –OCH_3), 4.01 (s, 1H, NH), 3.97 (s, 6H, –OCH_3), 2.68 (br s, 4H, –CH_2–), 2.52 (br s, 4H, –CH_2–), 2.36 (br s, 4H, –CH_2–), 1.96 (br s, 4H, –CH_2–), 1.61 (br s, 4H, –CH_2–), 1.43 (br s, 4H, –CH_2–), −2.75 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=159.1, 150.2, 140.6, 134.9, 131.6, 129.7, 121.0, 119.8, 117.7, 114.6, 113.7, 111.5, 99.9, 95.9, 70.3, 68.4, 64.1, 55.6, 48.5, 46.6. HRMS (ES$^+$) Calcd for $C_{61}H_{65}N_8O_9$ $(M+H)^+$ 1053.4874. Found, 1053.4867. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\,mol^{-1}\,cm^{-1}$): 419 (215.3), 512 (14.7), 548 (4.3), 588 (4.4), 646 (2.3).

4.2.5. 1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7,16-dicarboxylic acid bis-{2-[α-15-(2-amino-phenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin-α-5-yl]-phenyl}-diamide 3a. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.76 (d, J=4.5 Hz, 4H, βpyr), 8.59 (d, J=4.5 Hz, 8H, βpyr), 8.51 (d, J=4.5 Hz, 4H, βpyr), 8.34 (d, J=8 Hz, 2H, aro), 7.86 (d, J=7.5 Hz, 2H, aro), 7.77 (d, J=7.5 Hz, 2H, aro), 7.63 (t, J=8 Hz, 2H, aro), 7.57 (t, J=7.5 Hz, 2H, aro), 7.27 (m, 2H, aro), 7.24 (s, 4H, aro), 7.19 (s, 4H, aro), 7.14–7.08 (m, 4H, aro), 6.88 (s, 2H, NHCO), 3.60 (br s, 4H, NH_2), 2.62 (s, 12H, –CH_3), 1.76 (s, 12H, –CH_3), 1.58 (s, 8H, –CH_2–), 1.38 (m, 8H, –CH_2–), 1.29 (s, 12H, –CH_3), −1.02 (br s, 8H, –CH_2–), −2.80 (s, 4H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=158.1, 153.5, 145.3, 139.0, 138.7, 138.2, 136.9, 136.6, 135.2, 130.5, 129.7, 128.4, 124.1, 120.8, 119.7, 119.3, 116.2, 114.0, 71.5, 69.8, 68.8, 50.7, 46.8, 22.5, 22.1, 21.7. HRMS (ES$^+$) Calcd for $C_{114}H_{111}N_{14}O_6$ $(M+H)^+$ 1771.8811. Found, 1771.8813. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\,mol^{-1}\,cm^{-1}$): 418 (512.3), 515 (40.3), 547 (19.8), 592 (19.1), 647 (12.5).

4.2.6. 1,4,10,13-Tetraoxa-7,16-diaza-cyclooctadecane-7,16-dicarboxylic acid bis-{2-[α-15-(2-amino-phenyl)-10,20-bis-(3,5-dimethoxy-phenyl)-porphyrin-α-5-yl]-phenyl}-diamide 3b. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.87 (d, J=4.8 Hz, 4H, βpyr), 8.82 (d, J=4.8 Hz, 4H, βpyr), 8.79 (d, J=4.8 Hz, 4H, βpyr), 8.65 (d, J=4.8 Hz, 4H, βpyr), 8.38 (d, J=8.1 Hz, 2H, aro), 7.85 (d, J=7.2 Hz, 2H, aro), 7.79 (d, J=7.2 Hz, 2H, aro), 7.68 (t, J=7 Hz, 2H, aro), 7.62 (t, J=7.8 Hz, 2H, aro), 7.26 (m, 6H, aro), 7.17 (m, 6H, aro), 7.08 (d, J=7.8 Hz, 2H, aro), 6.87 (br s, 4H, aro), 6.78 (br s, 2H, NHCO), 3.93 (s, 12H, –OCH_3), 3.90 (s, 12H, –OCH_3), 3.53 (br s, 4H, NH_2), 1.82 (br s, 8H, –CH_2–), 1.13 (br s, 8H, –CH_2–), −0.46 (br s, 8H, –CH_2–), −2.93 (s, 4H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=158.8, 146.8, 140.5, 134.9, 130.7, 129.9, 120.7, 119.3, 117.5, 114.3, 113.7, 99.9, 68.4, 67.5, 55.6, 48.9. HRMS (ES$^+$) Calcd for $C_{110}H_{102}N_{14}O_{14}Na$ $(M+Na)^+$ 1865.7598. Found, 1865.7577. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\,mol^{-1}\,cm^{-1}$): 418 (523.5), 514 (33.4), 549 (9.6), 589 (10.2), 645 (4.7).

4.2.7. 1,3-Bis-{2-[1,4,10,13-tetraoxa-7,16-diaza-cyclooctadecane-7,16-dicarboxylic acid bis-{2-[2-{10,20-bis-(3,5-dimethoxy-phenyl)}-α-15-phenyl]-amide}-porphyrin-α-5,5′-diyl]-diphenyl}-urea 4b. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.73 (d, J=4.2 Hz, 4H, βpyr), 8.67 (d, J=5.1 Hz, 4H, βpyr), 8.65 (d, J=5.1 Hz, 4H, βpyr), 8.60 (d, J=4.2 Hz, 4H, βpyr), 8.51 (d, J=8.2 Hz, 2H, aro), 8.43 (d, J=8.2 Hz, 2H, aro), 7.84 (t, J=8.4 Hz, 2H, aro), 7.71 (m, 4H, aro), 7.61 (d, J=7.5 Hz, 2H, aro), 7.40 (t, J=7.5 Hz, 2H, aro), 7.30 (t, J=7.5 Hz, 2H, aro), 7.16 (s, 4H, aro), 6.98 (s, 4H, aro), 6.81 (s, 4H, aro), 6.77 (s, 2H, NHCO), 5.69 (s, 2H, NHCO), 3.87 (s, 12H, –OCH_3), 3.78 (s, 12H, –OCH_3), 3.80 (br s, 8H, –CH_2–), 2.15 (br s, 8H, –CH_2–), 0.89 (br s, 8H, –CH_2–), −3.25 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=158.9, 140.0, 139.3, 129.6, 129.2, 128.1, 127.5, 126.2, 125.4, 124.6, 121.2, 115.2, 105.5, 55.8, 52.8, 29.7. HRMS (ES$^+$) Calcd for $C_{111}H_{100}N_{14}O_{15}Na$ $(M+Na)^+$ 1891.7390. Found, 1891.7372. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\,mol^{-1}\,cm^{-1}$): 422 (435.5), 515 (24.4), 550 (8.7), 589 (8.8), 646 (4.7).

4.2.8. α-5,15-Bis-(2-aminophenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin 5aαα and α-5-β-15-(2-aminophenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin 5aαβ. The two atropisomers of **7a** (200 mg, 0.25 mmol) were dissolved in CH_2Cl_2 (50 mL) in a 250 mL round flask.

$SnCl_2 \cdot 2H_2O$ (0.95 g, 5 mmol) and concentrated hydrochloric acid (50 mL) were added and the resulting green mixture was stirred for 12 h at room temperature; then cautiously neutralized at 0 °C with concentrated aqueous ammonia. CH_2Cl_2 (100 mL) was added and the organic layer was washed with aqueous $NaHCO_3$ (3×100 mL) and brine (2×100 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue was chromatographed on a silica gel column. The **5a**αβ atropisomer was eluted with CH_2Cl_2 and obtained in 62% yield (114 mg) where **5a**αα atropisomer was eluted with 0.5% ethanol/CH_2Cl_2 and obtained in 34% yield (61 mg). **5a**αα. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.84 (d, J=5 Hz, 4H, βpyr), 8.69 (d, J=5 Hz, 4H, βpyr), 7.92 (dd, J_1=7.2 Hz, J_2=1.5 Hz, 2H, aro), 7.59 (td, J_1=8 Hz, J_2=1.5 Hz, 2H, aro), 7.28 (s, 2H, aro), 7.27 (s, 2H, aro), 7.17 (td, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.11 (dd, J_1=7.2 Hz, J_2=1.5 Hz, 2H, aro), 3.54 (s, 4H, NH_2), 2.63 (s, 6H, –CH_3), 1.88 (s, 6H, –CH_3), 1.80 (s, 6H, –CH_3), −2.58 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ= 147.3, 139.7, 138.5, 138.1, 135.2, 131.7, 130.9, 130.0, 128.3, 127.4, 118.7, 117.9, 115.7, 115.5, 22.1, 22.0, 21.9. HRMS (ES^+) Calcd for $C_{50}H_{45}N_6Na$ $(M+Na)^+$ 751.3525. Found, 751.3518. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\ mol^{-1}\ cm^{-1}$): 418 (362.7), 514 (22.4), 550 (6.7), 588 (6.8), 649 (3.4). **5a**αβ. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.84 (d, J=5 Hz, 4H, βpyr), 8.69 (d, J=5 Hz, 4H, βpyr), 7.85 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.59 (td, J_1= 8.2 Hz, J_2=1.5 Hz, 2H, aro), 7.28 (s, 4H, aro), 7.15 (t, J= 7.5 Hz, 2H, aro), 7.12 (d, J=8.2 Hz, 2H, aro), 3.60 (s, 4H, NH_2), 2.63 (s, 6H, –CH_3), 1.84 (s, 12H, –CH_3), −2.58 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=147.2, 139.8, 138.2, 135.2, 131.5, 130.7, 130.0, 128.2, 118.6, 117.8, 115.6, 115.5, 22.1, 21.9. HRMS (ES^+) Calcd for $C_{50}H_{45}N_6Na$ $(M+Na)^+$ 751.3525. Found, 751.3518. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\ mol^{-1}\ cm^{-1}$): 418 (362.7), 514 (22.4), 550 (6.7), 588 (6.8), 649 (3.4).

4.2.9. α-5-(2-Aminophenyl)-α-15-(2-nitrophenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin 5aNO_2αα. To a solution of porphyrin **7a**αα (110 mg, 0.14 mmol) in CH_2Cl_2 (280 mL) was added concentrated hydrochloric acid (0.55 mL, 5.6 mmol). This was followed by addition of $SnCl_2 \cdot 2H_2O$ (0.16 g, 0.84 mmol), and the reaction mixture was stirred at 0 °C and monitored by TLC. After stirring for 9 h, concentrated aqueous ammonia (3 mL), was added to the reaction mixture, and then the mixture was washed with aqueous $NaHCO_3$ (3×100 mL) and brine (2×100 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue was chromatographed on a silica gel column. Compound **5aNO_2**αα was eluted with CH_2Cl_2 and obtained in 65% yield (69 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.87 (d, J=5 Hz, 2H, βpyr), 8.72 (d, J=5 Hz, 2H, βpyr), 8.70 (d, J=4.5 Hz, 2H, βpyr), 8.60 (d, J=4.5 Hz, 2H, βpyr), 8.46 (d, J=8 Hz, 1H, aro), 8.27 (d, J=7 Hz, 1H, aro), 7.95 (m, 2H, aro), 7.91 (d, J=7.5 Hz, 1H, aro), 7.61 (t, J=7.5 Hz, 1H, aro), 7.31 (s, 2H, aro), 7.29 (s, 2H, aro), 7.18 (t, J=7.5 Hz, 1H, aro), 7.13 (d, J=7.5 Hz, 1H, aro), 3.61 (s, 2H, NH_2), 2.64 (s, 6H, –CH_3), 1.91 (s, 6H, –CH_3), 1.83 (s, 6H, –CH_3), −2.52 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=152.0, 147.1, 139.8, 138.4, 138.2, 137.4, 137.0, 135.0, 131.7, 131.2, 131.1, 130.3, 130.2, 128.3, 128.1, 127.0, 124.9, 124.5, 119.1, 117.8, 116.0, 115.5, 114.0, 22.2, 22.0, 21.9. HRMS (ES^+) Calcd for $C_{50}H_{43}N_6O_2$ $(M+H)^+$ 759.3447. Found, 759.3446. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\ mol^{-1}\ cm^{-1}$): 419 (343.8), 515 (24.0), 549 (7.7), 591 (7.5), 647 (3.6).

4.2.10. α-5-(2-Aminophenyl)-β-15-(2-nitrophenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin 5aNO_2αβ. To a solution of porphyrin **7a**αβ (287 mg, 0.36 mmol) in $CHCl_3$ (680 mL) was added concentrated hydrochloric acid (1.43 mL, 14.4 mmol). This was followed by addition of $SnCl_2 \cdot 2H_2O$ (410 mg, 2.16 mmol), and the reaction mixture was stirred was stirred at 0 °C and monitored by TLC. After stirring for 4 h, concentrated aqueous ammonia (7 mL), was added to the reaction mixture, and then the mixture was washed with aqueous $NaHCO_3$ (3×100 mL) and brine (2× 100 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue was chromatographed on a silica gel column. Compound **5aNO_2**αβ was eluted with CH_2Cl_2/ hexane 6:4 and obtained in 21% yield (57 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.84 (d, J=5 Hz, 2H, βpyr), 8.69 (m, 4H, βpyr), 8.59 (d, J=4.5 Hz, 2H, βpyr), 8.47 (dd, J_1= 8 Hz, J_2=1 Hz, 1H, aro), 8.21 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 1H, aro), 7.98–7.91 (m, 2H, aro), 7.89 (dd, J_1=7.5 Hz, J_2= 1 Hz, 1H, aro), 7.60 (td, J_1=8 Hz, J_2=1 Hz, 1H, aro), 7.28 (s, 2H, aro), 7.27 (s, 2H, aro), 7.17 (t, J=7.5 Hz, 1H, aro), 7.12 (d, J=8 Hz, 1H, aro), 3.60 (s, 2H, NH_2), 2.63 (s, 6H, –CH_3), 1.85 (s, 12H, –CH_3), −2.54 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=152.0, 147.1, 139.2, 138.3, 138.1, 137.4, 137.0, 135.2, 131.7, 131.1, 130.9, 130.2, 130.1, 130.0, 128.3, 128.1, 127.4, 124.4, 119.1, 118.0, 116.0, 115.6, 114.0, 22.1, 21.9. HRMS (ES^+) Calcd for $C_{50}H_{43}N_6O_2$ $(M+H)^+$ 759.3447. Found, 759.3446. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\ mol^{-1}\ cm^{-1}$): 419 (343.8), 515 (24.0), 549 (7.7), 591 (7.5), 647 (3.6).

4.2.11. α-5,15-Bis-(2-aminophenyl)-10,20-bis-(3,5-dimethoxy-phenyl)-porphyrin 5bαα and α-5-β-15-bis-(2-aminophenyl)-10,20-bis-(3,5-dimethoxy-phenyl)-porphyrin 5bαβ. In a 250 mL beaker, the two atropisomers of **7b** (1 g, 1.2 mmol) were dissolved in concentrated hydrochloric acid (100 mL) at room temperature and $SnCl_2 \cdot 2H_2O$ (2.17 g, 9.6 mmol) was added. The resulting green mixture was stirred for 2 days, then cautiously neutralized at 0 °C with aqueous potassium hydroxide. Ethyl acetate (100 mL) was added and the mixture stirred for 1 h. The ethyl acetate layer was separated and the aqueous layer extracted several times with ethyl acetate. The organic layer was concentrated and the residue was chromatographed on a silica gel column. The **5b**αβ atropisomer was eluted with CH_2Cl_2 and obtained in 38% yield (348 mg), where the **5b**αα atropisomer was eluted with 0.4% methanol/CH_2Cl_2 and obtained in 40% yield (367 mg). **5b**αα. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.97 (d, J=4.5 Hz, 4H, βpyr), 8.91 (d, J=4.5 Hz, 4H, βpyr), 7.91 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.63 (td, J_1=8 Hz, J_2=1.5 Hz, 2H, aro), 7.40 (d, J=2.5 Hz, 4H, aro), 7.20 (t, J=7.5 Hz, 2H, aro), 7.14 (d, J=8 Hz, 2H, aro), 6.91 (t, J=2 Hz, 2H, aro), 3.97 (s, 12H, –OCH_3), 3.53 (s, 4H, NH_2), −2.73 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=164.7, 150.1, 140.9, 139.2, 137.5, 135.6, 133.2, 130.7, 128.6, 126.6, 123.9, 123.1, 122.2, 121.9. HRMS (ES^+) Calcd for $C_{48}H_{40}N_6O_4Na$ $(M+Na)^+$ 787.3008. Found, 787.2982. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, $dm^3\ mol^{-1}\ cm^{-1}$): 420 (337.6), 514 (21.9), 549

(5.2), 588 (5.9), 646 (2.3). **5bαβ**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.97 (d, J=4.5 Hz, 4H, βpyr), 8.91 (d, J=4.5 Hz, 4H, βpyr), 7.88 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.64 (td, J_1=8 Hz, J_2=1.5 Hz, 2H, aro), 7.41 (d, J=2.5 Hz, 4H, aro), 7.20 (t, J=7.5 Hz, 2H, aro), 7.15 (d, J=8 Hz, 2H, aro), 6.92 (t, J=2 Hz, 2H, aro), 3.98 (s, 12H, –OCH_3), 3.58 (s, 4H, NH_2), −2.72 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=164.2, 149.7, 140.9, 139.1, 137.5, 135.6, 133.3, 130.5, 128.6, 126.6, 123.9, 123.0, 122.2, 121.7. HRMS (ES^+) Calcd for $C_{48}H_{40}N_6O_4Na$ $(M+Na)^+$ 787.3008. Found, 787.2982. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, dm^3 mol^{-1} cm^{-1}): 420 (337.6), 514 (21.9), 549 (5.2), 588 (5.9), 646 (2.3).

4.2.12. 2-[(1*H*-Pyrrol-2-yl)-(2,4,6-trimethyl-phenyl)-methyl]-1*H*-pyrrole 6a. A solution of 2,4,6-trimethyl-benzaldehyde (2.65 mL, 18 mmol) and pyrrole (50 mL, 720 mmol) was degassed by argon bubbling for 15 min. Trifluoroacetic acid (138 μL, 1.8 mmol) was then added and the solution was stirred under argon at room temperature for an additional hour and then quenched with triethylamine (0.4 mL). The mixture was diluted with toluene (150 mL) then washed with brine (2×100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and then the unreacted pyrrole was removed by vacuum distillation at room temperature. The residue was dissolved in CH_2Cl_2 and filtered through a short pad of silica using CH_2Cl_2 as the eluent. Evaporation of the solvent under reduced pressure resulted in a brown solid. This solid was washed with cyclohexane and then with hexane, giving a pale yellow solid, which was collected by filtration (1.85 g). Yield: 70%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.95 (br s, 2H, NHpyr), 6.87 (s, 2H, Ar), 6.67 (br s, 2H, pyr), 6.18 (m, 2H, pyr), 6.02 (br s, 2H, pyr), 5.93 (s, 1H, *meso*), 2.27 (s, 3H, –CH_3), 2.06 (s, 6H, –CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=138.0, 137.0, 135.0, 131.7, 130.8, 116.6, 109.1, 106.9, 38.8, 21.2, 21.0. HRMS (ES^+) Calcd for $C_{18}H_{20}N_2$ $(M^{\cdot})^+$ 264.1626. Found, 264.1615.

4.2.13. 2-[(1*H*-Pyrrol-2-yl)-(3,5-dimethoxy-phenyl)-methyl]-1*H*-pyrrole 6b. A solution of 3,5-dimethoxy-benzaldehyde (3 g, 18 mmol) and pyrrole (50 mL, 720 mmol) was degassed by argon bubbling for 15 mL, then trifluoroacetic acid (138 μL, 1.8 mmol) was added. After 1 h, the reaction mixture was neutralized with Et_3N (0.44 mL, 3.2 mmol). The unreacted pyrrole was removed by vacuum distillation and the mixture was diluted with toluene and washed with aqueous 10% NaCl (2×100 mL). The organic phase was dried with $MgSO_4$, filtered and the solvent removed under vacuum. Finally, the residue was chromatographed on a silica gel column and eluted with (hexane/ethyl acetate/triethylamine; 80:20:1). The expected compound was recrystallized with (hexane/ethyl acetate; 98:2) at 0 °C, washed with hexane (100 mL), and obtained in 71% yield (3.6 g). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.94 (br s, 2H, NHpyr), 6.71 (q, J=4.5 Hz, 2H, pyr), 6.41–6.38 (m, 3H, Ar), 6.18 (q, J=3.1 Hz, 2H, pyr), 5.98 (br s, 2H, pyr), 5.43 (s, 1H, *meso*), 3.76 (s, 6H, –OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ=118.8, 108.1, 105.7, 109.3, 108.0, 45.2, 55.5. HRMS (ES^+) Calcd for $C_{17}H_{18}N_2O_2$ $(M^{\cdot})^+$ 282.1368. Found, 282.1371.

4.2.14. α-5,15-Bis-(2-nitro-phenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin 7aαα and α-5-β-15-(2-nitro-phenyl)-10,20-bis-(2,4,6-trimethyl-phenyl)-porphyrin 7aαβ. A solution of **6a** (2 g, 7.6 mmol) and 2-nitro-benzaldehyde (1.15 g, 7.6 mmol) in CH_2Cl_2 (780 mL) was degassed by argon bubbling for 15 mL, and then trifluoroacetic acid (1.11 mL, 14.5 mmol) was added. The solution was stirred for 30 mL at room temperature, then, DDQ (1.9 g, 8.4 mmol) was added and the mixture was stirred for an additional 1 h. The reaction mixture was poured onto a pad of alumina and eluted with CH_2Cl_2 until the eluting solution was pale brown. Removal of the solvent under reduced pressure gave **7a** (2 atropisomers: αα and αβ) in 20% yield (220 mg). The mixture of the two atropisomers was chromatographed on a silica gel column. The **7a**αβ atropisomer was eluted with CH_2Cl_2/hexane 1:1 and obtained in 13% yield (143 mg), where **7a**ααα atropisomer was eluted with CH_2Cl_2/hexane 3:2 and obtained in 7% yield (77 mg). **7aααα**. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.67 (d, J=4.5 Hz, 4H, βpyr), 8.58 (d, J=4.5 Hz, 4H, βpyr), 8.47 (dd, J_1=8 Hz, J_2=1.5 Hz, 2H, aro), 8.21 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.97 (td, J_1=8 Hz, J_2=1.5 Hz, 2H, aro), 7.92 (td, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.29 (s, 2H, aro), 7.26 (s, 2H, aro), 2.62 (s, 6H, –CH_3), 1.87 (s, 6H, –CH_3), 1.82 (s, 6H, –CH_3), −2.50 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=152.0, 140.2, 139.5, 138.4, 138.3, 137.4, 136.9, 131.3, 131.0, 130.5, 129.9, 128.4, 128.0, 124.5, 119.5, 114.4, 22.3, 22.0, 21.8. HRMS (ES^+) Calcd for $C_{50}H_{41}N_6O_4$ $(M+H)^+$ 789.3189. Found, 789.3164. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, dm^3 mol^{-1} cm^{-1}): 419 (333.6), 516 (18.7), 550 (6.1), 592 (5.7), 649 (2.9). **7a**αβ. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.65 (d, J=4.5 Hz, 4H, βpyr), 8.57 (d, J=4.5 Hz, 4H, βpyr), 8.46 (dd, J_1=8 Hz, J_2=1.5 Hz, 2H, aro), 8.23 (dd, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.95 (td, J_1=8 Hz, J_2=1.5 Hz, 2H, aro), 7.94 (td, J_1=7.5 Hz, J_2=1.5 Hz, 2H, aro), 7.26 (s, 4H, aro), 2.61 (s, 6H, –CH_3), 1.83 (s, 12H, –CH_3), −2.52 (s, 2H, NHpyr). ^{13}C NMR (125 MHz, $CDCl_3$): δ=152.0, 139.8, 138.4, 138.2, 137.4, 136.9, 131.4, 130.8, 130.4, 129.9, 128.2, 124.6, 119.0, 114.1, 22.1, 21.9. HRMS (ES^+) Calcd for $C_{50}H_{41}N_6O_4$ $(M+H)^+$ 789.3189. Found, 789.3164. UV–vis (CH_2Cl_2) λ nm ($10^{-3}\varepsilon$, dm^3 mol^{-1} cm^{-1}): 419 (333.6), 516 (18.7), 550 (6.1), 592 (5.7), 649 (2.9).

4.2.15. 5,15-Bis-(2-nitrophenyl)-10,20-bis-(3,5-dimethoxy-phenyl)-porphyrin 7b. A solution of **6b** (3 g, 10.6 mmol) and 2-nitro-benzaldehyde (1.6 g, 10.6 mmol) in dry CH_2Cl_2 (1.1 L) was degassed by argon bubbling for 15 mL, then trifluoroacetic acid (787 μL, 10.6 mmol) was added. The solution was stirred for 12 h at room temperature, then, DDQ (2.4 mg, 10.6 mmol) was added and the mixture was stirred for an additional 1 h, and neutralized with Et_3N (440 mL, 10.6 μmol). The solvent was removed under vacuum, and the expected compound was recrystallized with a minimum of CH_2Cl_2 at 0 °C, and finally washed with CH_2Cl_2 (500 mL) and methanol (500 mL). Compound **7b** (2 atropisomers: αα and ββ) was obtained in 30% yield (1.3 g). HRMS (ES^+) Calcd for $C_{48}H_{37}N_6O_8$ $(M+H)^+$ 825.2672. Found, 825.2660.

4.2.16. X-ray crystallographic studies. 7aαα: crystal data: formula $C_{50}H_{40}N_6O_4 \cdot C_6H_{14}$, $M_w = 875.05$, monoclinic, space group $P2_1/n$, $a = 14.054(7)$ Å, $b = 11.269(6)$ Å, $c = 28.422(9)$ Å, $\beta = 91.72(3)°$, $V = 4499(4)$ Å^3, $Z = 4$, $D_c = 1.292$ g cm^{-3}, $\mu = 0.082$ mm^{-1}. Diffraction data were collected at room temperature in difficult conditions, since the material did not diffract strongly and only low-angle reflections could be measured. Nevertheless, the structure determination could be unambiguously performed and it was considered to be sufficiently detailed to the limited purpose of the present study. All operations were performed with a Nonius-Bruker MACH3 diffractometer, using graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods[16] and refined[17] on F_o^2 values, isotropically for the porphyrin ring atoms and anisotropically for the most peripheral atoms of the attached groups. Phenyl rings were treated as rigid groups with idealized geometry. Hydrogens were in calculated positions, riding, with temperature factors linked to those of the respective carrier atoms. There is a disordered hexane solvate molecule, which was modeled as two fractions with complementary population parameters. Hydrogen atoms were not added to the hexane carbon atoms backbones, since this was not found to yield improvements. The final values of the agreement factors are $R1$ 0.095 (on the 1370 observed reflections, having $I > 2\sigma I$) and 0.295 (on all of the measured 3916 reflections); $wR2$ 0.243 (observed) and 0.327 (all); GoF 1.026. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 277156. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.01.029. Complete NMR spectra (1D and 2D) of new compounds described in this work.

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Construction of divergent anthracene arrays within dendritic frameworks

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Abstract—This publication presents simple methodologies for construction of divergent anthracene arrays either within structural interior or at peripheral positions of dendritic frameworks. The synthetic approaches employed multiple coupling reactions between two types of 10-functionalized 9-anthryl chlorides and two types of polyphenolic linkers, resulting in four types of dendritic architectures. Successful implementation of the syntheses was confirmed by a range of spectroscopies along with elemental analyses and size exclusion chromatography studies. The resulting dendritic molecules showed a range of solubilities in chloroform fairly affected by the dendritic backbone structures. Fluorescence spectroscopic experiments of the multichromophoric dendritic systems indicated pronounced energy delocalization functionalities via an energy migration within the branched molecular frameworks as expressed in reduced fluorescence quantum yields and complex emission decay profiles.

1. Introduction

Over the last decade, there has been a rapid increase in the literature published on new dendritic architectures because of their potential applications in the new emerging field of nanotechnology.[1,2] The dendritic frameworks provide unique nanometer-size environments, which may serve as a polymer backbone for effective three-dimensional matrices due to their highly branched and compressed globular structures.[3,4] In this context, functional elements embedded within the dendritic skeletal frameworks may define shell effects of the dendritic architectures, which render the resulting hyperbranched systems potentially versatile. Nevertheless, a major focus of contemporary synthetic approaches to dendrimers is functionalization of surface groups and structural modification of core units because most of the functionalized molecular materials are synthetically dormant due to their structural complexity, which may result in poor feasibility to be incorporated into the dendritic systems.[5] In previous publications, we have reported that first-generation architectures such as *n*-hexyl substituted dendron **1** and dendrimer **2** (Fig. 1) showed cooperative action of the chromophoric groups leading to energy delocalization of absorbed photons.[6,7] It has been recognized in this context that such chromophore-clustering systems can serve as potential molecular antennae in creation of effective light-harvesting devices and synthetic elaboration of new multichromophoric dendrimer system is therefore of great significance.[8–11] In the present work, we intend to investigate the possibility of accessing higher-generation dendritic architectures as a logical extension of the synthetic methodology, which allows us to generate a variety of dendrimer systems with higher local density of light-collecting units. Despite our intention, incorporation of the anthracene groups into the dendritic frameworks was initially hampered by the low branching configurations.[12] Accordingly, key to the successful implementation of the synthetic plan is utilization of junction units for introduction of branching elements into the anthracene nucleus, converting it to the branched building blocks. Based on this functionalization strategy, we established a simple methodology for construction of four types of second-generation dendritic architectures **3B**, **3L**, **4B**, and **4L** (Fig. 1) as representative members of the higher-generation

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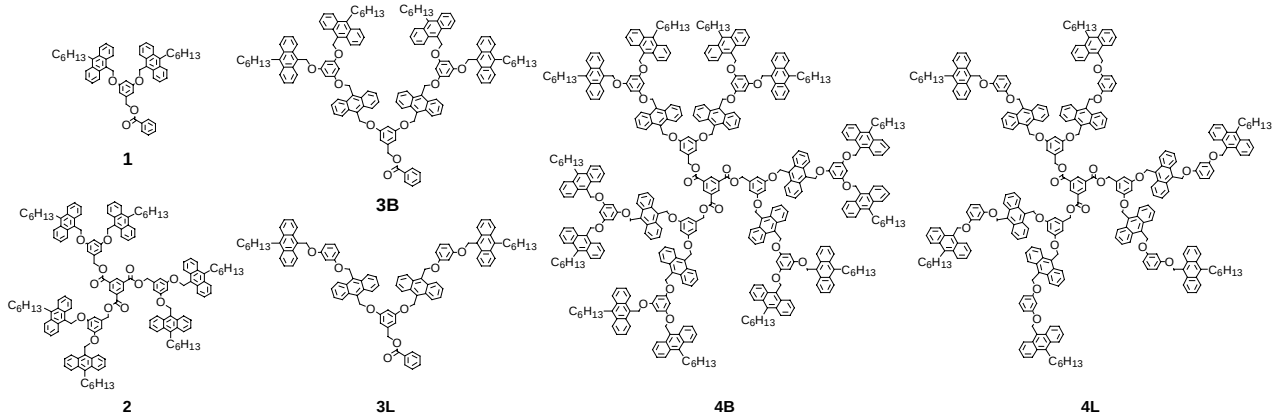


Figure 1. Structures of dendritic molecules **1**–**4**.

family, where we shall occasionally employ the letters **B** and **L** to designate branching and linear geometries of multichromophoric substituents, respectively. Along with the synthetic achievement and property investigation of the dendritic compounds, we disclose photophysical characteristics for energy delocalization functionalities of the new multichromophoric systems.

2. Results and discussion

Our previous report has shown that direct coupling of variously substituted 10-alkyl-9-anthryl chlorides and polyphenolic linkers **5** and **6** was viable for the syntheses of the lowest dendritic generations.[7] In an attempt to apply this methodology to the second-generation dendritic architectures, our attention focused on preparations of requisite anthryl chlorides **7B** and **7L** carrying additional anthracene functionalities at the C10-position of the anthracene ring system (Fig. 2).

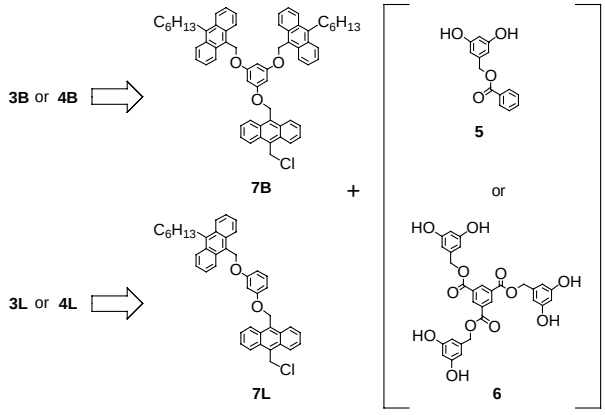
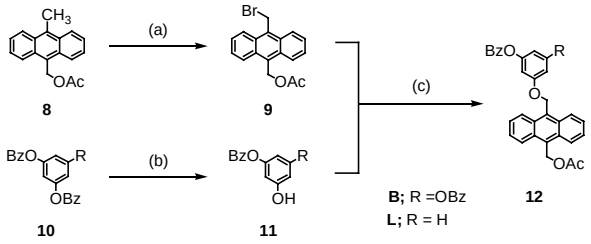


Figure 2. Retrosynthetic analyses.

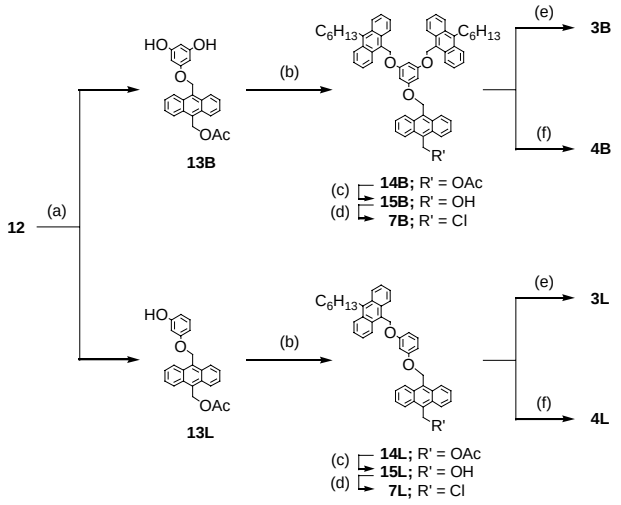
Our approach to the dendritic architectures started with preparation of an asymmetrically 9,10-disubstituted anthracene through site-selective bromination. In general, the course of free radical bromination with *N*-bromosuccinimide is influenced profoundly by local electron density of active methylene groups.[13] When 9-acetoxy-10-methylanthracene **8** was employed as the reactant, hydrogen abstraction took place predominantly at the methyl group adjacent to the anthracene ring as a result of deactivation of the benzylic counterparts by neighboring acetoxy group, giving rise to 9-acetoxy-10-bromomethylanthracene **9** in 95% yield (Scheme 1).



Scheme 1. Syntheses of **12**. Conditions: (a) NBS, AIBN, $CHCl_3$, reflux, 95%; (b) Cs_2CO_3, DME, reflux, **11B** (79%), **11L** (72%); (c) 18-crown-6, K_2CO_3, DMF, 55 °C, **12B** (90%), **12L** (92%).

For the preparation of branching skeletal series, the corresponding junction unit was synthesized by selective removal of benzoyl groups from phloroglucinol tribenzoate **10B**.[14] The controlled hydration of **10B** was accomplished with cesium carbonate under an anhydrous condition to give 3,5-dibenzoyloxyphenol **11B** in 79% yield. This compound possesses one phenolic hydroxyl group available for nucleophilic coupling with **9**, leading to **12B** in 90% yield (Scheme 2).

Deprotection of two remaining benzoyl groups in **12B** using excess *n*-butylamine gave bisphenolic derivative **13B** in 81% yield without affecting the terminal acetoxy group.[15] The subsequent transformation of **13B** into **14B** was conducted by the established protocol for the synthesis of first-generation dendrons.[7] As for an endcapping reagent required for this reaction, 10-(*n*-hexyl)-9-anthryl chloride was selected due to the fact that attaching the long alkyl side chain on the peripheral anthracene groups enhanced solubility of the resulting dendrimer in a variety of organic solvents.[7] Thus, the coupling between **13B** and 2 mol equiv of the anthryl chloride underwent efficient ether bond formation providing **14B** in 60% yield. The acetyl endgroup of **14B** underwent efficient deprotection by hydrolysis with sodium methoxide in methanol solution to give the corresponding alcohol **15B**



Scheme 2. Syntheses of **3** and **4**. Conditions: (a) *n*-$BuNH_2$, THF, reflux, **13B** (81%), **13L** (85%); (b) 10-(*n*-hexyl)-9-anthryl chloride, 18-crown-6, K_2CO_3, DMF, 55 °C, **14B** (84%), **14L** (94%); (c) CH_3ONa, 1:1 THF/CH_3OH, reflux, **15B** (95%), **15L** (92%); (d) MsCl, LiCl, DMAP, Et_3N, THF, rt, **7B** (87%), **7L** (91%); (e) **5**, 18-crown-6, K_2CO_3, DMF, 55 °C, **3B** (75%), **3L** (69%); (f) **6**, 18-crown-6, K_2CO_3, DMF, 55 °C, **4B** (57%), **4L** (48%).

in 95% yield. In the final step of the reaction sequence, we attempted to convert the hydroxyl group of **15B** by generation of the corresponding mesylate followed by in situ displacement reaction in the presence of excess lithium chloride to the desired anthryl chloride **7B** in 87% yield. A similar set of reactions was employed to prepare the linear segment **7L**, where a resorcinol moiety was incorporated as another junction unit in place of the phloroglucinol building component in **7B**. Starting from resorcinol dibenzoate **10L**, all synthetic reactions proceeded with good to excellent yields (72–94%) and gave rise to **7L** through six sequential steps.

Subsequent covalent attachment of **7B** and **7L** to two types of the polyphenolic linkers **5** and **6**, available from previous works,[7] was facilitated by the successive nucleophilic substitution reactions at the multiple sites, giving rise to the second-generation dendritic molecules **3B** (75%), **3L** (69%), **4B** (57%), and **4L** (48%), respectively. All these compounds were fully characterized by a range of spectroscopies along with elemental analyses. For instance, simplicity of the ^1H and ^{13}C NMR spectra is consistent with the highly symmetric structures. In particular, the ^1H NMR of **4B** and **4L** exhibited low-field singlets at 8.95 and 9.01 ppm, respectively, due to aromatic protons attached to the cores, indicating that all three dendritic branching units of this molecule should be chemically equivalent. The molecular weights of these compounds were examined by electrospray ionization mass spectrometry (ESI-MS).[16] This allowed a qualitative analysis of **3B** exhibiting the parent ion peaks at *m/z* 2020.9, attributable to $[M+Na]^+$ (calcd *m/z* 2020.0), with a calculated isotopic distribution pattern (Fig. 3a). During this measurement, three minor peaks were simultaneously observed at *m/z* 2036.9, 2052.9, and 2069.0 possibly due to oxidized molecular ions (calcd *m/z* 2036.0 $[M+NaO]^+$, 2052.0 $[M+NaO_2]^+$, and 2068.0 $[M+NaO_3]^+$, respectively). This observation indicates the poly(anthryl ether) dendritic compounds are very susceptible to oxidative degradation under the instrumental

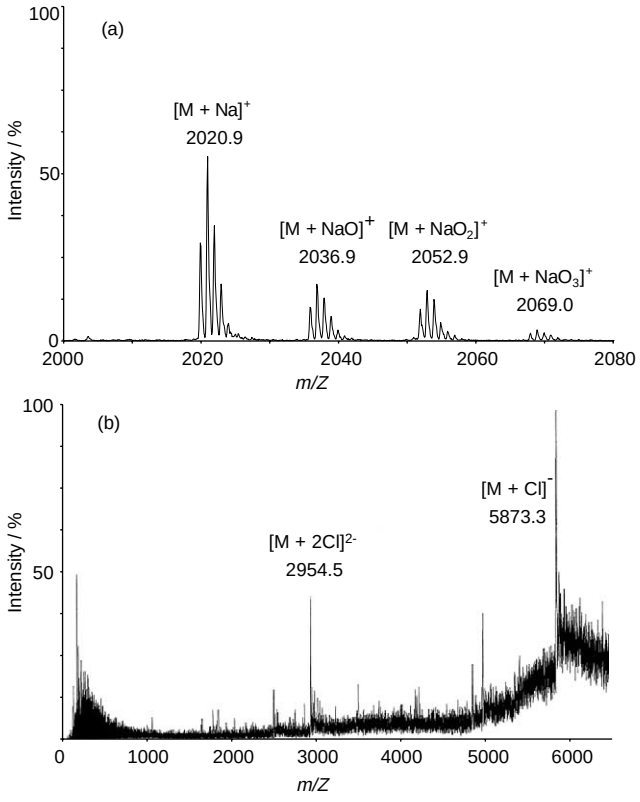


Figure 3. (a) ESI-MS spectrum of **3B**. (b) CSI-MS spectrum of **4B**.

conditions of operation. In fact, the analogous dendron **3L** provided predominantly molecular ion peaks at *m/z* 1471.5 as an oxidized substrate $[M+NaO_2]^+$ (calcd *m/z* 1471.6) under the identical experimental condition. On the other hand, the dendrimers **4B** and **4L** did not exhibit any parent ion peak by similar ESI-MS measurements and fragmented exclusively to stabilized anthryl ionic species. Further investigations by coldspray ionization mass spectral (CSI-MS) technique provided compelling evidence for the formation of **4B** and **4L**.[17] The CSI-MS analysis of **4B** exhibited singly and doubly charged molecular ion peaks at *m/z* 5873.3 $[M+Cl]^-$ (calcd 5874.8) and 2954.5 $[M+2Cl]^{2-}$ (calcd 2954.9), respectively (Fig. 3b), while **4L** gave only a singly charged ion peak at *m/z* 4131.8 $[M+Cl]^-$ (calcd 4131.8). These results clearly indicate the success of our synthetic strategy achieving complete coverage of the dendrimer backbones.

Alternatively, the molecular weights of these materials were also estimated using a relative method such as gel permeation chromatography (GPC) calibrated with polystyrene standards. In chloroform solutions, all dendritic compounds exhibited sharp and symmetrical peaks at discrete retention times with low polydispersity values ($M_w/M_n<1.01$) that should be in the range typically found for unified dendrimers (Table 1). Figure 4 demonstrates that either a series of dendrons **1**, **3B**, and **3L** or a series of dendrimers **2**, **4B**, and **4L** provided almost monomodal distributions fitted well with the linear polystyrene series in the correlation diagram, where observed retention volumes of all dendritic compounds exhibited a linear dependence on logarithmic numbers of the averaged molecular weights. Table 1 presents the molecular weights of the dendrimers

Table 1. Structural details, GPC results, and maximum solubilities of **1–4**

Entry	Number of anthracene units	Formula	M_w/M_n[a]	Nominal M_w	M_w	c (mol/L)[b]
1	2	$C_{56}H_{56}O_4$	1.001	792	746	3.8×10^{-1}
2[c]	6	$C_{156}H_{156}O_{12}$	1.004	2221	2074	1.0×10^{-2}
3B	6	$C_{142}H_{132}O_{10}$	1.002	1997	2258	1.3×10^{-2}
3L	4	$C_{100}H_{88}O_8$	1.001	1417	1553	5.9×10^{-3}
4B	18	$C_{414}H_{384}O_{30}$	1.003	5835	5460	6.8×10^{-4}
4L	12	$C_{288}H_{252}O_{24}$	1.008	4094	3940	1.4×10^{-5}

[a] Calibrated with narrow-dispersity polystyrene standards.
[b] Maximum concentrations dissolved in chloroform at 20 °C.
[c] See Ref. 7.

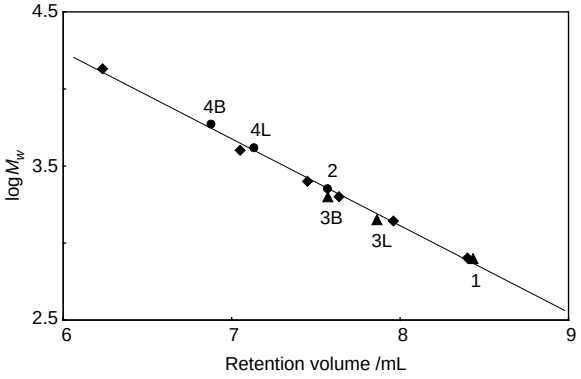


Figure 4. Semilogarithmic plot of average molecular weights (M_w) versus GPC retention volumes for polystyrene standards (◆), dendrons (▲), and dendrimers (●).

(M_w) determined by the GPC analyses calibrated with the polystyrene standards. As can be seen in Table 1, the estimated values for both series are satisfactorily close to the nominal molecular weights with small differences less than 13%, indicating this analytical experiment provides reliable information on the approximate molecular sizes.

The degree of branching in the three-dimensional dendritic skeletal frameworks allows for direct control of solubility in common organic solvents. Table 1 also includes maximum solubilities of the dendritic macromolecules in chloroform solutions, which were determined by dissolving the samples in chloroform and measuring their UV absorption maxima around 380 nm. From these data, impressive differences were observed in the solubilities between the branching (B) and linear (L) dendritic architectures. In comparison, the maximum solubility of **3B** was increased by 2.2-fold compared with **3L**, while **4B** displayed significantly enhanced solubility as large as about 49-fold relative to **4L**. It should be noted that the branching skeletal systems offer the advantage of higher solubility although they contain large numbers of insoluble anthracene moieties in confined molecular spaces. These solubilization phenomena may be understood on the basis of net lipophilic properties of the molecules functionalized by the alkyl solubilizing groups. In general, the branching dendritic architectures are designed to bring greater number of peripheral groups in defined geometries than the linear systems, thus reinforcing the extent of surface functionalization of the dendritic shells. For the case of our model systems, such a structural aspect may result in an increase of incorporation ratio of the terminal solubilizing groups within the branching dendritic frameworks, which should significantly enhance solubilities of the resulting compounds. Consequently, the experimental results obtained are in good agreement with this proposal, demonstrating that the branching geometry of the macromolecular systems strongly influences the intrinsic maximum solubility for the dendritic architectures.

In an effort to gain insight into the scope of photophysical properties, we investigated absorption and fluorescence behavior of the two analogous series of the new dendritic molecules **3–4**. All these compounds showed comparable absorption profiles giving three intense peaks at around 360, 380, and 400 nm attributed to anthracene absorptions whose molar absorption coefficients are approximately proportional to the number of anthracene units. On the other hand, individual dendritic molecules behaved differently with respect to the fluorescence spectroscopic features. Figure 5 shows a series of steady-state fluorescence emission spectra of all the dendritic architectures **1–4** upon excitation at 378 nm. As illustrated, the emission spectra of the both dendrons **3B** and **3L** displayed vibronic fine-structures with two sharp bands at around 410 and 430 nm and shoulders in the longer wavelength region, resembling closely the emission spectrum of the first-generation analogue **1** with diminished intensity levels. Furthermore, the two dendrimers **4B** and **4L** exhibited slightly red-shifted and less efficient emissions relative to the first-generation analogue **2**.

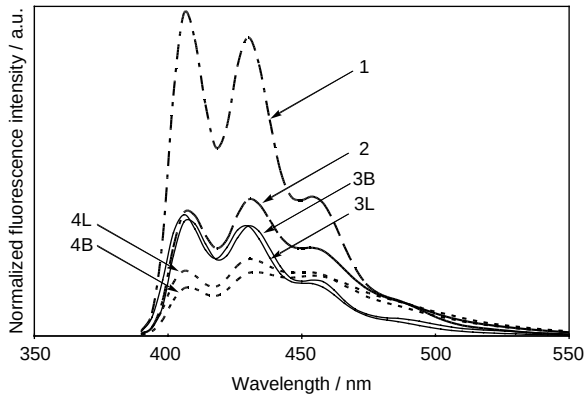


Figure 5. Steady-state fluorescence spectra of **1** and **2** (dashed lines), **3B** and **3L** (solid lines), and **4B** and **4L** (dotted lines) in chloroform solutions. The spectra were obtained by excitation at 378 nm and normalized to the same optical density at the excitation wavelength. All measurements were conducted in sufficiently low concentrations ($10^{-8}\sim10^{-7}$ M) of the analytes to exclude the possibilities of intermolecular interactions.

Indeed, the second-generation **3**–**4** exhibited weaker emission bands than the first-generation **1**–**2** as expressed by lower fluorescence quantum yields (Table 2). This suggested the new dendritic molecules allowed fast energy delocalization driven by the chromophore cluster effects that were strongly dependent on the branching molecular geometry and the number of chromophores present in the dendritic systems.[18] At this point, it is of interest to note that **3B** showed a significantly lowered fluorescence quantum efficiency in comparison to that of its geometric isomer **2**, while the estimated values for the second-generation family were substantially unaffected by the number of chromophores incorporated within the dendritic frameworks. The observed dependence of the quantum yields on the molecular geometry can be rationalized in terms of interchromophore separations defined by differences in local packing density of the chromophoric groups, which should be the most important factor in governing energy migration rates.[19] It is well accepted that the energy transfer rates due to either electron exchange (Dexter) mechanism through collision interactions or dipole–dipole (Förster) mechanism through Coulombic interactions are extremely influenced by the average distances between the donor and acceptor.[20,21] This rationale suggests a tentative conclusion that these two mechanisms may dominate the energy migration processes in the dendritic anthracene arrays. However, these mechanistic possibilities cannot be substantially distinguished by uncertainties in interchromophoric distances because of inherent flexibility in the dendrimer conformations.

Table 2. Absorption and fluorescence maxima, and fluorescence quantum yields of **1**–**4**

Entry	λ_{abs} (nm)	λ_F (nm)	Φ_F
1[a]	360, 379, 400	410, 430, 454	0.36
2[a]	360, 379, 400	409, 433, 454	0.20
3B	358, 378, 398	409, 432, 456	0.13
3L	357, 375, 396	406, 430, 450	0.14
4B	359, 378, 399	409, 434, 458	0.13
4L	358, 377, 397	406, 430, 450	0.14

[a] See Ref. 7.

To investigate energy migration dynamics of the second-generation dendrimer systems, time-resolved fluorescence decay measurements were performed on the largest dendrimer **4B** as a representative example of the second-generation dendritic architectures. Figure 6 illustrates the fluorescence intensity traces of **1**, **2**, and **4B**, which demonstrated **4B** decayed faster than the first-generations **1** and **2** following a multiexponential curve.[22] An attempt to analyze the data of **4B** with a triexponential function gave a satisfactory fit with lifetimes of 5.6 ns (44%), 1.6 ns (33%), and 0.37 ns (23%). As demonstrated previously for first-generation analogues carrying ethyl substituents at the peripheral positions, the decay profile for **1** followed satisfactorily a monoexponential function with a decay component of 5.6 ns, while the decay for **2** was well fitted with a biexponential yielding two components of 5.6 ns (68%) and 1.6 ns (32%).[7] In comparison, the two slower decay components of 5.6 and 1.6 ns found in **4B** can be assigned to originate from the first-generation dendrimer **2**, which may include the dynamic character of the bichromophoric dendron **1** with the longest decay component of 5.6 ns. During the course of our studies, we found that all the three multichromophoric dendritic systems examined may share a common mechanistic feature with respect to the energy migration channels and thus the second-generation dendrimer **4B** may cover all the decaying elements of the constituent molecules. Based on this consideration, the fast decay component of 0.37 ns observed for **4B** can be deduced to be a newly introduced energy migration channel caused by the densely multichromophoric array of the second-generation dendrimer.[23]

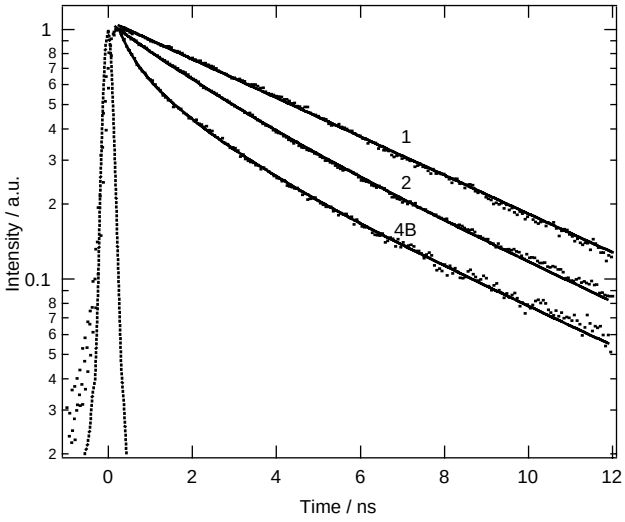


Figure 6. Fluorescence decay profiles at 433 nm of **1**, **2**, and **4B** in THF solutions (excitation at 355 nm).

3. Conclusion

In conclusion, we described simple methodologies that allowed ready access to the four types of second-generation dendritic architectures containing up to 18 anthracene units either within their structural interior or at their periphery. The synthetic procedure presented here provides a promising strategy to construct the higher-generation dendritic architectures, which realizes denser arrays of anthracene groups in well-defined molecular spaces. The developed dendritic molecules have been shown to undergo the intramolecular energy migration extending over a large part of the dendritic architectures. Finally, the present multichromophoric systems represent a potential light-harvesting antenna that can capture photons and transfer them to neighboring photoactive units within supramolecular environments.

4. Experimental

4.1. General

All solvents and reagents were of reagent grade quality from Wako Pure Chemicals used without further purification. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were recorded on a JEOL JNM-AL300 spectrometer

in chloroform-*d* ($CDCl_3$) or acetone-d_6 ($(CD_3)_2CO$). Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in hertz (Hz). Fourier transform infrared (FT-IR) spectra were recorded on a JASCO FT/IR-410 spectrometer as KBr disks. Absorption spectra were recorded on a JASCO model V-570 UV–vis–NIR spectrophotometer. Fluorescence spectra were measured on a Hitachi F-4500 spectrofluorometer. Melting points were measured with a Yanaco MP-S3 melting point apparatus. Fast atom bombardment (FAB) mass measurements were performed by a JASCO JMS-HX110A spectrometer using a 3-nitrobenzyl alcohol matrix. Electrospray ionization-time-of-flight (ESI-TOF) mass spectra of **3B**, **3L**, and **9** were recorded on a Micromass LCT mass spectrometer KB 201. Coldspray ionization mass (CSI-MS) spectral measurements of **4B** and **4L** were performed by two-sector (BE) mass spectrometer (JMS-700, JEOL) equipped with a cold-spray ionization (CSI) source. Elemental analyses were obtained from Thermo Flash EA 1112 instrument. Gel permeation chromatography (GPC) was performed on a system consisting of a JASCO model 880-PU pump at a flow rate of 0.5 mL/min and JASCO 875-UV absorbance detector (254 nm) equipped with a Shodex K-802.5 column, where chloroform was used as mobile phase. Time-resolved fluorescence decay measurements of **1**, **2**, and **4B** were performed on a system consisting of a Hamamatsu C5094 imaging spectrograph and a B. M. Industries 5022 D. PS. DP.10 passively/actively mode-locked Nd:YAG laser employing the third harmonic at 355 nm. These measurements were conducted in THF solutions. The decays were fitted with the least-squares (LS) method to evaluate the fluorescence lifetimes. The quality of the fits has been judged from the estimated values and residuals. Preparative high-performance liquid chromatography (HPLC) was performed on a Japan Analytical Industry LC-918 recycling system. Samples of first-generation dendron **1**, dendrimer **2**, multibranched polyphenolic linkers **5** and **6**, 9-acetoxymethyl-10-methylanthracene **8**, resorcinol dibenzoate **10L**, 3-benzoyloxyphenol **11L**, and 10-(*n*-hexyl)-9-anthryl chloride were prepared by the procedures reported in the previous publications.[7,14] Synthetic intermediates of phloroglucinol tribenzoate **10B** and 3,5-dibenzoyloxyphenol **11B** were prepared by alternative approaches to improve reaction yields for comparison with published procedures.[24] The fluorescence quantum yields of **3B**, **3L**, **4B**, and **4L** were determined in comparison to those of **1** and **2** in chloroform solutions, which were employed as standards.

4.1.1. Synthetic procedure for 9. A solution containing **8** (0.86 g, 3.26 mmol), *N*-bromosuccinimide (0.57 g, 3.22 mmol), and 2,2′-azobisisobutyronitrile (0.027 g, 0.16 mmol) in chloroform (100 mL) was heated to reflux stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and then the solvent was removed in vacuo. This resulting solid was dissolved in DMF (20 mL), and the solution was poured into excess water to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a yellow solid. After complete vacuum drying, the resulting solid was purified by recrystallization from chloroform–hexane, affording **9** (1.06 g, 95%) as a yellow powder: mp 192–194 °C; IR (KBr) 1730 cm^{-1} (C=O); MS (ESI, positive) *m/z* 365 (*MNa*+); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, CH_3), 5.52 (s, 2H, CH_2Br), 6.14 (s, 2H, CH_2O), 7.58–7.69 (m, 4H, Ar*H*), 8.34–8.41 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 26.6 (CH_2), 58.8 (CH_2), 124.2 (*C*H), 124.8 (*C*H), 126.5 (*C*H), 126.6 (*C*H), 128.7 (*C*), 129.4 (*C*), 130.3 (*C*), 131.0 (*C*), 171.1 (*C*). Anal. Calcd for $C_{18}H_{15}BrO_2$: C, 62.99; H, 4.41; N, 0.00. Found: C, 62.69; H, 4.68; N, 0.07.

4.1.2. Synthetic procedure for 10B. Commercially available phloroglucinol dihydrate was dried in a vacuum oven for 1 day prior to use. To a solution containing the dehydrated phloroglucinol (3.69 g, 0.0293 mol) and triethylamine (24.4 mL, 0.175 mol) in THF (10 mL), a solution of benzoyl chloride (11.8 mL, 0.102 mol) in THF was added dropwise under vigorous stirring at 0 °C. The reaction was allowed to continue for additional 3 h at room temperature. The reaction mixture was then quenched by slow addition of diluted HCl (3.0 mol/L, 100 mL) to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a white solid. Purification of the resulting solid by recrystallization from chloroform solution gave **10B** (10.0 g, 78%) as a white powder. This compound was identified by comparison of the ^1H NMR chemical shifts with the literature data.[24]

4.1.3. Synthetic procedure for 11B. The synthetic procedure for **11B** was achieved by following a new method. A solution containing **10B** (3.03 g, 6.92 mmol) and cesium carbonate (1.80 g, 5.52 mmol) in anhydrous dimethoxyethane (50 mL) was heated to reflux with vigorous stirring under argon atmosphere. After 18 h, the reaction mixture was cooled to room temperature, quenched by slow addition of diluted HCl (3.0 mol/L, 40 mL), and then extracted twice with ethyl acetate (30 mL). The combined organic layers were washed with water (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in chloroform (30 mL), and the solution was filtered through Celite to remove the remaining starting material. After the filtrate was concentrated in vacuo, the residue was purified by silica-gel column chromatography (chloroform as eluent) to give **11B** (1.83 g, 79%) as a white powder. This compound was identified by comparison of the ^1H NMR chemical shifts with the literature data.[24]

4.1.4. Synthetic procedure for 12B. A solution containing **9** (0.36 g, 1.05 mmol), **11B** (0.32 g, 0.96 mmol), potassium carbonate (0.20 g, 1.44 mmol), and 18-crown-6 (0.13 g, 0.49 mmol) in DMF (5 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. Purification of the residue by silica-gel column chromatography (70% chloroform, 30% hexane) gave **12B** (0.52 g, 90%) as a pale yellow powder. Further purification was achieved by recrystallization from

$CHCl_3$–methanol solution: mp 188–190 °C; IR (KBr) 1597 cm^{-1} (C=C), 1738 cm^{-1} (C=O); MS (FAB, positive) *m/z* 596 (*M*+), 597 (*MH*+); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, CH_3), 5.99 (s, 2H, CH_2), 6.18 (s, 2H, CH_2), 6.91 (t, *J*=2.0 Hz, 1H, Ar*H*), 6.99 (d, *J*=2.0 Hz, 2H, Ar*H*), 7.49–7.54 (m, 4H, Ar*H*), 7.58–7.64 (m, 6H, ArH), 8.19–8.22 (m, 4H, Bz*H*), 8.32–8.42 (m, 4H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 20.9 (*C*H_3), 58.8 (*C*H_2), 63.3 (*C*H_2), 106.4 (*C*H), 108.9 (*C*H), 124.7 (*C*H), 126.3 (*C*H), 126.4 (*C*H), 128.5 (*C*), 128.6 (*C*H), 128.8 (*C*), 129.3 (*C*), 130.2 (*C*H), 130.8 (*C*), 133.8 (*C*H), 152.2 (*C*), 160.3 (*C*), 164.8 (*C*), 171.2 (*C*). Anal. Calcd for $C_{38}H_{28}O_7$: C, 76.50; H, 4.73; N, 0.00. Found: C, 76.19; H, 4.97; N, 0.00.

4.1.5. Synthetic procedure for 12L. A solution containing **9** (1.43 g, 4.18 mmol), **11L** (0.81 g, 3.80 mmol), potassium carbonate (0.79 g, 5.72 mmol), and 18-crown-6 (0.50 g, 1.89 mmol) in DMF (8 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum. Purification by recrystallization from $CHCl_3$–hexane solution gave **12L** (1.66 g, 92%) as a pale yellow solid: mp 234–236 °C; IR (KBr) 1603 cm^{-1} (C=C), 1736 cm^{-1} (C=O); MS (FAB, positive) *m/z* 476 (*M*+), 477 (*MH*+); ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, COCH_3), 5.95 (s, 2H, CH_2), 6.17 (s, 2H, CH_2), 6.91–6.95 (m, 1H, Ar*H*), 7.02–7.06 (m, 2H, Ar*H*), 7.39–7.44 (m, 2H, Ar*H*), 7.49–7.66 (m, 7H, Ar*H*), 8.21–8.24 (m, 2H, Bz*H*), 8.30–8.41 (m, 4H, Ar*H*); ^{13}C NMR (CDCl*3*) δ 21.0 (*C*H_3), 58.8 (*C*H_2), 63.0 (*C*H_2), 108.5 (*C*H), 112.7 (*C*H), 114.6 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 126.3 (*C*H), 128.6 (*C*H), 128.7 (*C*), 128.9 (*C*), 129.5 (*C*), 130.1 (*C*H), 130.2 (*C*H), 130.7 (*C*), 130.8 (*C*), 133.7 (*C*H), 152.1 (*C*), 160.1 (*C*), 165.2 (*C*), 171.2 (*C*). Anal. Calcd for $C_{31}H_{24}O_5$: C, 78.14; H, 5.08; N, 0.00. Found: C, 78.03; H, 5.11; N, 0.00.

4.1.6. Synthetic procedure for 13B. A solution containing **12B** (0.68 g, 1.14 mmol) and *n*-butylamine (2.26 mL, 22.9 mmol) in THF (15 mL) was heated to reflux with stirring under argon atmosphere. After 18 h, the reaction mixture was cooled to room temperature, and concentrated in vacuo. Purification of the residue by silica-gel column chromatography (67% hexane, 33% ethyl acetate) and recrystallization from hexane–ethyl acetate solution gave **13B** (0.36 g, 81%) as a pale yellow powder: dp 186–188 °C; IR (KBr) 1606 cm^{-1} (C=C), 1732 cm^{-1} (C=O), 3383 cm^{-1} (OH); MS (FAB, positive) *m/z* 388 (*M*+), 399 (*MH*+); ^1H NMR ($(CD_3)_2CO$) δ 2.03 (s, 3H, CH_3), 5.97 (s, 2H, CH_2), 6.09 (t, *J*=2.1 Hz, 1H, Ar*H*), 6.19 (s, 2H, CH_2), 6.15 (d, *J*=2.1 Hz, 2H, Ar*H*), 7.59–7.67 (m, 4H, Ar*H*), 8.31 (br s, 2H, O*H*), 8.41–8.51 (m, 4H, Ar*H*); ^{13}C NMR ($(CD_3)_2CO$) δ 20.8 (*C*H_3), 59.2 (*C*H_2), 63.2 (*C*H_2), 94.9 (*C*H), 97.0 (*C*H), 125.6 (*C*H), 125.9 (*C*H), 127.0 (*C*H), 127.1 (*C*H), 129.8 (*C*), 131.0 (*C*), 131.6 (*C*), 131.7 (*C*H), 160.3 (*C*), 162.3 (*C*), 171.1 (*C*). Anal. Calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19; N, 0.00. Found: C, 73.96; H, 5.35; N, 0.03.

4.1.7. Synthetic procedure for 13L. A solution containing **12L** (0.71 g, 1.49 mmol) and *n*-butylamine (1.47 mL, 14.9 mmol) in THF (20 mL) was heated to reflux with stirring under argon atmosphere. After 18 h, the reaction mixture was cooled to room temperature, and concentrated in vacuo. Purification of the residue by silica-gel column chromatography (60% hexane, 40% ethyl acetate) and recrystallization from hexane–ethyl acetate solution gave **13L** (0.47 g, 85%) as a pale yellow powder: mp 190–191 °C; IR (KBr) 1591 cm^{-1} (C=C), 1707 cm^{-1} (C=O), 3411 cm^{-1} (OH); MS (FAB+) *m/z* 372 (*M*+), 373 (*MH*+); ^1H NMR ($(CD_3)_2CO$) δ 2.04 (s, 3H, COCH_3), 6.02 (s, 2H, CH_2), 6.19 (s, 2H, CH_2), 6.51–6.55 (m, 1H, Ar*H*), 6.64–6.71 (m, 2H, Ar*H*), 7.15–7.21 (m, 1H, Ar*H*), 7.58–7.66 (m, 4H, Ar*H*), 8.38 (s, 1H, O*H*), 8.41–8.50 (m, 4H, Ar*H*); ^{13}C NMR ($(CD_3)_2CO$) δ 20.8 (*C*H_3), 59.2 (*C*H_2), 63.3 (*C*H_2), 103.3 (*C*H), 106.8 (*C*H), 109.3 (*C*H), 125.7 (*C*H), 125.9 (*C*H), 127.0 (*C*H), 127.1 (*C*H), 129.8 (*C*), 130.9 (*C*H), 131.6 (*C*), 131.7 (*C*), 159.7 (*C*), 161.6 (*C*), 171.1 (*C*). Anal. Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41; N, 0.00. Found: C, 77.28; H, 5.29; N, 0.00.

4.1.8. Synthetic procedure for 14B. A solution containing **13B** (0.26 g, 0.67 mmol), 10-(*n*-hexyl)-9-anthryl chloride (0.46 g, 1.48 mmol), potassium carbonate (0.25 g, 1.81 mmol), and 18-crown-6 (0.18 g, 0.68 mmol) in DMF (8 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. Purification of the residue by silica-gel column chromatography (70% chloroform, 30% hexane) gave **14B** (0.53 g, 84%) as a pale yellow power. Further purification was achieved by recrystallization from $CHCl_3$–methanol solution: mp 223–225 °C; IR (KBr) 1587 cm^{-1} (C=C), 1739 cm^{-1} (C=O); MS (FAB, positive) *m/z* 936 (*M*+), 937 (*MH*+); ^1H NMR ($CDCl_3$) δ 0.91 (t, *J*=7.1 Hz, 6H, $(CH_2)_5CH_3$), 1.31–1.42 (m, 8H, $(CH_2)_3(CH_2)_2CH_3$), 1.56–1.61 (m, 4H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.75–1.85 (m, 4H, $CH_2CH_2(CH_2)_3CH_3$), 3.61 (t, *J*=8.3 Hz, 4H, CH_2(CH_2)$_4$-CH_3), 5.88 (s, 4H, CH_2), 5.90 (s, 2H, CH_2), 6.16 (s, 2H, CH_2OAc), 6.66 (d, *J*=2.1 Hz, 2H, Ar*H*), 6.69 (t, *J*=2.1 Hz, 1H, Ar*H*), 7.48–7.60 (m, 12H, Ar*H*), 8.30–8.39 (m, 12H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (*C*H_3), 21.0 (*C*H_3), 22.7 (*C*H_2), 28.5 (*C*H_2), 30.1 (*C*H_2), 31.4 (*C*H_2), 31.8 (*C*H_2), 50.8 (*C*H_2), 62.8 (*C*H_2), 63.0 (*C*H_2), 94.9 (*C*H), 95.0 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 126.3 (*C*H), 128.6 (*C*), 129.2 (*C*), 129.4 (*C*), 130.8 (*C*), 130.9 (*C*), 131.0 (*C*), 138.1 (*C*), 161.2 (*C*), 161.4 (*C*), 171.8 (*C*). Anal. Calcd for $C_{66}H_{64}O_5$: C, 84.58; H, 6.88; N, 0.00. Found: C, 84.23; H, 7.10; N, 0.07.

4.1.9. Synthetic procedure for 14L. A solution containing **13L** (0.57 g, 1.53 mmol), 10-(*n*-hexyl)-9-anthryl chloride (0.53 g, 1.71 mmol), potassium carbonate (0.30 g, 2.17 mmol), and 18-crown-6 (0.20 g, 0.76 mmol) in DMF (8 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. Purification of the residue by recrystallization from

$CHCl_3$–methanol solution gave **14L** (0.93 g, 94%) as a pale yellow power: mp 198–200 °C; IR (KBr) 1587 cm^{-1} (C=C), 1732 cm^{-1} (C=O); MS (FAB+) *m/z* 646 (*M*+), 647 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J*=6.8 Hz, 3H, $(CH_2)_5CH_3$), 1.35–1.43 (m, 4H, $(CH_2)_3(CH_2)_2CH_3$), 1.54–1.63 (m, 2H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.79–1.82 (m, 2H, $CH_2CH_2(CH_2)_3CH_3$), 3.64 (t, *J*=7.8 Hz, 2H, $CH_2(CH_2)_4CH_3$), 5.95 (s, 2H, CH_2), 5.97 (s, 2H, CH_2), 6.19 (s, 2H, $CH_2O(C=O)CH_3$), 6.84–6.96 (m, 3H, Ar*H*), 7.35–7.41 (m, 1H, Ar*H*), 7.51–7.62 (m, 8H, Ar*H*), 8.31–8.4 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 21.0 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 30.1 (CH_2), 31.5 (CH_2), 31.8 (CH_2), 58.8 (CH_2), 62.8 (CH_2), 63.0 (CH_2), 102.0 (*C*H), 107.6 (*C*H), 107.7 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 126.3 (*C*H), 126.3 (*C*H), 128.6 (*C*), 129.3 (*C*), 129.4 (*C*), 130.3 (*C*H), 130.8 (*C*), 130.9 (*C*), 131.0 (*C*), 138.1 (*C*), 160.5 (*C*), 160.7 (*C*), 171.2 (*C*). Anal. Calcd for $C_{45}H_{42}O_4$: C, 83.56; H, 6.54; N, 0.00. Found: C, 83.49; H, 6.34; N, 0.00.

4.1.10. Synthetic procedure for 15B. A solution containing **14B** (1.07 g, 1.14 mmol) and sodium methoxide (0.20 g, 3.70 mmol) in a mixture of methanol (15 mL) and THF (15 mL) was heated to reflux with stirring under argon atmosphere. After 12 h, the reaction mixture was cooled to room temperature, and concentrated in vacuo. Dissolving the resulting material in chloroform (20 mL), insoluble solid was removed by filtration through Celite. After the solvent was removed in vacuo, the residue was purified by recrystallization from chloroform–hexane solution to give **15B** (0.97 g, 95%) as a pale yellow powder: mp 214–216 °C; IR (KBr) 1597 cm^{-1} (C=C), 3568 cm^{-1} (OH); MS (FAB, positive) *m/z* 893 (*M*+), 894 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J*=7.1 Hz, 6H, $(CH_2)_5CH_3$), 1.32–1.45 (m, 8H, $(CH2)_3(CH_2)_2CH_3$), 1.55–1.62 (m, 4H, $(CH_2)_2CH_2(CH_2)2CH_3$), 1.76–1.85 (m, 4H, $CH_2CH_2(CH_2)_3CH_3$), 3.63 (t, *J*=8.1 Hz, 4H, $CH_2(CH_2)_4CH_3$), 5.68 (br s, 2H, CH_2OH), 5.90 (s, 2H, CH_2), 5.91 (s, 4H, CH_2), 6.66 (d, *J*=2.0 Hz, 2H, Ar*H*), 6.70 (t, *J*=2.0 Hz, 1H, Ar*H*), 7.49–7.61 (m, 12H, Ar*H*), 8.31–8.36 (m, 10H, Ar*H*), 8.46–8.49 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 30.1 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 57.6 (CH_2), 62.9 (CH_2), 63.1 (CH_2), 94.9 (*C*H), 95.0 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 126.2 (*C*H), 126.3 (*C*H), 128.4 (*C*), 129.4 (*C*), 130.1 (*C*), 130.9 (*C*), 131.0 (*C*), 133.3 (*C*), 138.2 (*C*), 161.2 (*C*), 161.4 (*C*). Anal. Calcd for $C_{64}H_{62}O_4$: C, 85.87; H, 6.98; N, 0.00. Found: C, 85.95; H, 7.14; N, 0.00.

4.1.11. Synthetic procedure for 15L. A solution containing **14L** (0.74 g, 1.14 mmol) and sodium methoxide (0.20 g, 3.70 mmol) in a mixture of methanol (20 mL) and THF (25 mL) was heated to reflux with stirring under argon atmosphere. After 12 h, the reaction mixture was cooled to room temperature, and concentrated in vacuo. Dissolving the resulting material in chloroform (20 mL), insoluble solid was removed by filtration through Celite. After the solvent was removed in vacuo, the residue was purified by recrystallization from chloroform–hexane solution to give **15L** (0.64 g, 92%) as a pale yellow powder: mp 207–208 °C; IR (KBr) 1579 cm^{-1} (C=C), 3423 cm^{-1} (C=O); MS (FAB+) *m/z* 604 (*M*+), 605 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J*=6.8 Hz, 3H, $(CH_2)_5CH_3$), 1.30–1.46 (m, 4H, $(CH_2)_3(CH_2)_2CH_3$), 1.57–1.66 (m, 2H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.74 (t, *J*=5.4 Hz, 1H, O*H*), 1.80–1.87 (m, 2H, $CH_2CH_2(CH_2)_3CH_3$), 3.64 (t, *J*=8.1 Hz, 2H, $CH_2(CH_2)_4CH_3$), 5.72 (d, *J*=5.4 Hz, 2H, CH_2OH), 5.95 (s, 2H, CH_2), 5.96 (s, 2H, CH_2), 6.85–6.90 (m, 2H, Ar*H*), 6.97 (br s, 1H, Ar*H*), 7.36–7.41 (m, 1H, Ar*H*), 7.49–7.62 (m, 8H, Ar*H*), 8.31–8.37 (m, 6H, Ar*H*), 8.48–8.52 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 30.1 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 57.6 (CH_2), 62.8 (CH_2), 63.0 (CH_2), 101.9 (*C*H), 107.5 (*C*H), 107.7 (*C*H), 124.6 (*C*H), 124.7 (*C*H), 124.8 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 126.2 (*C*H), 126.3 (*C*H), 128.4 (*C*), 129.3 (*C*), 130.0 (*C*), 130.3 (*C*H), 130.9 (*C*), 131.0 (*C*), 133.2 (*C*), 138.1 (*C*), 160.5 (*C*), 160.6 (*C*). Anal. Calcd for $C_{43}H_{40}O_3$: C, 85.40; H, 6.67; N, 0.00. Found: C, 85.10; H, 6.64; N, 0.00.

4.1.12. Synthetic procedure for 7B. To a solution containing **15B** (0.37 g, 0.41 mmol), 4-dimethylaminopyridine (0.10 g, 0.82 mmol), lithium chloride (0.52 g, 12.3 mmol), and triethylamine (1.15 mL, 8.25 mmol) in anhydrous THF (15 mL), a solution of methanesulfonyl chloride (0.16 mL, 2.07 mmol) in anhydrous THF (5 mL) was added dropwise at 0 °C. After stirring at room temperature for additional 12 h, the reaction mixture was quenched by slow addition of HCl (3.0 mol/L, 10 mL), and then extracted twice with chloroform (30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by recrystallization from chloroform–hexane solution gave **7B** (0.33 g, 87%) as a pale yellow powder: mp 223–225 °C; IR (KBr) 1585 cm^{-1} (C=C); MS (FAB, positive) *m/z* 912 (*M*+), 913 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J*=7.1 Hz, 6H, $(CH_2)_5CH_3$), 1.31–1.42 (m, 8H, $(CH2)_3(CH_2)_2CH_3$), 1.54–1.61 (m, 4H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.75–1.85 (m, 4H, $CH_2CH_2(CH_2)_3CH_3$), 3.61 (t, *J*=8.1 Hz, 4H, $CH_2(CH_2)_4CH_3$), 5.57 (s, 2H, CH_2Cl), 5.85 (s, 2H, CH_2), 6.88 (s, 4H, CH_2), 6.64 (d, *J*=2.1 Hz, 2H, Ar*H*), 6.68 (t, *J*=2.1 Hz, 1H, Ar*H*), 7.47–7.62 (m, 12H, Ar*H*), 8.30–8.35 (m, 12H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 30.1 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 38.9 (CH_2), 62.7 (CH_2), 63.0 (CH_2), 94.9 (*C*H), 95.1 (*C*H), 124.1 (*C*H), 124.7 (*C*H), 124.9 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 126.4 (*C*H), 126.6 (*C*H), 129.2 (*C*), 129.4 (*C*), 129.7 (*C*), 130.0 (*C*), 130.9 (*C*), 131.0 (*C*), 138.2 (*C*), 161.1 (*C*), 161.4 (*C*). Anal. Calcd for $C_{64}H_{61}ClO_3$: C, 84.14; H, 6.73; N, 0.00. Found: C, 84.37; H, 6.66; N, 0.02.

4.1.13. Synthetic procedure for 7L. To a solution containing **15L** (0.25 g, 0.41 mmol), 4-dimethylaminopyridine (0.10 g, 0.82 mmol), lithium chloride (0.52 g, 12.3 mmol), and triethylamine (1.15 mL, 8.25 mmol) in anhydrous THF (15 mL), a solution of methanesulfonyl chloride (0.16 mL, 2.07 mmol) in anhydrous THF (5 mL) was added dropwise at 0 °C. After stirring at room temperature for additional 12 h, the reaction mixture was quenched by slow addition of HCl (3.0 mol/L, 10 mL), and then extracted twice with chloroform (30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by recrystallization from chloroform–hexane solution gave **7L**

(0.23 g, 91%) as a pale yellow powder: mp 178–180 °C; IR (KBr) 1589 cm^{-1} (C═C); MS (FAB+) *m/z* 622 (*M*+), 623 (*MH*+); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J=6.9 Hz, 3H, $(CH_2)_5CH_3$), 1.32–1.44 (m, 4H, $(CH_2)_3(CH_2)_2CH_3$), 1.58–1.66 (m, 2H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.77–1.85 (m, 2H, $CH_2CH_2(CH_2)_3CH_3$), 3.64 (t, J=8.1 Hz, 2H, $CH_2(CH_2)_4CH_3$), 5.64 (s, 2H, CH_2Cl), 5.95 (s, 4H, CH_2), 6.84–6.98 (m, 2H, Ar*H*), 7.39 (t, J=8.3 Hz, 1H, Ar*H*), 7.50–7.67 (m, 8H, Ar*H*), 8.31–8.40 (m, 8H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 30.1 (CH_2), 31.5 (CH_2), 31.8 (CH_2), 39.0 (CH_2), 62.7 (CH_2), 63.0 (CH_2), 102.0 (*C*H), 107.6 (*C*H), 107.7 (*C*H), 124.2 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 125.2 (*C*H), 126.1 (*C*H), 126.4 (*C*H), 126.6 (*C*H), 129.4 (*C*), 129.8 (*C*), 130.0 (*C*), 130.3 (*C*H), 130.9 (*C*), 131.0 (*C*), 138.2 (*C*), 160.4 (*C*), 160.7 (*C*). Anal. Calcd for $C_{43}H_{39}ClO_2$: C, 82.87; H, 6.31; N, 0.00. Found: C, 82.56; H, 6.17; N, 0.08.

4.1.14. Synthetic procedure for 3B. A solution containing **7B** (0.15 g, 0.16 mmol), **5** (0.018 g, 0.074 mmol), potassium carbonate (0.028 g, 0.20 mmol), and 18-crown-6 (0.039 g, 0.15 mmol) in DMF (5 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. Purification of the residue by silica-gel column chromatography (80% chloroform, 20% hexane) and recrystallization from chloroform–hexane solution gave **3B** (0.11 g, 75%) as a pale yellow powder: mp 135–137 °C; UV ($CHCl_3$) 358 nm (ε 33,800), 378 nm (ε 54,700), 398 nm (ε 54,100); IR (KBr) 1591 cm^{-1} (C═C), 1720 cm^{-1} (C═O); MS (ESI, positive) *m/z* 2020.9 (*MNa*+), 2036.9 (*MNaO*+), 2052.9 ($MNaO_2$+), 2069.0 ($MNaO_3$+); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=7.1 Hz, 12H, $(CH_2)_5CH_3$), 1.25–1.37 (m, 16H, $(CH_2)_3(CH_2)_2CH_3$), 1.48–1.55 (m, 8H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.66–1.79 (m, 8H, $CH_2CH_2(CH_2)_3CH_3$), 3.45–3.57 (m, 8H, $CH_2(CH_2)_4CH_3$), 5.28 (s, 2H, CH_2OBz), 5.74 (s, 16H, CH_2O), 6.60 (s, 4H, Ar*H*), 6.62 (s, 2H, Ar*H*), 6.82 (s, 3H, Ar*H*), 7.26–7.35 (m, 3H, Ar*H*), 7.38–7.50 (m, 24H, Ar*H*), 8.02–8.04 (m, 2H, Bz*H*), 8.15–8.27 (m, 24H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.4 (CH_2), 30.0 (CH_2), 31.4 (CH_2), 31.7 (CH_2), 62.7 (CH_2), 62.9 (CH_2), 66.4 (CH_2), 94.8 (*C*H), 95.0 (*C*H), 101.2 (*C*H), 107.3 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 126.2 (*C*H), 128.3 (*C*H), 128.8 (*C*), 129.0 (*C*), 129.3 (*C*), 129.7 (*C*H), 130.0 (*C*), 130.6 (*C*), 130.7 (*C*), 130.9 (*C*), 133.0 (*C*H), 138.0 (*C*), 138.8 (*C*), 160.6 (*C*), 161.2 (*C*), 161.3 (*C*), 166.3 (*C*). Anal. Calcd for $C_{142}H_{132}O_{10}$: C, 85.34; H, 6.66; N, 0.00. Found: C, 85.28; H, 6.63; N, 0.00.

4.1.15. Synthetic procedure for 3L. A solution containing **7L** (0.12 g, 0.19 mmol), **5** (0.022 g, 0.090 mmol), potassium carbonate (0.034 g, 0.25 mmol), and 18-crown-6 (0.047 g, 0.18 mmol) in DMF (5 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a pale yellow solid. Purification of the residue by silica-gel column chromatography (80% chloroform, 20% hexane) and recrystallization from chloroform–hexane solution gave **3L** (0.088 g, 69%) as a pale yellow powder: mp 141–142 °C; UV ($CHCl_3$) 357 nm (ε 23,400), 375 nm (ε 37,400), 396 nm (ε 37,000); IR (KBr) 1589 cm^{-1} (C═C), 1718 cm^{-1} (C═O); MS (ESI, positive) *m/z* 1471.5 ($MNaO_2$+); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J=6.6 Hz, 6H, $(CH_2)_5CH_3$), 1.26–1.44 (m, 8H, $(CH_2)_3(CH_2)_2CH_3$), 1.51–1.62 (m, 4H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.73–1.87 (m, 4H, $CH_2CH_2(CH_2)_3CH_3$), 3.58–3.64 (m, 4H, $CH_2(CH_2)_4CH_3$), 5.39 (s, 2H, CH_2OBz), 5.91 (s, 4H, CH_2O), 5.93 (s, 4H, CH_2O), 5.95 (s, 4H, CH_2O), 6.82–6.95 (m, 9H, Ar*H*), 7.33–7.42 (m, 5H, Ar*H*), 7.49–7.55 (m, 16H, Ar*H*), 8.08–8.11 (m, 2H, Bz*H*), 8.26–8.36 (m, 16H, Ar*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.5 (CH_2), 30.1 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 62.9 (CH_2), 63.0 (CH_2), 66.5 (CH_2), 101.4 (*C*H), 102.0 (*C*H), 107.3 (*C*H), 107.6 (*C*H), 107.8 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.2 (*C*H), 126.0 (*C*H), 126.3 (*C*H), 129.3 (*C*H), 128.4 (*C*), 128.9 (*C*), 129.2 (*C*), 129.8 (*C*), 130.2 (*C*), 130.8 (*C*H), 130.9 (*C*), 138.1 (*C*), 160.5 (*C*), 160.6 (*C*), 166.4 (*C*). Anal. Calcd for $C_{100}H_{88}O_8$: C, 84.72; H, 6.26; N, 0.00. Found: C, 84.74; H, 6.28; N, 0.00.

4.1.16. Synthetic procedure for 4B. A solution containing **7B** (0.55 g, 0.61 mmol), **6** (0.043 g, 0.075 mmol), potassium carbonate (0.094 g, 0.68 mmol), and 18-crown-6 (0.18 g, 0.68 mmol) in DMF (10 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration, intensively washed with water, and dried in a vacuum to afford a yellow solid. Purification of the residue by the preparative HPLC (chloroform as eluent) gave **4B** (0.25 g, 57%) as a yellow powder: mp 136–137 °C; UV ($CHCl_3$) 359 nm (ε 106,000), 378 nm (ε 171,000), 399 nm (ε 167,000); IR (KBr) 1593 cm^{-1} (C═C), 1728 cm^{-1} (C═O); MS (CSI, negative) *m/z* 2954.5 ($MCl_2$2−), 5873.3 (*MCl*−); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=6.9 Hz, 36H, $(CH_2)_5CH_3$), 1.28–1.37 (m, 48H, $(CH_2)_3(CH_2)_2CH_3$), 1.52–1.62 (m, 24H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.71–1.83 (m, 24H, $CH_2CH_2(CH_2)_3CH_3$), 3.53–3.60 (m, 24H, $CH_2(CH_2)_4CH_3$), 5.31 (s, 6H, CH_2OBz), 5.62 (s, 12H, OCH_2), 5.66 (s, 12H, OCH_2), 5.74 (s, 24H, OCH_2), 6.55 (s, 12H, Ar*H*), 6.61 (s, 6H, Ar*H*), 6.72 (s, 3H, Ar*H*), 6.80 (s, 6H, Ar*H*), 7.37–7.56 (m, 72H, Ar*H*), 8.14–8.35 (m, 72H, Ar*H*), 8.95 (s, 3H, Bz*H*); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.7 (CH_2), 28.4 (CH_2), 30.0 (CH_2), 31.4 (CH_2), 31.7 (CH_2), 62.6 (CH_2), 62.9 (CH_2), 67.1 (CH_2), 94.8 (*C*H), 95.1 (*C*H), 102.1 (*C*H), 107.8 (*C*H), 124.7 (*C*H), 125.0 (*C*H), 125.1 (*C*H), 126.0 (*C*H), 126.1 (*C*H), 128.7 (*C*), 128.9 (*C*), 129.3 (*C*), 130.6 (*C*), 130.9 (*C*), 134.9 (*C*), 138.0 (*C*), 138.1 (*C*), 160.5 (*C*), 161.2 (*C*), 161.3 (*C*), 164.6 (*C*). Anal. Calcd for $C_{414}H_{384}O_{30}$: C, 85.15; H, 6.63; N, 0.00. Found: C, 84.95; H, 6.43; N, 0.00.

4.1.17. Synthetic procedure for 4L. A solution containing **7L** (0.50 g, 0.80 mmol), **6** (0.058 g, 0.10 mmol), potassium carbonate (0.13 g, 0.91 mmol), and 18-crown-6 (0.24 g, 0.91 mmol) in DMF (10 mL) was heated at 55 °C with stirring under argon atmosphere. After 4 h, the reaction mixture was cooled to room temperature, and poured into saturated ammonium chloride solution to precipitate the product. The precipitate was collected by filtration,

intensively washed with water, and dried in a vacuum to afford a yellow solid. Purification of the residue by recrystallization from chloroform solution gave **4L** (0.20 g, 48%) as a pale yellow powder. This compound was so insoluble in $CDCl_3$ and other deuterated solvents that the ^{13}C NMR spectrum could not be recorded: mp 159–160 °C; UV ($CHCl_3$) 358 nm (ε 74,400), 377 nm (ε 113,000), 397 nm (ε 112,000); IR (KBr) 1591 cm^{-1} (C═C), 1726 cm^{-1} (C═O); MS (CSI, negative) *m*/*z* 4131.8 (*MCl*−); ^1H NMR ($CDCl_3$) δ 0.88 (t, $J=6.9$ Hz, 18H, $(CH_2)_5CH_3$), 1.21–1.39 (m, 24H, $(CH_2)_3(CH_2)_2CH_3$), 1.46–1.57 (m, 12H, $(CH_2)_2CH_2(CH_2)_2CH_3$), 1.68–1.82 (m, 12H, $CH_2CH_2(CH_2)_3CH_3$), 3.55–3.62 (m, 12H, $CH_2(CH_2)_4CH_3$), 5.40 (s, 6H, CH_2OBz), 5.73–5.91 (m, 36H, OCH_2), 6.75–6.89 (m, 27H, Ar*H*), 7.24–7.59 (m, 54H, Ar*H*), 8.17–8.31 (m, 48H, Ar*H*), 9.01 (s, 3H, Bz*H*). Anal. Calcd for $C_{288}H_{252}O_{24}$: C, 84.43; H, 6.20; N, 0.00. Found: C, 84.57; H, 6.27; N, 0.16.

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16. The ESI-MS measurements were conducted in the presence of excess sodium iodide in chloroform–methanol solutions, which led to the observations of sodium adduct ion peaks in a positive ion mode.
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22. Reproducible experimental results were obtained from the time-resolved fluorescence measurements of the three samples operated under anaerobic and aerobic conditions. This indicates the anthracene groups incorporated within the dendritic architectures were tolerant of oxidative degradation on the time scale of the decay runs.
23. To understand a general trend in changes in fluorescence decay profiles for the branching series of dendritic architectures, the dynamic process of **3B** was also examined by the time-resolved techniques under the same conditions employed for the other cases. As a result, **3B** was found to exhibit anomalous behavior in the fluorescence intensity traces decaying much faster than those of the other samples examined, which was quite difficult to be rationalized on the basis of the interpretations stated above. Details on these experimental results will be discussed elsewhere.
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Stereospecific synthesis of conjugated (1*E*,3*E*)- and (1*Z*,3*Z*)-1,4-di(*n*-*N*,*N*-dimethylaminophenyl)-1,3-butadienes from 2-chloro-1-(*n*-*N*,*N*-dimethylaminophenyl)ethenes: fluorescence properties

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Abstract—The conjugated 1,4-di(*n*-*N*,*N*-dimethylaminophenyl)-1,3-butadienes (*n*=*o*-, *m*-, *p*-) were efficiently synthesised by homocoupling of the appropriate 2-chloro-1-(*n*-*N*,*N*-dimethylaminophenyl)ethene (*n*=*o*-, *m*-, *p*-) with stoichiometric amounts of zerovalent nickel complexes. The 1,3-butadienes were obtained as a mixture of stereoisomers, with independence of the starting *E* or *Z* chlorovinyl isomer. Moreover, the stereospecific (*Z*,*Z*) stereoisomer was obtained by partial hydrogenation of the corresponding 1,3-butadiyne, while the stereospecific (*E*,*E*) stereoisomer was obtained by exposure to the sunlight radiation of the (*Z*,*Z*) or the (*Z*,*E*) compound in ethanol.

1. Introduction

The synthesis of the highly conjugated polyene structures as molecular organic materials show a wide spread interest because these exhibit semiconductor and optical properties. Methods for the synthesis of 1,3-butadiene compounds have been reported.[1] An elegant and practical synthesis for 1,4-diphenyl-1,3-butadiene was the homocoupling of the (*E*)- or (*Z*)-β-bromostyrene with zerovalent nickel complexes giving the (*E*,*E*)- or (*Z*,*Z*)-1,4-diphenyl-1,3-butadiene, respectively, while the (*E*,*Z*) isomer was isolated in low yield.[2]

However, the zerovalent nickel complexes were more investigated in the homocoupling reaction of arylhalides or arylsulfonates,[3,4,5] or Grignard reagents with catalytic amounts of nickel complexes,[6,7,8] to the preparation of diaryl or diheteroaryl or polyaryl derivatives.[9] The homocoupling of organic halides or heteroarylhalides was efficiently catalysed by electroreductive nickel complexes in organic solvent or ionic liquid solvent.[10] (*Z*)-3-Halopropenoates were homocoupled using catalytic amounts of nickel chloride and zinc in the presence of water in pyridine, affording a mixture of (*Z*) and (*E*)-3-hexenedioates.[11]

In general, the active zerovalent nickel species can be prepared in situ from stoichiometric amounts of zinc powder and catalytic amounts of nickel salts or complexes.[12]

Now, we report the homocoupling of (*E*)- or (*Z*)-2-chloro-1-(*n*-*N*,*N*-dimethylaminophenyl)ethene (*n*=*o*-, *m*-, *p*-) with zerovalent nickel complexes and the stereochemistry of the reaction.

2. Results and discussions

The 2-chloro-1-(*n*-*N*,*N*-dimethylaminophenyl)ethene (*n*=*o*-, *m*- and *p*-) (**1**–**3**) were obtained by means of the Wittig reaction between the appropriate aldehyde and the chloromethylen(triphenyl)phosphonium ylide,[13,14] as yellow oils, in good yield, Scheme 1. The separation of phosphine and phosphine oxide by extraction with hexane followed by silica gel column chromatography with toluene as eluent give pure *Z*/*E* mixtures (1:1 and 4:1 for compound **3**), which were used for the homocoupling reaction. The *Z* and *E* isomers can be purely isolated using hexane–toluene (2/1) as eluent, excepting for compound **2**.

The homocoupling reaction of 2-chloro-1-arylethenes **1**–**3** was carried out with stoichiometric amounts of zerovalent nickel complexes, which were prepared in situ by reaction between dichloro bis(triphenylphosphine) nickel and powder of zinc as the reducing agent in presence of

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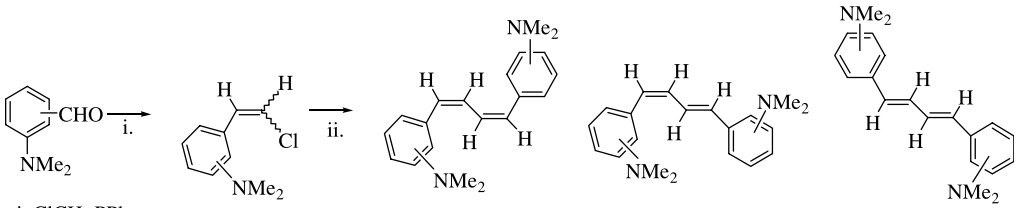


Isomer		%	Z	E	1Z,3Z	1Z,3E	1E,3E
ortho,	**1**	96	3	2	**4a**	**4b**	**4c**
meta,	**2**	82	2	3	**5a**	**5b**	**5c**
para,	**3**	80	3	2	**6a**	**6b**	**6c**

Scheme 1.

Table 1. Homocoupling of 2-chloro-1-(*n*-*N*,*N*-dimethylaminophenyl)ethenes with zerovalent nickel complexes

Compound	Isomer	1,3-Butadiene (%)[a]		
1 *o*-NMe_2	Z	**4a** (1*Z*,3*Z*), 22	**4b** (1*Z*,3*E*), 42	**4c** (1*E*,3*E*), 34
1 *o*-NMe_2	*E*	**4a** (1*Z*,3*Z*), Traces	**4b** (1*Z*,3*E*), 19	**4c** (1*E*,3*E*), 75
2 *m*-NMe_2	*Z*/*E* (2:3)	**5a**, —	**5b** (1*Z*,3*E*), 43	**5c** (1*E*,3*E*), 45
3 *p*-NMe_2	*E*	**6a**, —	**6b**, —	**6c** (1*E*,3*E*), 95
3 *p*-NMe_2	*Z*/*E* (1:1)	**6a** (1*Z*,3*Z*), 2	**6b** (1*Z*,3*E*), 77	**6c**, —
3 *p*-NMe_2	*Z*/*E* (4:1)	**6a** (1*Z*,3*Z*), 4	**6b** (1*Z*,3*E*), 79	**6c**, —

[a] Yield refers to isolated product after purification by column chromatography.

tetra-*n*-butylammonium iodide as a phase transfer component in dry THF, Scheme 1.[15] The results of the homocoupling reaction are summarised in Table 1.

In this way, the homocoupling of (*Z*)-2-chloro-1-(*o*-*N*,*N*-dimethylaminophenyl)ethene (**1**) affords to a mixture of stereoisomers characterised by IR and ^{1}H NMR spectra, in good yield (98%): (1*Z*,3*Z*)-**4a** (22%); (1*Z*,3*E*)-**4b** (42%); (1*E*,3*E*)-1,4-di(*o*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**4c**) (34%) as yellow oils.

However, the homocoupling of the (*E*)-**1** isomer gives (1*E*,3*E*)-**4c** as the main product (75%) and (1*Z*,3*E*)-**4b** (19%). Moreover, (1*Z*,3*Z*)-**4a** isomer was detected in traces, Table 1, Scheme 1.

Compound **4c** shows fluorescence radiation emission with important quantum yield, Table 2.

Table 2. UV–vis and fluorescence spectra of 1,3-butadienes and 1,3-butadiyne **9**

Compound	UV–vis (CH_2Cl_2)[a] λ_{max} (nm)	ε (M^{-1} cm^{-1})	F (CH_2Cl_2)[a,b] λ_{em} (nm)	Φ_f[c]
4c	377	49,500	465	0.25
5c	342	42,600	477	0.29
9	378	97,600	428	8.3×10^{-4}
6a	405	82,400	438	0.32
6c	405	203,200	440	0.26

[a] At room temperature.
[b] $[c]\cong10^{-8}$ M.
[c] Fluorescence quantum yield in dichloromethane referred to quinine sulfate in H_2SO_4 (1 N) and $\lambda_{exc.}$ 365 nm.

Hence, the homocoupling reaction of the (*Z*)-**1** stereoisomer gives the (1*Z*,3*Z*)-1,3-butadiene, which retains the configuration of the starting (*Z*)-chlorovinyl derivative but as the mino product, while an important isomerization to (1*Z*,3*E*) and (1*E*,3*E*) takes place. Moreover, the homocoupling of (*E*)-**1** isomer gives the (1*E*,3*E*) stereoisomer as the main product, while the isomerized product (1*Z*,3*E*) was the minoritary one, Table 1.

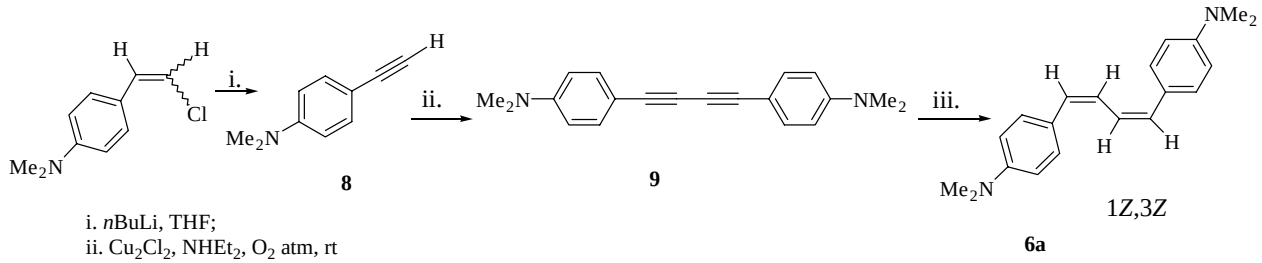
On the other hand, the (1*Z*,3*Z*)-**4a** and (1*Z*,3*E*)-**4b** 1,3-butadienes in ethanol, were completely transformed in (1*E*,3*E*)-**4c**, by exposure to the sunlight radiation, in presence of iodine crystals.[16]

The homocoupling of the (*Z*/*E*)-2-chloro-1-(*m*-*N*,*N*-dimethylaminophenyl)ethene (**2**) mixture (*Z*/*E*, 2:3), gives a practically equimolar mixture of (1*Z*,3*E*)-**5b** and (1*E*,3*E*)-1,4-di(*m*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**5c**) in good yield (88%). The **5c** isomer shows fluorescent emission radiation in solution, Table 2.

In the same way, the homocoupling of (*E*)-2-chloro-1-(*p*-*N*,*N*-dimethylaminophenyl)ethene (**3**), gives exclusively the (1*E*,3*E*)-1,3-butadiene **6c**, in excellent yield (95%), as a white solid mp 245–246 °C. Thus, compound **6c** retains the stereochemistry of the starting chlorovinyl derivative.

However, the homocoupling of the (*Z*/*E*)-2-chloro-1-(*p*-*N*,*N*-dimethylaminophenyl)ethene mixtures (*Z*/*E*, 1:1 or 4:1), gives (1*Z*,3*E*)-**6b** (mp 255–256 °C, 77 and 79%, respectively) and (1*Z*,3*Z*)-**6a** in low yield (2 or 4%, respectively, by HPLC, mp 231.7 °C by DSC), Table 1.

On the other hand, both **6a** and **6b** stereoisomers in solution of ethanol were completely transformed in the (1*E*,3*E*) stereoisomer **6c** by sunlight exposure, in presence of iodine crystals.[16] Compounds **6a** and **6c**, in solution, show fluorescent emission radiation, Table 2.

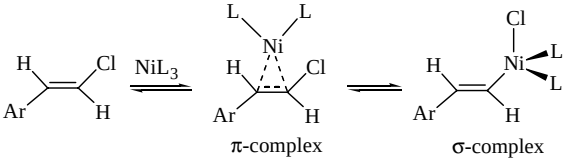


Scheme 2.

Moreover, the minoritary (1*Z*,3*Z*)-**6a** stereoisomer was purely synthesised as a reference in the analysis of the homocoupling mixture. The stereospecific synthesis was carried out by partial hydrogenation of 1,4-di(*p*-*N*,*N*-dimethylaminophenyl)-1,3-butadiyne (**9**) catalysed by palladium on barium sulfate treated with lead acetate and quinoline (Lindlar type catalyst). Compound **6a** was isolated as a yellow solid, mp 231.7 °C (DSC), in 96% yield, Scheme 2.

The synthesis of 1,3-butadiyne **9** was carried out by oxidative dimerization of the corresponding acetylene **8** under the Glaser reaction conditions, catalysed by cuprous chloride under oxygen atmosphere in dry pyridine at 40 °C, in practically quantitative yield. The terminal acetylene **8** was prepared by treatment of 2-chloro-1-(*p*-*N*,*N*-dimethylaminophenyl)ethene (**3**) with butyl lithium in good yield.[13,17]

The anomalous (*E*)→(*Z*) isomerization, observed during the homocoupling reaction, could be due to the formation of a π-nickel-double bond complex, decreasing the double bond order, which permit the rotation of the C–C bond in the complex. The formation of a π-complex was usually proposed prior to the oxidative addition to the C–halogen bond by the nickel complexes.[12,13,18] The sterical interactions on the π–σ nickel complex equilibrium, are responsible of the pathway of the homocoupling and the resulting 1,3-butadiene stereochemistry, being of minor importance the thermodynamical stability,[18,19,20] Scheme 3.



Scheme 3.

The conjugated stereoisomers of 1,4-di(*n*-*N*,*N*-dimethylaminophenyl)-1,3-butadienes, in solution of dichloromethane show fluorescence emission radiation, with important quantum yields (25–32%), which are not dependent of the stereochemistry. In contrast, the conjugated 1,3-butadiyne **9** shows fluorescence radiation emission in very low quantum yield, Table 2.

3. Conclusions

The conjugated 1,4-di(*n*-*N*,*N*-dimethylaminophenyl)-1,3-butadienes (*n*=*o*-, *m*-, *p*-) can be efficiently obtained by homocoupling of the appropriate 2-chloro-1-(*n*-*N*,*N*-dimethylaminophenyl)ethene (*n*=*o*-, *m*-, *p*-) with stoichiometric amounts of zerovalent nickel complexes prepared in situ by reduction of dichloro bis(triphenyl)phosphine nickel with powder zinc in tetrahydrofuran. The 1,3-butadienes were obtained as a mixture, which is independent of the starting *E* or *Z* chlorovinyl derivative. Moreover, stereospecific (*Z*,*Z*) stereoisomer was obtained by partial hydrogenation of the corresponding 1,4-di(*n*-*N*,*N*-dimethylaminophenyl)-1,3-butadiyne. The last can be obtained by catalytic homocoupling of the *n*-(*N*,*N*-dimethylaminophenyl)acetylene. The (*E*,*E*) stereoisomer can be stereospecifically isolated by exposure to the sunlight radiation of the (*Z*,*Z*) or (*Z*,*E*) isomers or their mixture in ethanol.

4. Experimental

4.1. General

Melting points were determined in open capillaries using a Buchi or Reichert hot stage microscope and are uncorrected. IR spectra of solids were recorded as KBr pellets and IR spectra of oils were recorded as thin films on NaCl plates with a Bruker Vector 22 spectrophotometer, and the wave numbers are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 75 MHz, respectively, on a Bruker Aspect spectrometer. Chemical shifts are given in δ with TMS as an internal reference and constants coupling J are given in Hz, the solvent is $CDCl_3$. Mass spectra were recorded on a VG AutoSpec spectrometer at 70 eV. Elemental analyses were performed with a LECO CHN-900. The UV–vis spectra were recorded on a Hewlett Packard 8453 spectrometer, frequencies are given in nm and ε in $L\,mol^{-1}\,cm^{-1}$. All fluorescence spectra were recorded at room temperature at 10^{-8} M on a SLM Aminco Bowman series 2, the fluorescence quantum yield was determined in dichloromethane on freshly prepared samples (air-equilibrated) with absorbances at the excitation wavelength (365 nm for the standard quinine sulfate). The quinine sulfate samples in 1 N H_2SO_4 concentration were employed as a standard ($\Phi_f=0.55$) to measure the fluorescence quantum yields, which were corrected taking into account the refractive indices of the solvents used. Yields are given after silica gel column chromatography separation (silica gel 60, 200–400 mesh) using the solvents or solvent crystallization referred in the corresponding experiment.

4.2. Preparation of 2-chloro-1-(*n*-*N*,*N*-dimethylaminophenyl)ethenes (1–3). General procedure

A solution of *n*-butyllithium 1.6 M in hexane (90 mL, 144 mmol) was slowly added to a suspension of chloromethylen(triphenyl)phosphonium ylide (38 g, 109 mmol) in 210 mL of dry THF, under argon atmosphere at 0 °C. The mixture was stirred for 30 min until an intense red colour, and then *n*-*N*,*N*-dimethylaminobenzene carboxaldehyde (11 g, 73 mmol) was added with stirring at room temperature overnight. After, the solvent was evaporated to leave a brown oil, that was purified by silica gel column chromatography, to give the 2-chloroethenyl derivative.

4.2.1. 2-Chloro-1-(*o*-*N*,*N*-dimethylaminophenyl)ethene (1). Toluene was used as the eluent, giving both isomers as a yellow oil, 12.68 g (*Z*/*E*, 3:2). The *Z* and *E* isomers were isolated using hexane–toluene (2/1): (*Z*)-**1**, 7.66 g (60%) as a pale-yellow oil; (*E*)-**1**, 5.02 g (40%) as a pale-yellow oil.

Isomer (*Z*)-**1**. IR (film, cm^{-1}): 2800, 1600, 740, 660. ^1H NMR ($CDCl_3$): δ 7.84–7.80 (m, 1H), 7.24–7.13 (m, 1H), 7.06–6.90 (m, 2H), 6.85 (d, 1H, $J=7.9$ Hz), 6.28 (d, 1H, $J=7.9$ Hz, 1H), 2.70 (s, 6H). EM (70 eV): 181 (M^+, 14), 166 (2), 146 (72), 131 (100). $C_{10}H_{12}NCl$ (181.66). Anal. Calcd: C 66.12, H 6.66, N 7.71. Found: C 65.97, H 6.55, N 7.65.

Isomer (*E*)-**1**. IR (film, cm^{-1}): 2800, 1600, 960, 740. ^1H NMR ($CDCl_3$): δ 7.33–7.18 (m, 2H), 7.12 (d, 1H, $J=13.7$ Hz), 7.07–6.93 (m, 2H), 6.62 (d, 1H, $J=13.7$ Hz), 2.73 (s, 6H). EM (70 eV): 181 (M^+, 6), 166 (10), 146 (88), 131 (100). $C_{10}H_{12}NCl$ (181.66). Anal. Calcd: C 66.12, H 6.66, N 7.71. Found: C 66.06, H 6.37, N 7.54.

4.2.2. 2-Chloro-1-(*m*-*N*,*N*-dimethylaminophenyl)ethene (2). Toluene was used as the eluent, giving the mixture of both isomers as a yellow oil, 10.83 g (*Z*/*E*, 2:3, 82%).

Mixture (*Z*/*E*)-**2**. IR (film, cm^{-1}): 2790, 1590, 990, 840, 760, 710, 690. ^1H NMR ($CDCl_3$): 7.24 (dd, 1H, $J=7.8$ Hz, *Z*), 7.17 (dd, 1H, $J=7.8$ Hz, *E*), 7.09–7.07 (m, 1H, *Z*), 7.03–6.99 (m, 1H, *Z*), 6.80 (d, 1H, $J=13.6$ Hz, *E*), 6.73–6.65 (m, 4H, *Z*/*E*), 6.61 (d, 1H, $J=13.6$ Hz, 1H, *E*), 6.22 (d, 1H, $J=8.2$ Hz, *Z*), 6.22 (d, 1H, $J=8.2$ Hz, *Z*), 2.95 (s, 6H, *Z*), 2.94 (s, 6H, *E*). EM (70 eV): 181 (M^+, 72), 180 (100), 165 (8), 144 (6), 130 (6). $C_{10}H_{12}NCl$ (181.66). Anal. Calcd: C 66.12, H 6.66, N 7.71. Found: C 65.78, H 6.74, N 7.46.

4.2.3. 2-Chloro-1-(*p*-*N*,*N*-dimethylaminophenyl)ethene (3). Hexane–toluene (1/1) was used as the eluent, recovering two fractions containing the mixture of both isomers as yellow oils: (5.40 g, *Z*/*E*, 1:1, 40.9% and; 5.22 g, *Z*/*E*, 4:1, 39.5%). The *E* and *Z* isomer were isolated from the *Z*–*E* (1/1) mixture toluene as eluent, giving (*E*)-**3**, 2.70 g as a yellow oil, and (*Z*)-**3**, 2.29 g as a pale-yellow solid, mp 37–39 °C.

Isomer Z-**3**. IR (film, cm^{-1}): 2810, 1600, 1360, 830, 700. ^1H NMR ($CDCl_3$): δ 7.63–6.69 (m, 4H), 6.50 (d, 1H, $J=8.1$ Hz), 6.04 (d, 1H, $J=8.1$ Hz), 2.99 (s, 6H). EM (70 eV): 181 (M^+, 92), 180 (100), 165 (18), 144 (9), 130 (8). $C_{10}H_{12}NCl$ (181.66). Anal. Calcd: C 66.12, H 6.66, N 7.71. Found: C 66.22, H 6.57, N 7.63.

Isomer E-**3**. IR (KBr, cm^{-1}): 2810, 1600, 1360, 960, 830. ^1H NMR ($CDCl_3$): δ 7.17–6.66 (m, 4H), 6.73 (d, 1H, $J=13.7$ Hz), 6.42 (d, 1H, $J=13.7$ Hz), 2.96 (s, 6H). EM (70 eV): 181 (M^+, 75), 180 (100), 165 (25), 144 (12), 130 (4). $C_{10}H_{12}NCl$ (181.66). Anal. Calcd: C 66.12, H 6.66, N 7.71. Found: C 66.35, H 6.41, N 7.50.

4.3. Homocoupling reactions with tris(triphenylphosphine)nickel prepared from dichlorobis(triphenylphosphine)nickel. General procedure

To a suspension of dichlorobis(triphenylphosphine) nickel (719 mg, 1.1 mmol), tetrabutylammonium iodide (407 mg, 1.1 mmol) and powdered zinc (107 mg, 1.65 mmol) in 5 mL of dry THF, under argon atmosphere, was stirred for 30 min until the mixture becomes dark red. Then a solution of the chloroethenyl derivative **1**–**3** (200 mg, 1.1 mmol) in 2 mL of dry THF was added and stirred at room temperature for 24 h. Then, hexane was added to the mixture, filtered and the solvent removed. The crude product was purified by chromatography on a silica gel column, using dichloromethane as the eluent.

4.3.1. 1,4-Di(*o*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (4). Following the general method, three isomers were separated as yellow oils: (1*Z*,3*Z*)-1,4-di(*o*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**4a**), 35 mg (22%); (1*Z*,3*E*)-1,4-di(*o*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**4b**), 70 mg (40%); (1*E*,3*E*)-1,4-di(*o*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**4c**), 55 mg (34%).

(1Z,3Z)-1,4-Di(o-N,N-dimethylaminophenyl)-1,3-butadiene (**4a**). IR (film, cm^{-1}): 2800, 1600, 1500, 770, 700. ^1H NMR ($CDCl_3$): δ 7.56–7.52 (m, 2H), 7.26–7.17 (m, 2H), 7.07–6.99 (m, 4H), 6.70–6.52 (m, 4H), 2.81 (s, 12H). EM (70 eV): 292 (M^+, 100), 277 (12), 248 (14), 233 (3), 172 (24), 158 (29), 145 (48). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 82.01, H 8.42, N 9.62.

(1Z,3E)-1,4-Di(o-N,N-dimethylaminophenyl)-1,3-butadiene (**4b**). IR (film, cm^{-1}): 2800, 1600, 1500, 960, 770, 700. ^1H NMR ($CDCl_3$): δ 7.73–7.64 (m, 2H), 7.55–7.42 (m, 2H), 6.94–6.73 (m, 4H), 6.63–6.45 (m, 4H), 2.78 (s, 12H). EM (70 eV): 292 (M^+, 100), 277 (18), 248 (9), 233 (10), 172 (13), 158 (41), 145 (58). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 82.41, H 8.30, N 9.42.

(1E,3E)-1,4-Di(o-N,N-dimethylaminophenyl)-1,3-butadiene (**4c**). UV–vis (CH_2Cl_2), λ_{max} (nm): 377 (ε, 49,500). Fluorescence (CH_2Cl_2), λ_{max} (nm): 465 ($\phi=0.25$). IR (film, cm^{-1}): 2800, 1600, 1500, 960, 770. ^1H NMR ($CDCl_3$): δ 7.49 (dd, 2H, $J=8.0$, 2.0 Hz), 7.28–7.20 (m, 2H), 7.05–6.97 (m, 4H), 6.70–6.52 (m, 4H), 2.72 (s, 12H). EM (70 eV): 292 (M^+, 100), 277 (12), 248 (15), 233 (9), 172 (25), 158 (45), 145 (41). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 82.38, H 8.02, N 9.34.

4.3.2. 1,4-Di(*m*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (5). Following the general method, were separated two isomers: (1*Z*,3*E*)-1,4-di(*m*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**5b**) as an oil 69 mg (43%); (1*E*,3*E*)-1,4-di(*m*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**5c**), as an oil 73 mg (45%).

(1Z,3E)-1,4-Di(m-N,N-dimethylaminophenyl)-1,3-butadiene (**5b**). IR (film, cm^{-1}): 2820, 1590, 1500, 990, 840, 775, 690. ^1H NMR ($CDCl_3$): δ 7.26–7.15 (m, 2H), 6.89–6.61 (m, 6H), 6.52–6.33 (m, 4H), 2.96 (s, 12H). EM (70 eV): 292 (M^+, 100), 277 (14), 248 (10), 233 (5), 172 (19), 158 (31), 145 (53). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 81.99, H 8.37, N 9.39.

(1E,3E)-1,4-Di(m-N,N-dimethylaminophenyl)-1,3-butadiene (**5c**). IR (film, cm^{-1}): 2820, 1590, 1500, 990, 840, 775. UV–vis (CH_2Cl_2), λ_{max} (nm): 283 (ε, 35,000), 316s (ε, 53,400), 327 (ε, 57,300), 342 (ε, 42,600). Fluorescence (CH_2Cl_2), λ_{max} (nm): 477 ($\phi=0.29$). ^1H NMR ($CDCl_3$): δ 7.26–7.15 (m, 2H), 6.95 (dd, 4H, $J=15.5$, -0.5 Hz), 6.89–6.61 (m, 6H), 3.00 (s, 12H). EM (70 eV): 292 (M^+, 100), 277 (10), 248 (5), 233 (8), 172 (24), 158 (39), 145 (41). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 81.92, H 8.45, N 9.75.

4.3.3. 1,4-Di(*p*-*N*,*N*-dimethylaminophenyl)1,3-butadiene (6a and 6b). Following the general method to the (*Z*/*E*)-2-chloro-1-(*p*-*N*,*N*-dimethylaminophenyl)ethene mixtures (*Z*/*E*, 1:1 or 4:1), two isomers were separated: (1*Z*,3*Z*)-1,4-di(*p*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**6a**), as a yellow solid, mp 231.7 °C by DSC, 3 mg (2%) or 6 mg (4%) (mixture 1:1 or 1:4, respectively); (1*Z*,3*E*)-1,4-di(*p*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (**6b**), yellow solid, mp 255–256 °C, 124 mg (77%) or 127 mg (79%) (mixture 1:1 or 1:4, respectively).

(1Z,3Z)-1,4-Di(p-N,N-dimethylaminophenyl)-1,3-butadiene (**6a**). UV–vis (CH_2Cl_2), λ_{max} (nm): 386 (ε, 104,200), 405 (ε, 82,400). Fluorescence (CH_2Cl_2), λ_{max} (nm): 438 ($\phi=0.32$). IR (KBr, cm^{-1}): 2910, 1605, 1510, 800, 710. ^1H NMR ($CDCl_3$): δ 7.32 (d, 4H, $J=8.3$ Hz), 6.74 (d, 4H, $J=8.3$ Hz), 6.73 (d, 2H, $J=7.5$ Hz), 6.55 (d, 2H, $J=7.5$ Hz), 2.97 (s, 12H). EM (70 eV): 292 (M^+, 100), 248 (9), 172 (23), 146 (34), 77 (3). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 82.47, H 8.33, N 9.41.

(1Z,3E)-1,4-Di(p-N,N-dimethylaminophenyl)-1,3-butadiene (**6b**). IR (KBr, cm^{-1}): 2950, 1605, 1510, 800, 710. ^1H NMR ($CDCl_3$): δ 7.32 (d, 4H, $J=8.3$ Hz), 6.81 (d, 4H, $J=8.3$ Hz), 6.80 (m, 2H), 6.53 (m, 2H), 2.98 (s, 12H). EM (70 eV): 292 (M^+, 100), 248 (10), 172 (30), 146 (28), 77 (2). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 82.40, H 8.39, N 9.50.

4.3.4. 1,4-Di(*p*-*N*,*N*-dimethylaminophenyl)1,3-butadiene (6c). Following the general method to (*E*)-2-chloro-1-(*p*-*N*,*N*-dimethylaminophenyl)ethene (**3**), 152 mg (95%) of the (1*E*,3*E*)-1,4-di(*p*-*N*,*N*-dimethylaminophenyl)1,3-butadiene (**6c**) was obtained as a yellow solid, mp 245–246 °C.

UV–vis (CH_2Cl_2), λ_{max} (nm): 388 (ε, 24,400), 405 (ε, 203,200). Fluorescence (CH_2Cl_2), λ_{max} (nm): 440 ($\phi=0.26$). IR (film, cm^{-1}): 2800, 1610, 1520, 990, 815. ^1H NMR ($CDCl_3$): δ 7.32 (dd, 4H, $J=8.8$, -0.1 Hz), 6.78 and 6.71 (dd, 4H, $J=15.5$, -0.1 Hz), 6.70 (dd, 4H, $J=8.8$, -0.1 Hz), 2.97 (s, 12H). EM (70 eV): 292 (M^+, 100), 277 (9), 248 (16), 202 (32), 172 (45), 158 (68), 77 (2). $C_{20}H_{24}N_2$ (292.42). Anal. Calcd: C 82.15, H 8.27, N 9.58. Found: C 82.23, H 8.19, N 9.69.

4.3.5. Stereospecific synthesis of (1*Z*,3*Z*)-1,4-di(*p*-*N*,*N*-dimethylaminophenyl)-1,3-butadiene (6a). To a solution of 1,4-di(*p*-*N*,*N*-dimethylaminophenyl)-1,3-butadiyne (**9**) (0.25 g, 0.867 mmol) in toluene (5 mL) was added deactivated palladium on barium sulfate (0.048 g) and quinoline (0.095 mL). Deactivation was carried out by previous treatment with an aqueous solution of lead acetate (7%) at 80 °C, for 45 min.

The mixture was treated with hydrogen at room pressure and temperature with stirring for 6 h. After, solvent was removed and the residual solid purified by silica gel column chromatography dichloromethane–hexane (3/2) giving the (1*Z*,3*Z*)-diene derivative **6a** (0.24 g, 96%) as a yellow solid (mp 231.7 °C, by DSC).

4.3.6. Preparation of *p*-(*N*,*N*-dimethylamino)phenylacetylene (8). To a solution of 2-chloro-1-(*p*-*N*,*N*-dimethylaminophenyl)ethene 200 mg (1.10 mmol) in dry THF (15 mL) was slowly added a solution of *n*-butyl lithium in hexane (2.0 mL, 1.6 M). The mixture was stirred for 3 h. Then, was hydrolysed with a saturated aqueous ammonium chloride solution and extracted with dichloromethane, dried with anhydrous $MgSO_4$. After, solvent was removed at reduced pressure and the residual brown solid was purified by silica gel column chromatography, using toluene as eluent. The acetylene derivative **8** was isolated as a yellow solid, mp 51–52 °C, 139 mg (86%).

IR (KBr, cm^{-1}): 3290, 2810, 2100, 1610, 1520, 1360, 820. ^1H NMR ($CDCl_3$): δ 7.37 (dd, 2H, $J=8.3$, -0.1 Hz), 6.62 (dd, 2H, $J=8.3$, -0.1 Hz), 2.97 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 150.2, 133.0 (2C), 115.5 (2C), 108.5, 84.8, 74.7, 39.9. EM (70 eV): 145 (M^+, 100), 144 (96), 129 (27), 115 (9), 101 (24), 77 (10). $C_{10}H_{11}N$ (145.20). Anal. Calcd: C 82.72, H 7.64, N 9.65. Found: C 82.63, H 7.44, N 9.73.

4.3.7. 1,4-Di(*p*-*N*,*N*-dimethylaminophenyl)-1,3-butadiyne (9) by homocoupling of compound 8. A solution of cuprous chloride (0.037 g) in pyridine and the acetylene **8** (0.53 g, 3.7 mmol), under an oxygen atmosphere. The mixture was stirred at room temperature for 1 h. After, pyridine was removed at reduced pressure and hydrolysed with an aqueous solution (50 mL) of ammonium chloride (5 g), and potassium cyanide (1.25 g), and extracted with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate and after filtration, the solvent was evaporated giving 1,4-di(*p*-*N*,*N*-dimethylaminophenyl)-1,3-butadiyne (**9**), which was purified by flash silica gel column chromatography giving a brown solid 0.512 g, 96% mp 235–238 °C.

UV–vis (CH_2Cl_2), λ_{max} (nm): 351 (ε, 113,000), 378 (ε, 97,600). Fluorescence (CH_2Cl_2), λ_{max} (nm): 428 ($\phi=8.3\times10^{-4}$). IR (KBr, cm^{-1}): 2930, 2120, 1600, 1505, 1350, 810. ^1H NMR ($CDCl_3$): δ 7.40 (d, 4H, $J=8.2$ Hz), 6.63 (d, 4H, $J=8.2$ Hz), 2.98 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 150.2, 133.5 (2C), 111.6 (2C), 108.4, 82.2, 72.5, 39.9. EM (70 eV): 288 (M^+, 100), 272 (16), 144 (13). $C_{20}H_{20}N_2$ (288.39). Anal. Calcd: C 83.30, H 6.99, N 9.71. Found: C 83.09, H 6.63, N 9.66.

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Synthesis, NMR characterization and ion binding properties of 1,3-bridged *p-tert*-butyldihomooxacalix[4]crown-6 bearing pyridyl pendant groups

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Abstract—1,3-Di(2-pyridylmethoxy)-*p-tert*-butyldihomooxacalix[4]arene-crown-6 (**2**) was synthesized for the first time. **2** was isolated in a cone conformation in solution at room temperature, as established by NMR spectroscopy (^{1}H, ^{13}C and NOESY). Complete assignment of both proton and carbon NMR spectra was achieved by a combination of COSY, HSQC and HMBC experiments. The binding properties of ligand **2** towards alkali, alkaline earth, transition and heavy metal cations have been assessed by phase transfer and proton NMR titration experiments. The results are compared to those obtained with other dihomooxacalix[4]arene-crowns-6 and closely-related calix[4]arene-crown derivatives. **2** shows a preference for the soft heavy metal cations (except for Cd^{2+}), with a very strong affinity for Ag^+. Some transition metal cations are also well extracted. **2** forms 1:1 complexes with K^+, Ca^{2+} and Ag^+, and ^{1}H NMR titrations indicate that they should be encapsulated into the cavity defined by the crown ether unit and by the two pyridyl pendant arms. A 1:2 (ML_2) complex is formed with Zn^{2+} and two species, probably 1:1 and 1:2 complexes, are obtained with Pb^{2+}.

1. Introduction

Calixarenes[1–3] are an extremely versatile class of macrocyclic receptors, able to bind and transport selectively ions and neutral molecules, and to serve as building blocks for the design of more elaborate structures. The parent compounds are readily available and can be further lower rim functionalised into a large variety of derivatives.

In particular, the calixcrowns,[4] where a poly(oxyethylene) chain links two phenolic oxygens of the calixarene framework, have been widely investigated since their first synthesis in 1983.[5] Calixcrowns have shown remarkable ionophoric properties towards, mainly, alkali metal cations. They exhibit highly selective metal ion recognition, which depends on the crown size, on the macrocyclic conformation (especially for calix[4]arene derivatives) and on the substituents at the upper and lower rims. It has been shown that calix[4]-crowns-4 show a preference for Na^+, while calix[4]-crowns-5 and -crowns-6 are selective for K^+ and Cs^+ cations, respectively. Thus, the design and synthesis of these molecules have been extensively developed in the last few years.

Among these compounds, some calix[4][6–9] and calix[5]-crowns[10,11] bearing pyridyl pendant groups at the lower rim have been synthesised, which combine within the same molecule two potential binding sites with hard and soft character: a crown ether moiety and *N*-heteroaromatic rings, respectively. Therefore, these compounds are potential receptors for a large variety of cations, including alkali, alkaline earth, transition and heavy metal ions. This kind of molecular association has already been successfully studied with pyridine-armed diaza-crown ethers.[12]

Following our studies on metal cation binding and transport properties of *p-tert*-butyl dihomooxacalix[4]arene derivatives containing the carbonyl group at the lower rim,[13–16] we have extended these studies to dihomooxacalix[4]-crowns,[17,18] as well. This paper presents the synthesis, the NMR conformational analysis and the binding properties towards alkali, alkaline earth, transition and heavy metal cations of the 1,3-di(2-pyridylmethoxy)-*p-tert*-butyl-dihomooxacalix[4]arene-crown-6 (**2**). These properties have been assessed by extraction studies of metal picrates

Keywords: Calixcrowns; Conformational analysis; Metal cations; Extraction; ^{1}H NMR titration.
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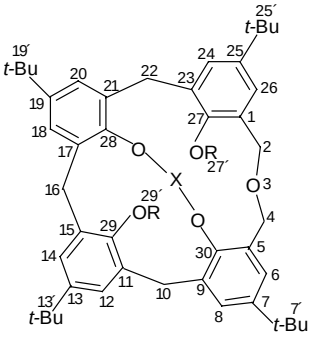
from an aqueous solution into dichloromethane and by proton NMR titration experiments. The results are discussed in the light of those obtained with other dihomooxacalix[4]-arene-crowns-6 and also with closely-related calix[4]arene-crown derivatives.



X = $(CH_2CH_2O)_4CH_2CH_2$

1 R = H

2 R = CH_2–Py

3 R = CH_3

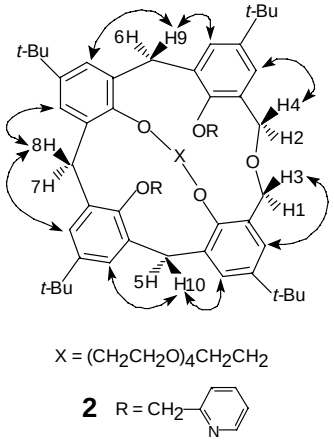
2. Results and discussion

2.1. Synthesis and NMR characterization

Calixcrown **2** was synthesized by the reaction of *p-tert*-butyldihomooxacalix[4]arene-crown-6 (**1**)[17] with 2-(chloromethyl)pyridine hydrochloride and NaH in dry DMF at 65 °C for 48 h. Proton, carbon-13, COSY, NOESY, HSQC and HMBC experiments were carried out in chloroform at room temperature to establish its structure and conformation.

The complete absence of symmetry in compound **2** is reflected by its proton and carbon NMR spectra. The ^1H NMR spectrum displays four singlets for the *tert*-butyl groups, five AB quartets for the CH_2 bridge protons, a complex multiplet for the polyether chain protons and four pairs of doublets for the aromatic protons. In addition, the OCH_2Py groups exhibit one AB quartet and one pseudo singlet for the CH_2 protons and only four of the eight expected multiplets, due to overlapping of some signals, for the heteroaromatic protons.

Due to overlapping of signals in the ^{13}C NMR spectrum, fewer lines than expected were obtained. Thus, this spectrum shows a pattern containing 33 of the 34 expected downfield resonances arising from the aromatic carbon atoms, 12 of the 14 expected midfield resonances arising from the methylene carbon atoms of the OCH_2Py and CH_2OCH_2 groups and crown moiety, and 11 upfield resonances arising from the quaternary carbon atoms $C(CH_3)$ (four lines), the methyl carbon atoms of the *tert*-butyl groups $C(CH_3)$ (four lines) and the methylene carbon atoms $ArCH_2Ar$ (three lines). All resonances were assigned by DEPT experiments. The three pertinent $ArCH_2Ar$ resonances appear in the range 29.5–30.8 ppm, indicating a cone conformation[19] for calixcrown **2**. Also the resonances of the OCH_2Py groups appear at $\approx$77.7 ppm, as observed for other pyridyl dihomooxa[20] and calix[4]arene[21] derivatives in the cone conformation. This conformation was further confirmed by proton–proton correlations observed in a NOESY spectrum. The more relevant NOE enhancements are shown in Figure 1. However, this conformation should be a distorted cone conformation, since the difference in the chemical shifts between the axial and equatorial protons of the $ArCH_2Ar$ bridges is larger than 0.9 ppm[22] ($\Delta\delta \geq 1.2$). Moreover, the peaks due to the *tert*-butyl and aromatic protons appear in a very large range (0.56–1.36 and 6.15–7.27 ppm, respectively), suggesting a less regular structure. A similar situation was found for the analogue di(2-pyridylmethoxy)-*p-tert*-butylcalix[4]arene-crown-5 derivative.[7]



X = $(CH_2CH_2O)_4CH_2CH_2$

2 R = CH_2–Py

Figure 1. Relevant NOE enhancements used to confirm the cone conformation in calixcrown **2**.

The assignment for both proton and carbon spectra (Table 1) was obtained from cross-peak correlations in a COSY spectrum and by the analysis of a HSQC spectrum, which correlates directly bonded ^1H and ^{13}C

Table 1. Chemical shifts (δ, ppm) of protons and carbons of calixcrown **2**

Atom	δ_C	δ_H (eq), (ax)
2	68.8	4.58; 4.66
4	68.4	4.66; 4.94
10	29.5	3.18; 4.48
16	30.8	3.23; 4.43
22	30.2	3.21; 4.43
6	126.6	7.26
8	126.7	7.18
12	124.6	6.90
14	125.2	6.80
18	123.7	7.26
20	127.2	7.12
24	125.3	6.15
26	124.3	6.87
7′	31.7	1.30
13′	31.18	1.05
19′	31.6	1.36
25′	31.24	0.56
27	151.6	—
28	153.5	—
29	151.3	—
30	152.2	—
27′	77.0	4.74; 4.95
29′	78.5	4.89

nuclei. Identification of four pertinent quaternary carbon atoms (C27, C28, C29 and C30) was achieved by a HMBC spectrum, that correlates protons and carbons two and three bonds away. Thus, it was possible to confirm that the *t*-Bu and aromatic protons resonate at higher fields are on the aryl rings bearing the pyridyl substituents, and those resonate at lower fields are on the rings carrying the polyether chain.

2.2. Extraction studies

The ionophoric properties of dihomooxa calixcrown **2** towards alkali, alkaline earth, transition and heavy metal cations were first evaluated by the standard picrate extraction method.[23] The results, expressed as a percentage of cation extracted (%*E*), are reported in Tables 2 and 3. The corresponding values for calixcrowns **1** and **3** are included for comparison.

The data reveal that calixcrown **2** is a reasonably good phase transfer agent for the alkali cations (%*E* ranges from 22 to 34), displaying a slight preference for Cs^+(34%). This cation is usually preferred by the calix[4]-crown-6 derivatives. Within the alkaline earth cations, compound **2** is a weak extractant, showing a plateau selectivity from Mg^{2+} to Ba^{2+} with almost no discrimination among the four cations of the series (%*E* ranges from 14 to 17).

The comparison with the unsubstituted calixcrown **1** shows that ligand **2** is a much stronger extractant for both kinds of cations, especially for the alkali ones. The larger size of the pyridyl groups and the possibility of acting cooperatively with the crown ether moiety on cation binding, may account for this behaviour of **2**. When the comparison is made with calixcrown **3** a similar situation is observed for the alkaline earth and the smaller alkali cations. However, this derivative exhibits slightly higher extraction percentages for the larger alkali cations Rb^+ and Cs^+. This can be due to its partial cone conformation.[18] The binding efficiency of this type of compounds is strongly conformationally dependent. Among calix[4]-crowns-5 and crowns-6, the partial cone conformation is preferred over cone conformation.[7,24,25] The former conformation is less polar and less solvated than the cone,[25] and the bound cations can interact not only with the crown ether moiety but also with one rotated aromatic nucleus (cation/π interaction) of the partial cone conformation.[24]

A comparison with pyridino derivative analogues of the calix[4]-crown-6 and calix[5]-crown-6 is not possible since, to our knowledge, no extraction studies with these compounds exist in the literature. Extraction studies toward a variety of metal picrates were done with the monopyridyl of the 1,2-bridged *p-tert*-butylcalix[4]-crown-6 (**1Py[4]-C6**) in the cone conformation.[6] However, a direct comparison with ligand **2** can not be made due to the superior efficiency of 1,3-bridged calix[4]crowns as ionophores. But, if we compare ligand **2** with dipyridyl derivative of the *p-tert*-butylcalix[4]-crown-5 (**2Py[4]-C5**) also in the cone conformation,[7] we observe that **2** is a better extractant than **2Py[4]-C5**, except for K^+ (Table 2). The comparison between these two derivatives allows the evaluation of the effect of two control factors of selectivity in cation binding: the crown size and the conformational flexibility of the calixarene. While **2Py[4]-C5** shows a peak selectivity for K^+, dihomooxa derivative **2**, with a larger macrocyclic cavity and crown size, displays a plateau selectivity with a slight preference for Cs^+.

For the transition metal cations, Lewis acids of intermediate nature (except Mn^{2+}, that is considered hard),[26] calixcrown **2** ranges from being a weak to an efficient extractant, mainly for Fe^{2+}(43%) and Cu^{2+}(37%). The highest percentages are shown towards the soft heavy metal cations (except for Cd^{2+}). **2** displays a very high extraction level for Ag^+(87%) and a good level for Hg^{2+}(44%). Towards Pb^{2+}, of intermediate nature,[26] ligand **2** also displays a significant preference (37%). The comparison of these results with those obtained with calixcrown derivatives **1**

Table 2. Percentage extraction of alkali and alkaline earth metal picrates into CH_2Cl_2 at 25 °C[a]

	Li^+	Na^+	K^+	Rb^+	Cs^+	Mg^{2+}	Ca^{2+}	Sr^{2+}	Ba^{2+}
Ionic radius (Å)[b]	0.78	0.98	1.33	1.49	1.65	0.78	1.06	1.27	1.43
1[c]	4.4	4.4	3.6	5.8	6.1	4.8	4.8	3.7	5.8
2	22	29	32	29	34	15	17	14	14
3[c]	5.4	12	22	36	40	1.0	3.0	3.3	2.5
2Py[4]-C5[d]	3.3	8.5	37.5	7.2	3.0	—	—	—	—

[a] Values with uncertainties less than 5%.
[b] Goldschmidt, V. M. *Skrifter Norske Videnskaps-Akad. Oslo, I, Mat.-Naturv. Kl*, **1926**; data quoted in Marcus, I. *Ion Properties*, Marcel Dekker: New York, 1997; pp 46–47.
[c] Data taken from Ref. 18.
[d] Data taken from Ref. 7.

Table 3. Percentage extraction of transition and heavy metal picrates into CH_2Cl_2 at 25 °C[a]

	Mn^{2+}	Fe^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Ag^+	Cd^{2+}	Hg^{2+}	Pb^{2+}
Ionic radius (Å)[b]	0.83	0.78	0.75	0.69	0.73	0.75	1.15	0.95	1.02	1.18
1	5.8	1.7	1.4	2.5	2.2	2.2	1.5	1.5	6.5	2.5
2	14	43	15	13	37	17	87	11	44	37
3	7.9	1.3	1.6	3.2	9.6	4.6	18	3.2	9.1	7.3

[a] Values with uncertainties less than 5%.
[b] Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr., Sect. B* **1969**, *25*, 925; **1970**, *26*, 1046; data quoted in Marcus, I. *Ion Properties*, Marcel Dekker: New York, 1997; pp 46–47.

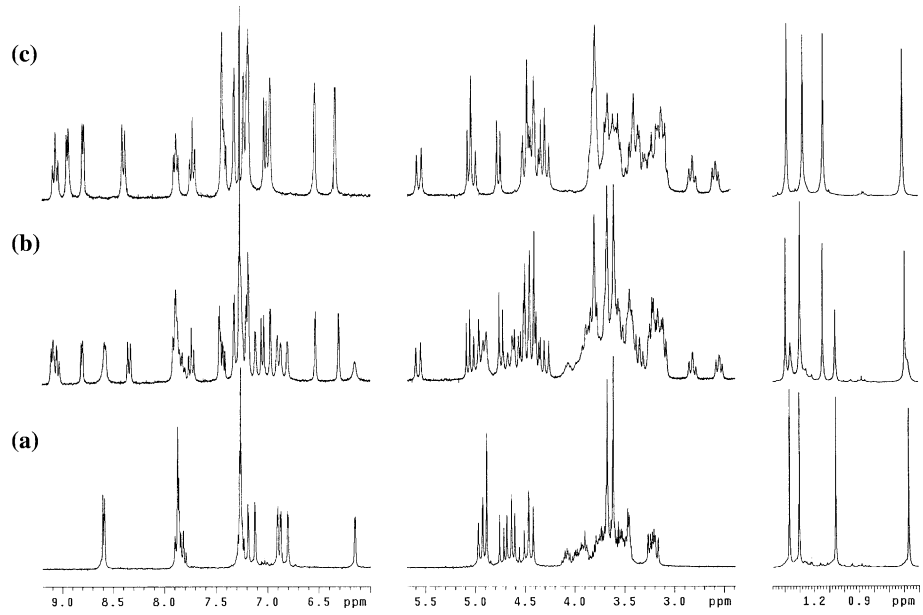


Figure 2. 300 MHz. ^{1}H NMR spectra of **2** in $CDCl_3$ at 22 °C. (a) Free ligand, (b) upon addition of 0.25 and (c) 0.5 equiv of Zn triflate 300MHz.

and **3** clearly shows the higher extraction ability of ligand **2** towards transition and heavy metal cations. The softer character of the nitrogen donor atoms may explain this behaviour. Interestingly, among the nineteen cations studied in this work, the six exhibiting the highest extraction percentages are soft Lewis acids or of intermediate nature ($Ag^+ \gg Hg^{2+} \approx Fe^{2+} > Pb^{2+} = Cu^{2+} > Cs^+$).

2.3. Proton NMR studies

To obtain further information on the cation binding behaviour of calixcrown **2**, namely concerning the binding sites, ^{1}H NMR studies were performed. The cations studied were K^+, Ca^{2+}, Zn^{2+}, Ag^+, Hg^{2+} and Pb^{2+}. Variable amounts of the salts were added to **2** and the proton spectra recorded after each addition.

Different situations were found after the addition of the salts to ligand **2**.

Titrations of calixcrown **2** with K^+ and Ca^{2+} salts initially induce broadening of the signals until the [salt]/[ligand] ratio reaches the unity value, when the signals become sharp. This indicates a fast exchange rate between the two species on the NMR time scale, at room temperature, and consequently a weak affinity of ligand **2** towards these two cations. This is in agreement with the extraction results, mainly in the case of Ca^{2+}. The ^{1}H NMR titration experiments suggest a 1:1 metal-to-ligand stoichiometry, since all signals remain unchanged after subsequent additions of the salts. In contrast, the titration of **2** with Ag^+ cation shows that with [salt]/[ligand] ratios lower than 1 both signals of the complexed and uncomplexed ligand are present in the spectra, indicating that on the NMR time scale the exchange rate between the two species is slow, at room temperature. This reflects the high binding ability of ligand **2** towards Ag^+, as previously observed in extraction. Upon reaching a 1:1 ratio, all signals for the free ligand disappear and those of the complexed ligand remain unaltered after subsequent additions of the salts, indicating a 1:1 metal-to-ligand stoichiometry. In the case of Zn^{2+}, the addition of 0.25 equiv of the salt shows that both signals of the complexed and uncomplexed ligand are present in the spectrum with the same intensity (Fig. 2). Upon the addition of 0.5 equiv all the signals for the free ligand disappear and those of the complexed ligand remain unchanged after subsequent additions of the salt. This indicates a 1:2 metal-to-ligand stoichiometry. In order to confirm this stoichiometry a Job plot based on ^{1}H NMR data between calixcrown **2** and Zn^{2+} cation was carried out. As shown in Figure 3, the curve maximum appears between 0.6 and 0.7 mol fraction of **2**, clearly indicating that Zn^{2+} forms a ML_2 complex with ligand **2**. A complex between Zn^{2+} and **1Py[4]-C6** was obtained some time ago,[27] but with a 1:1 stoichiometry.

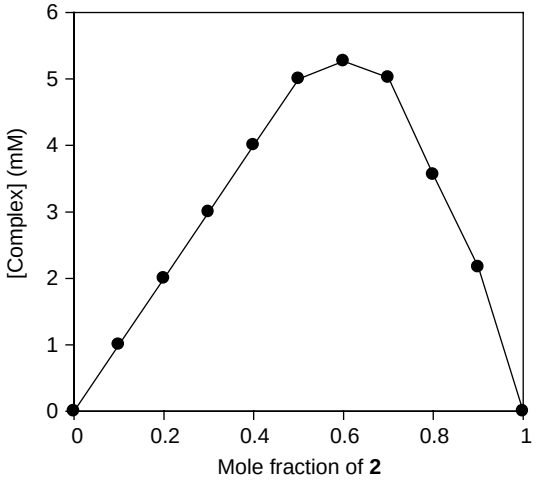


Figure 3. Job's plot based on ^{1}H NMR data for the system **2**+Zn^{2+}; total concentration 1×10^{-2} M in $CDCl_3$–CD_3OD (9/1, v/v).

Table 4. Relevant proton chemical shifts (δ, ppm) of ligand **2** and its metal complexes

	t-Bu	Crown	OCH_2Py	ArH	PyH					
					3	4	5	6	3′	4′	5′	6′
2	0.56, 1.05, 1.30, 1.36	3.43–4.13	4.66, 4.89,[a] 4.95	6.15, 6.80, 6.87, 6.90, 7.12, 7.18, 7.26, 7.27	7.87	7.81	7.25	8.59	7.87	7.87	7.25	8.59
2+K^+ (ML)	0.92, 1.18, 1.19, 1.25	3.54–4.11	5.03, 5.07, 5.16, 5.38	6.63, 6.87, 6.99, 7.13, 7.15, 7.17, 7.30, 7.31	7.20	7.70	7.33	8.68	7.35	7.83	7.43	8.91
2+Ca^{2+} (ML)	0.83, 1.10, 1.21, 1.26	3.72–4.31	4.96, 5.15, 5.46, 5.50	6.70, 6.74, 7.04, 7.13, 7.14, 7.21, 7.21, 7.29	7.08	7.75	7.51	8.84	7.25	7.86	7.51	9.08
2+Ag^+ (ML)	0.79, 0.87, 1.30, 1.36	3.14–3.93, 4.11–4.30	5.43, 5.59, 5.63, 5.73	6.63, 6.63, 6.65, 6.77, 7.12, 7.17, 7.21, 7.22	6.94	7.81	7.56	9.10	7.71	7.91	7.70	9.24
2+Zn^{2+} (ML_2)	0.61, 1.14, 1.28, 1.39	2.59, 2.82, 3.08–3.89	4.39, 4.51, 5.02, 5.57	6.34, 6.54, 6.98, 7.19, 7.21, 7.24, 7.33, 7.45	7.03	7.73	7.44	8.80	8.40	7.89	9.07	8.95
2+Pb^{2+} (ML) A	1.08, 1.15, 1.22, 1.24	3.45–4.22	5.17, 5.76,[a] 6.26	6.79, 7.06, 7.30, 7.36, 7.36, 7.40, 7.40, 7.45	7.24	7.84	7.64	9.01	7.74	8.14	[b]	9.73
2+Pb^{2+} (ML_2) B	0.64, 1.15, 1.27, 1.39	2.65, 2.84,b	[b]	6.38, 6.58, 6.98, 7.19, 7.20, 7.23, 7.33, 7.42	7.16	[b]	7.52	8.80	8.37	7.92	9.01	8.91

[a] Singlet corresponding to two protons.
[b] Not possible to assign.

With Pb^{2+} a quite different situation was found. Three sets of sharp signals with approximately the same intensity, corresponding to the free ligand and to two other complexed species are present in the spectra from the addition of the first aliquot (0.5 equiv) of the salt. With 1 equiv all the peaks of the free ligand disappear, and further additions produce an increase of one of the complexes relative to the other. In this case, a Job plot was not possible to perform in order to determine the stoichiometry of these complexes, since a large number of peaks is present in every region of the proton spectrum and, therefore, no reliable integration of the signals was feasible. However, from a qualitative inspection of the spectra it is possible to verify that the chemical shifts of the minor complex (B) are identical to those of Zn^{2+} complex (Table 4), whereas the δ of the major complex (A) are similar to those of the other complexes, and that the intensity of B peaks decreases as the addition of the salt proceeds. Thus, it seems reasonable to assign the 1:1 stoichiometry for complex A and the 1:2 (ML_2) for complex B. A similar situation has already been observed by us before.[28]

Titration of calixcrown **2** with Hg^{2+} required a slightly different procedure, since the solubility of $Hg(ClO_4)_2$ in MeOH is very low. Thus, it was necessary to decrease the concentration of both ligand and salt (see Section 4). Upon the addition of 1 equiv of Hg^{2+} salt three sets of peaks with approximately the same intensity and apparently corresponding to three complexed species, are present in the spectra. As the addition of the salt proceeds (up to 4 equiv), the intensity of two of the three sets of signals decreases, but no further conclusions could be drawn due to the great complexity of the spectra.

Proton NMR data of the free and complexed ligand **2** are collected in Table 4. The complete interpretation of the spectra required additional COSY experiments. In the case of Pb^{2+} spectrum full proton assignment was not possible due to the presence of both complexed species. Nevertheless, the relevant protons of complexes A and B could be assigned. Complexation of the cations affects all the proton chemical shifts in the ligand. The largest downfield variations are observed for the methylene and heteroaromatic H6, H6′ protons of the OCH_2Py groups and the aromatic protons of the alkylated rings. The heteroaromatic H3, H3′ protons, the oxygen bridge equatorial methylene protons (CH_2OCH_2) and the bridging axial methylene protons ($ArCH_2Ar$), show the largest upfield shifts. Similar observations have been made for closely-related calix[4]-crown derivatives with K^+[8] and also for a homocalix[4]-arene[29] and a hexatrioxacalix[3]arene with Ag^+.[30]

A closer examination of the spectral changes upon complexation indicates very small variations ($\Delta\delta \approx 0.10$) for the three downfield *tert*-butyl groups. However, the fourth *t*-Bu group experiences considerable downfield shift variations, as those observed for Pb^{2+} (complex A) and K^+ ($\Delta\delta = 0.52$ and 0.36, respectively). Thus, upon complexation the difference in the chemical shifts among the four *t*-Bu groups decreases significantly. Identical situations were observed among the eight aromatic protons, with $\Delta\delta$ being after complexation approximately half of the

value of the free ligand. This suggests that upon complexation ligand **2** should adopt a more symmetrical conformation. Similar results were obtained for a polyether calix[4]arene derivative, analogue of a calixcrown, and K^+ cation.[31] Zn^{2+} cation behaves differently upon complexation with calixcrown **2**, according to its different metal-to-ligand stoichiometry. This cation shows practically the same $\Delta\delta$ values as before complexation (0.78 and 1.11 ppm for *t*-Bu and aromatic protons, respectively).

A systematic observation of the data reveals that the upfield shift variations experienced by the axial methylene protons of the CH_2 bridges follow the order H5<H6<H7 (Fig. 1). The axial methylene proton (H7) opposite to the bridging oxygen atom exhibits the largest upfield shifts, with the highest value recorded for Ca^{2+} ($\Delta\delta=0.61$). Similar observations have been made by us before for dihomooxacalix[4]arene derivatives containing the carbonyl group at the lower rim.[16,28] As observed for other calixarene derivatives, the variation in chemical shift experienced by the equatorial methylene protons ($ArCH_2Ar$) is downfield and much smaller than that of the axial protons, but the CH_2OCH_2 resonances behave differently, as reported before.[15,16,28,30] The axial and equatorial methylene protons of the oxygen bridge move upfield and the equatorial protons experience larger shift variations than the axial ones. These results suggest that the oxygen bridge conformation changes significantly upon complexation, with the equatorial protons undergoing a higher shielding effect. Concerning the heteroaromatic protons, their chemical shift variations are not the same in both groups. 3-PyH and 3′-PyH protons show similar upfield shifts for K^+ and Ca^{2+} ($\Delta\delta=0.79$ and 0.62, respectively, for Ca^{2+}), but very different for Ag^+ and Pb^{2+} in complex A ($\Delta\delta=0.93$ and 0.16, respectively, for Ag^+). In the case of Zn^{2+} this difference is even more pronounced, with 3-PyH undergoing an upfield shift of 0.84 ppm and 3′-PyH a downfield shift of 0.53 ppm. For 6-PyH and 6′-PyH a similar trend is observed, with the latter proton experiencing a higher downfield shift than the former. Complexation with Pb^{2+} (complex A) shows the highest difference ($\Delta\delta=1.13$ and 0.42, respectively). It is also to point out the very large downfield shift experienced by 5′-PyH proton ($\Delta\delta=1.82$) for Zn^{2+} complexation comparing to that of 5-PyH ($\Delta\delta=0.19$), as well as to those of both protons for the complexation of the other cations.

The deshielding effect observed for the aromatic protons indicates the involvement of the phenolic oxygens in complexation, as reported previously.[32] The largest shift changes shown by the methylene, H6, H6′, H3 and H3′ protons of the OCH_2Py groups indicate the participation of the pyridine nitrogen atoms in cation complexation. Therefore, this suggests that for 1:1 complexes all the cations must be inside the cavity defined by the crown ether unit and by the two pyridyl pendant arms. The cations should be bound into that cavity through metal–oxygen and metal–nitrogen interactions, in a geometrical arrangement that should depend on the nature of the cations.

In the case of Zn^{2+}, the unexpected 1:2 metal-to-ligand stoichiometry may be interpreted in terms of the too large size of the ionophoric cavity to accommodate that small cation. After complexation of Zn^{2+} the ionophoric cavity of **2** remains almost unchanged, as already pointed out by the invariance of *t*-Bu and aromatic protons. Moreover, the crown moiety protons undergo, in general, moderate downfield shifts, whereas complexation with Zn^{2+} induces a large upfield shift variation, mainly of two protons resonating at 2.59 and 2.82 ppm (Fig. 2). This clearly indicates a more effective coordination by the crown unit towards Zn^{2+} cation. Relative to the OCH_2Py groups, it seems that only one group from each calixcrown participates in complexation. Beyond the different behaviour observed by a set of heteroaromatic protons, also a CH_2 group shows an upfield variation (Table 4) contrary to all the others that undergo downfield shifts. Therefore, these facts suggest that Zn^{2+} cation is bound to some oxygen atoms of both crown ether units, placing the two ligands in an arrangement 'tail-to-tail', and also enveloped by one pyridine nitrogen atom from each calixarene.

Although comparable spectral changes had been observed for the complexation of the cations, ligand **2** showed some differences among them. The magnitude of the shift variations for protons adjacent to the donor atoms is higher for Pb^{2+} (complex A), followed by Ag^+ and Ca^{2+}. This preference of ligand **2** seems to be the result of the combination of three main factors affecting complexation: size, charge and nature of the cations. Thus, the different bound cations induce more or less marked conformational rearrangements on the ionophoric cavity of ligand **2**.

3. Conclusions

Dipyridylcalixcrown **2** was synthesized and obtained in a cone conformation in solution at room temperature. Extraction studies with metal picrates from an aqueous solution into CH_2Cl_2 have shown that, for the alkali and alkaline earth cations, dihomooxacalixcrown **2** is, in general, a better extractant than the other calixcrowns. However, **2** is a less selective ligand comparing with **2Py[4]-C5**, due to its larger macrocyclic cavity and crown sizes. Towards transition and heavy metal cations **2** is clearly the best phase transfer agent, displaying a strong affinity for soft metal cations as Ag^+ and Hg^{2+}, but also for some of intermediate nature as Fe^{2+}, Pb^{2+} and Cu^{2+} cations. The softer character of the nitrogen donor atoms may explain this behaviour. **2** forms 1:1 complexes with K^+, Ca^{2+} and Ag^+, and a 1:2 (ML_2) complex with Zn^{2+}. The structure for 1:1 complexes deduced from NMR experiments shows that the cations should be encapsulated into the cavity composed by the crown ether unit and the two pyridyl groups. For ML_2 complex, Zn^{2+} should be placed between the crown ether units of both ligands in an arrangement 'tail-to-tail', being also surrounded by one pyridyl group from each calixarene. In the case of Pb^{2+}, two complexes with a 1:1 and probably a 1:2 stoichiometries were obtained.

4. Experimental

4.1. Synthesis

All chemicals were reagent grade and were used without further purification. Melting points were measured on a

Stuart Scientific apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer and on a Varian Inova 300 spectrometer, with TMS as internal reference. The gradient version of the COSY spectrum was collected as 512×2 K complex points. The phase sensitive NOESY experiment was collected as 256×2 K complex points with a mixing time of 0.7 s, a delay of 1.5 s and 32 transients. Gradient versions of HSQC and HMBC experiments for connecting ^{1}H and ^{13}C were run with 32 scans for the former and 64 scans for the latter. In both cases a delay of 1.5 s was used. Elemental analysis was determined on a Fisons EA 1108 microanalyser.

4.1.1. 7,13,19,25-Tetra-*tert*-butyl-27,29-bis[(2-pyridylmethyl)oxy]-28,30-crown-6-2,3-dihomo-3-oxacalix[4]arene (2). A mixture of **1** (0.50 g, 0.568 mmol) and NaH (95%, 0.216 g, 8.55 mmol) in dry DMF (20 mL) was stirred and gently warmed under N_2 for 30 min. After cooling, 2-(chloromethyl)pyridine hydrochloride (0.56 g, 3.41 mmol) was added to the mixture and the reaction was then heated at 60–65 °C with stirring under N_2 for 48 h. Addition of MeOH (1 mL) and water (70 mL) to the cooled reaction mixture gave a white precipitate, which was recrystallized from *n*-heptane to afford 0.32 g (53%) of **2**: mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 0.56, 1.05, 1.30, 1.36 (4s, 36H, $C(CH_3)_3$), 3.18, 4.48 (ABq, 2H, $J=12.7$ Hz, $ArCH_2Ar$), 3.21, 4.43 (ABq, 2H, $J=14.1$ Hz, $ArCH_2Ar$), 3.23, 4.43 (ABq, 2H, $J=13.2$ Hz, $ArCH_2Ar$), 3.43–4.13 (m, 20H, crown), 4.58, 4.66 (ABq, 2H, $J=13.6$ Hz, CH_2OCH_2), 4.66, 4.94 (ABq, 2H, $J=13.6$ Hz, CH_2OCH_2), 4.74, 4.95 (ABq, 2H, $J=12.6$ Hz, OCH_2Py), 4.89 (s, 2H, OCH_2Py), 6.15, 6.80, 6.87, 6.90, 7.12, 7.18, 7.26, 7.27 (8d, 8H, ArH), 7.25 (m, 2H, 5-PyH and 5′-PyH), 7.81 (td, $J=7.7$, 1.7 Hz, 1H, 4′-PyH), 7.87 (m, 3H, 4-PyH, 3-PyH and 3′-PyH), 8.59 (m, 2H, 6-PyH and 6′-PyH); ^{13}C NMR ($CDCl_3$) δ 29.5, 30.2, 30.8 ($ArCH_2Ar$), 31.18, 31.24, 31.6, 31.7 ($C(CH_3)_3$), 33.8, 34.0, 34.2, 34.3 ($C(CH_3)_3$), 68.5, 68.9 (CH_2OCH_2), 69.4, 70.5, 70.7, 70.8, 70.9, 71.0, 71.5, 72.7 (crown), 77.0, 78.5 (OCH_2Py), 121.9, 122.66, 122.72, 123.2, 123.7, 124.3, 124.6, 125.2, 125.3, 126.6, 126.7, 127.2, 137.0, 137.1, 149.1 (ArH), 130.2, 132.4, 132.5, 132.6, 132.8, 134.0, 134.2, 135.4, 145.2, 145.4, 145.6, 145.7, 151.3, 151.6, 152.2, 153.5, 157.6, 157.7 (Ar). Anal. Calcd for $C_{67}H_{86}N_2O_9$: C, 75.67; H, 8.15; N, 2.63. Found: C, 75.69; H, 8.20; N, 2.63.

Dihomooxacalixcrowns **1**[17] and **3**[18] were synthesized in previous works.

4.2. Extraction studies

Equal volumes (5 mL) of aqueous solutions of metal picrates (2.5×10^{-4} M) and solutions of the calixarenes (2.5×10^{-4} M) in CH_2Cl_2 were vigorously shaken for 2 min, and then thermostated in a water bath with mechanical stirring at 25 °C overnight. After complete phase separation, the concentration of picrate ion in the aqueous phase was determined spectrophotometrically ($\lambda_{max}=354$ nm). For each cation–calixarene system the absorbance measurements were repeated, at least, four times. Blank experiments showed that no picrate extraction occurred in the absence of a calixarene. The details of metal picrate preparation have already been described.[13,15]

4.3. Proton NMR titration experiments

Several aliquots (up to 2–4 equiv) of the salt solutions (0.5 M) in CD_3OD were added to $CDCl_3$ solutions (1×10^{-2} M) of ligand **2** directly in the NMR tube. The salts used were KSCN, Ag and Zn triflates, Ca, Hg and Pb perchlorates. Due to the low solubility of Hg perchlorate in MeOH, it was necessary to decrease the concentration of the ligand (0.5×10^{-3} M) and of the salt (5×10^{-3} M). The spectra were recorded on a Varian Unity 300 Spectrometer after each addition of the salts. The temperature of the NMR probe was kept constant at 22 °C. Job's method was performed for calixcrown **2** and Zn triflate. The total concentration was maintained at 1×10^{-2} M in $CDCl_3$–CD_3OD (9/1, v/v).

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Synthesis of cyclic bis(3′-5′)diguanylic acid (*c*-di-GMP) analogs

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Abstract—This paper reports the synthesis of cyclic bis(3′-5′)diguanylic acid (*c*-di-GMP) analogs, including the monophosphorothioic acid of *c*-di-GMP (*c*-GpGps), cyclic bis(3′-5′)guanylic/adenylic acid (*c*-GpAp), and cyclic bis(3′-5′)guanylic/inosinic acid (*c*-GpIp). These compounds are expected to be important, both in elucidating the mechanism of bioactive *c*-di-GMP and in designing and creating new bioactive *c*-di-GMP-related artificial derivatives.

1. Introduction

Cyclic bis(3′-5′)diguanylic acid (*c*-di-GMP) has attracted great interest due to its various biological activities, including regulation of cellulose synthesis in the bacterium *Acetobacter xylinum*,[1,2] acceleration of DNA synthesis and retarding of cell division in Molt 4 cells,[3] elevation of CD4 receptor expression and cell cycle arrest in Jurkat cells,[4] inhibition of basal and growth factor-stimulated human colon cancer cell proliferation,[5] inhibition of *Staphylococcus aureus* cell–cell interactions and biofilm formation,[6] and reduction of the virulence of biofilm-forming *S. aureus* strains in a mouse model of mastitis infection.[7] Further, *c*-di-GMP is conceived to play an important role in regulating exopolysaccharide production, biofilm formation, and other phenotypes.[8] These attractive biological properties of *c*-di-GMP have prompted us to carry out a systematical investigation on the bioactivity of *c*-di-GMP related compounds, including derivatives with modified nucleoside bases, carbohydrates, or internucleotide bonds. This investigation may lead not only to the discovery of new bioactive compounds, but also to a determination of which function of *c*-di-GMP is involved in its various biological activities: that is, how *c*-di-GMP works on receptors in cells. Thus, we attempted the synthesis of various *c*-di-GMP analogs.[9] This paper describes the synthesis of the monophosphorothioic acid of *c*-di-GMP (*c*-GpGps) (**5**), cyclic bis(3′-5′)guanylic/adenylic acid (*c*-GpAp) (**9**), and cyclic bis(3′-5′)guanylic/inosinic acid (*c*-GpIp) (**13**).

2. Results and discussion

c-GpGps **5** was prepared via the procedure shown in Scheme 1. The nucleoside phosphoramidite **1**[10] was condensed with the 5′-*O*-free nucleoside 3′-phosphate **2**[10] using imidazolium perchlorate (IMP)[11] as a promoter in acetonitrile containing 3 Å molecular sieves (MS 3 Å)[12] (30 min). The resulting phosphite product was sulfurized with bis[3-(triethoxysilyl)propyl] tetrasulfide (TEST)[13] (30 min); then, the 5′-*O*-*p*,*p*′-dimethoxytrityl (DMTr) group was removed by treatment with a 20% dichloroacetic acid/dichloromethane solution (30 min) to give the nucleoside monophosphorothioate **3** in a 78% overall yield. Subsequently, the allyl group on the 3′-terminal phosphotriester moiety of **3** was removed by exposure to sodium iodide in refluxing acetone[14] (2 h), and the resulting linear dinucelotide 3′-phosphodiester was treated with a high-dilution mixture of 2,4,6-trisipropylbenzenesulfonyl chloride (TPSCl) (5 equiv) and *N*-methylimidazole (5 equiv) (36 h) in THF[15] to provide fully protected *c*-GpGps **4** in a 76% overall yield. Finally, deprotection was carried out using a 1:1 (v/v) mixture of concd aqueous ammonia and methanol at 50 °C (12 h) for dimethylformamidine (dmf) and cyanoethyl protecting groups, followed by $(C_2H_5)_3N\cdot 3HF$[16] for *tert*-butyldimethylsilyl (TBDMS) protecting groups (12 h) to afford the target compound **5**. The overall yield of this deprotection procedure was 64%.

Synthesis of *c*-GpAp (**9**) was achieved according to the strategy shown in Scheme 2, which is fundamentally identical to that for the synthesis of *c*-GpGps. Thus, condensation of the phosphoramidite **6**[17] and the 5′-*O*-free nucleoside 3′-phosphate **2** using IMP as a promoter in acetonitrile containing MS 3 Å (30 min) and subsequent oxidation with *tert*-butyl hydroperoxide (TBHP)[18] (30 min)

Keywords: Nucleotides; Phosphoramidites; Cyclization; *c*-Di-GMP.
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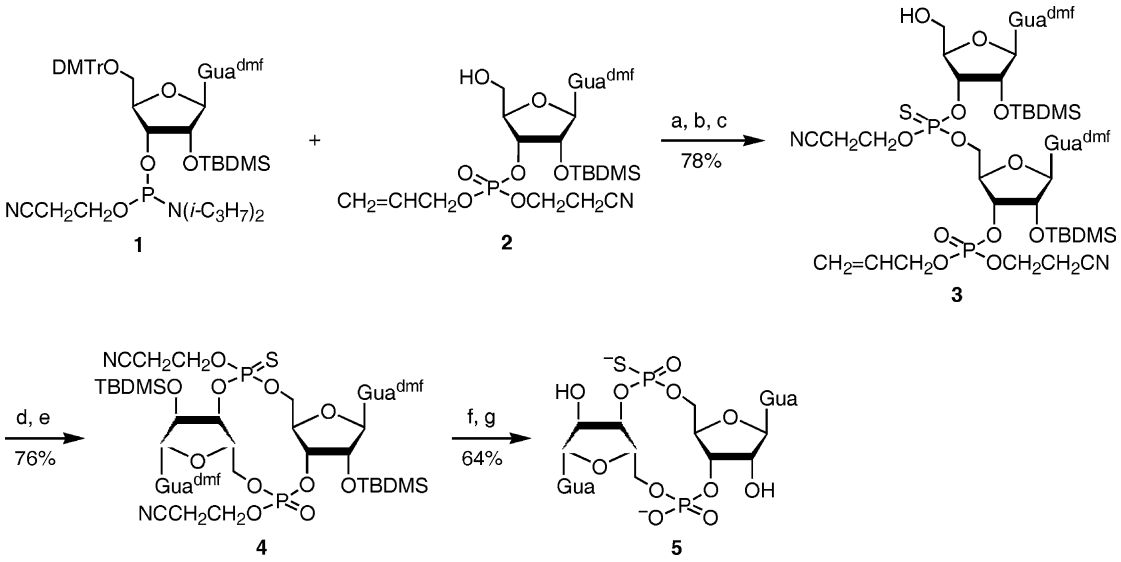
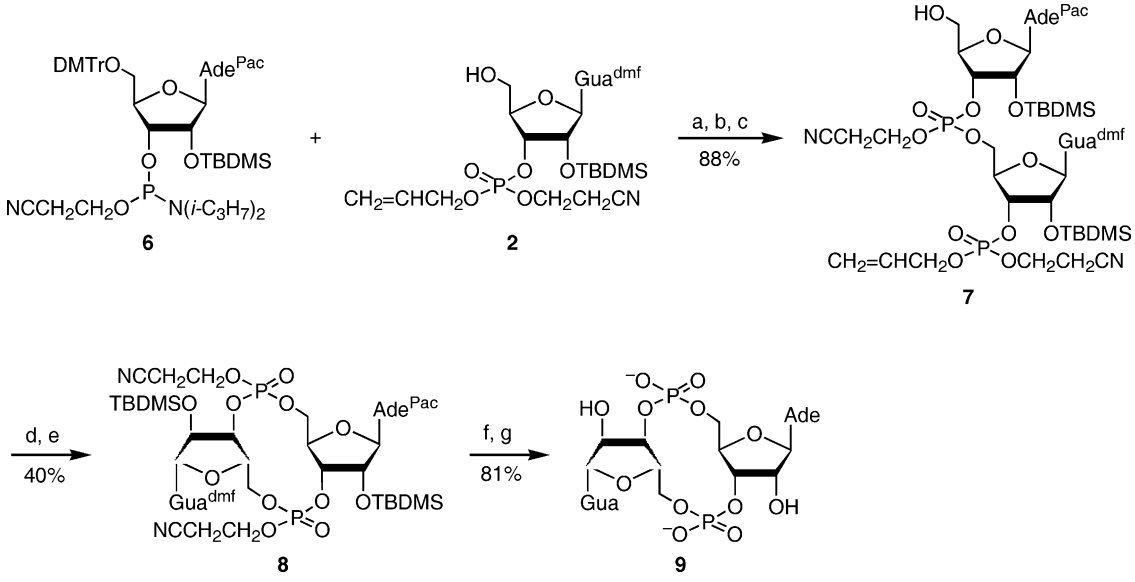


Scheme 1. Synthesis of *c*-GpGps (**5**): (a) IMP, MS 3 Å, CH_3CN, rt, 30 min; (b) TEST, rt, 30 min; (c) a 20% $Cl_2CHCOOH/CH_2Cl_2$ solution, rt, 30 min; (d) NaI, acetone, reflux, 2 h; (e) TPSCI, *N*-methylimidazole, THF, rt, 36 h; (f) concd aqueous NH_3–CH_3OH (1/1 v/v), 50 °C, 12 h; (g) $(C_2H_5)_3N\cdot 3HF$, rt, 12 h.

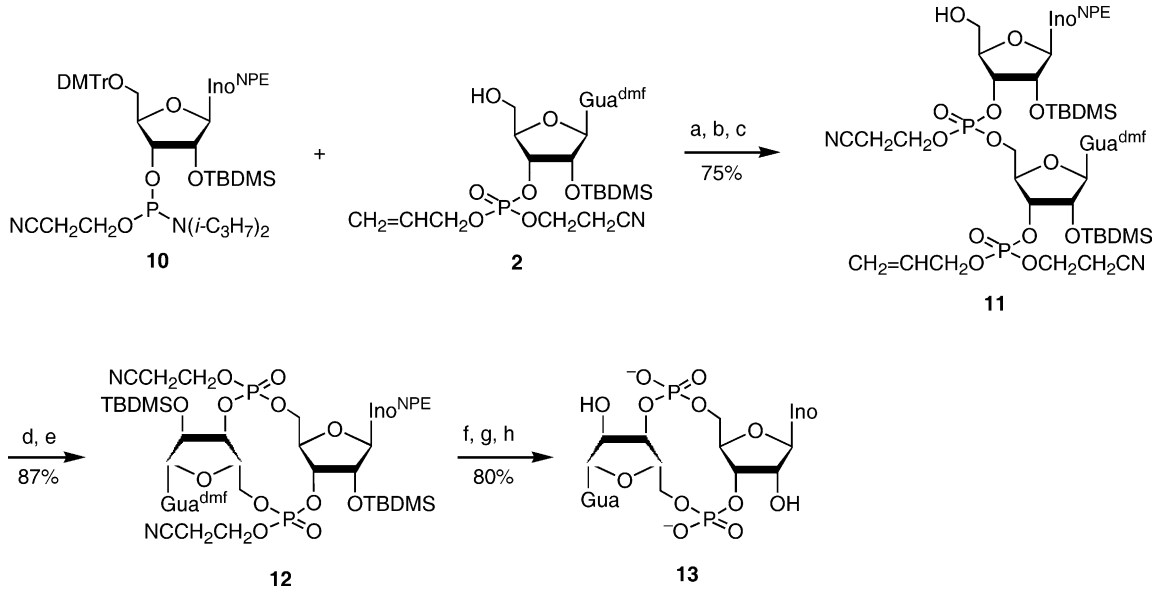
and detritylation using a 20% dichloroacetic acid solution in dichloromethane (20 min) furnished the dinucleotide **7** in an 88% overall yield. Then, **7** was converted to **8** in a 40% overall yield by removal of the allyl protector using sodium iodide in refluxing acetone followed by cyclization of the resulting product by treatment with TPSCl (5 equiv) in the presence of *N*-methylimidazole (5 equiv) in THF under high-dilution conditions. Finally, all protecting groups of **8** were removed by successive treatment with a 1:1 (v/v) mixture of concd aqueous ammonia and methanol (14 h) and with $(C_2H_5)_3N\cdot 3HF$ to produce the target compound **9** in an 81% overall yield.

c-GpIp (**13**) could be also prepared using **10**[19] as a starting material by a method essentially identical to that for the synthesis of the above-mentioned two analogs **5** and **9**. The synthetic route is shown in Scheme 3. In this process, 2-butanone peroxide (BPO)[20] was employed for oxidation of the dinucleoside phosphite intermediate obtained by condensation of **2** and **10** in the first step. Further, use of DBU (10 equiv) in pyridine (3 h)[21] was most effective for removal of cyanoethyl and *p*-nitrophenylethyl (NPE) protectors from the intermediate **12**. Yields of products were 75% for **11** from **2** and **10**, 87% for **11** from **12**, and 80% in for **13** from **12**, respectively.

The present synthesis of *c*-di-GMP analogs has a remarkable advantage over previously reported syntheses of related cyclic bis(3′-5′)dinucleic acids;[1,2,9f] that is, the present synthesis is capable of yielding a large amount of the desired compound. This advantage mainly results from the elimination of two major drawbacks of the previous syntheses. The first one concerns the regioselective production of a 2′-*O*-protected ribonucleoside, which is



Scheme 2. Synthesis of *c*-GpAp (**9**): (a) IMP, MS 3 Å, CH_3CN, rt, 30 min; (b) a 3.3 M TBHP/toluene solution, rt, 30 min; (c) a 20% $Cl_2CHCOOH/CH_2Cl_2$ solution, rt, 20 min; (d) NaI, acetone, reflux, 2 h; (e) TPSCI, *N*-methylimidazole, THF, rt, 30 h; (f) concd aqueous NH_3–CH_3OH (1/1 v/v), 50 °C, 14 h; (g) $(C_2H_5)_3N\cdot 3HF$, rt, 14 h.



Scheme 3. Synthesis of *c*-Gplp (**13**): (a) IMP, MS 3 Å, CH_3CN, rt, 30 min; (b) a 6.7% BPO/CH_2Cl_2 solution, rt, 30 min; (c) a 20% $Cl_2CHCOOH/CH_2Cl_2$ solution, rt, 30 min; (d) NaI, acetone, reflux, 2 h; (e) TPSCI, *N*-methylimidazole, THF, rt, 55 h; (f) DBU, pyridine, rt, 3 h; (g) concd aqueous NH_3–CH_3OH (1/1 v/v), 50 °C, 12 h; (h) $(C_2H_5)_3N\cdot 3HF$, rt, 12 h.

required as a precursor of a starting synthetic unit, namely, a ribonucleoside 3′-phosphoramidite[9f] or 3′-phosphotriester.[1,2] In previous syntheses, introduction of a protecting group was carried out using 2′-*O*- and 3′-*O*-free material, and took place in a nonregioselective manner to give nearly equal amounts of 2′-*O*- and 3′-*O*-protected products; in addition, a considerable amount of the 2′,3′-di-*O*-protected compound was produced. Consequently, yield of the desired 2′-*O*-protected compound was very low. The present synthesis eliminated this drawback by achieving perfectly regioselective, higher-yielding production of the 2′-*O*-protected material by means of a previously reported manner[10] that employs 3′,5′-di-*O*-protection of the 2′,3′,5′-tri-*O*-free ribonucleoside by the di-*tert*-butylsilanediyl group using Furusawa method,[22] followed by introduction of the TBDMS protecting group to the 2′-hydroxy group, and then removal of the 3′,5′-di-*O*-silanediyl protector. The other improvement in the present synthesis is the use of our original phosphoramidite strategy with imidazolium perchlorate as a promoter in the presence of MS 3 Å,[11,12] in place of the phosphoramidite method with 1*H*-tetrazole as a promoter without MS[9f] or the phosphotriester method[1,2] employed in previous syntheses, for production of a linear dinucleotide intermediate, such as **3**, **7**, or **11**. As reported before, the phosphoramidite method employed in the present synthesis is particularly effective for the internucleotide linkage formation using a ribonucleoside phosphoramidite with a bulky protecting group on the 2′-hydroxy function, such as **1**, **6**, or **10**. Thus, this modification also increased the yield of the product.

3. Conclusion

We developed a facile synthesis of three analogs of *c*-di-GMP: namely, *c*-GpGps (**5**), *c*-GpAp (**9**), and *c*-GpIp (**13**) using a fairly common procedure. These analogs are expected to have bioactivity similar to that of *c*-di-GMP. We are investigating the biological activities of these analogs and will report the results in the near future.

4. Experimental

4.1. General

A UV spectrum was measured on a JASCO V-500 spectrometer. NMR spectra were taken on a JEOL JNM-α400 or ECA-500 instrument. The ^1H, ^{13}C, and ^{31}P NMR chemical shifts are described as δ values in ppm relative to $(CH_3)_4Si$ (for ^1H and ^{13}C NMR) and 85% H_3PO_4 (for ^{31}P NMR), respectively. ESI-TOF high resolution mass (HRMS) spectra were obtained on Applied Biosystems Voyager MDE and Mariner spectrometers. HPLC analysis was carried out using a COSMOSIL $5C_{18}$-MS column (Nacalai Tesque, ODS-5 mm, 4.6×250 mm) on a Waters 2695 Separations Module chromatograph with a Waters 2996 Photodiode Array detector. Preparative HPLC was achieved using a COSMOSIL $5C_{18}$-AR-300 column (Nacalai Tesque, 25×200 mm) on an ÄKTA explorer (Amersham Biosciences). Column chromatography was performed using Nacalai Tesque silica gel 60 (neutrality, 75 mm). Unless otherwise noted, synthetic reactions were carried out at ambient temperature. The reactions requiring anhydrous conditions were achieved under an argon atmosphere in flasks dried by heating at 400 °C under 133–400 Pa, or by washing with a 5% solution of dichlorodimethylsilane in dichloromethane followed by anhydrous dichloromethane, and then heating at 100 °C.

4.2. Material and solvents

The nucleoside 3′-phosphoramidites **1**,[9] **6**,[16] **10**,[19] the 5′-*O*-free nucleoside 3′-phosphate **2**,[9] imidazolium perchlorate (IMP),[10] a 3.30 M solution of TBHP in toluene solution,[18] and a 6.7% 2-butanone peroxide/dimethyl phthalate–toluene

solution[17] were prepared by the reported methods. Bis[3′-(triethoxysilyl)propyl] tetrasulfide (TEST)[12] was supplied from Shin-etsu, Tokyo, Japan. THF was used after drying by reflux over sodium-diphenyl ketyl. Acetone, acetonitrile, and dichloromethane were distilled from calcium hydride. Other organic reagents were used as commercially supplied without any purification. Solid and amorphous organic substances were used after drying at 50–60 °C for 8–12 h under 133–400 Pa. Powdery molecular sieves (MS) 3 Å were employed after drying the commercially supplied product (Nacalai tesque) at 200 °C for 12 h under 133–400 Pa.

4.2.1. Preparation of the guanylyl(3′-5′)guanosine 3′-phosphate monophosphorothioate 3. A mixture of the phosphoramidite **1** (1.02 g, 1.07 mmol) and the 5′-*O*-free nucleoside phosphate **2** (674 mg, 1.07 mmol) in the presence of powdery MS 3 Å (200 mg) in acetonitrile (10 mL) was stirred at 25 °C for 30 min. To this mixture was added IMP (370 mg, 2.2 mmol) and stirring was continued for an additional 30 min. TEST (1.10 mL, 1.20 g, 2.20 mmol) was added to the resulting mixture. After stirring for 30 min, the reaction mixture was passed through a Celite 545 pad to remove MS 3 Å. The filtrate was concentrated to afford a viscous oil. This material was dissolved in dichloromethane (20 mL). To this solution was added dichloroacetic acid (1.50 mL, 2.30 g, 18.0 mmol) at 0 °C. After stirring for 30 min at 25 °C, the reaction mixture was poured into an aqueous sodium hydrogen carbonate solution (100 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (100 mL, 50 mL×2). The organic solutions were combined and concentrated. The resulting material was chromatographed on a silica gel (50 g) column successively using a 1:30 methanol/dichloromethane mixture, a 1:20 methanol/dichloromethane mixture, and a 1:10 methanol/dichloromethane mixture as eluents to afford **3** (923 mg, a 78% overall yield; a mixture of four diastereomers) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) −0.28–0.01 (m, 12H), 0.73–0.97 (m, 18H), 2.72–2.79 (m, 4H), 3.08–3.22 (m, 12H), 3.48 (d, J=4.8 Hz, 6H), 3.70–3.83 (m, 2H), 4.23–4.63 (m, 10H), 5.02–5.15 (m, 3H), 5.30–5.44 (m, 3H), 5.67–6.00 (m, 3H), 7.59–7.86 (m, 2H), 8.38, (s, 1H), 8.57–8.61 (m, 1H), 8.79–8.90 (br, 2H); ^{31}P NMR ($CDCl_3$) −0.92, −0.86, 67.07, 67.15, 68.20, 68.25; HRMS (ESI^+) calcd for $C_{47}H_{74}N_{14}O_{14}P_2SSi_2Na^+$ ($M+Na^+$) *m/z* 1231.4136, found *m/z* 1231.4430.

4.2.2. Conversion of 3 to the protected cyclic bis(3′-5′)diguanylic acid monophosphorothioate 4. To a solution of **3** (876 mg, 0.72 mmol) in acetone (15 mL) was added sodium iodide (1.10 g, 7.20 mmol) and the resulting solution was stirred under reflux for 2 h. The resulting colorless precipitate was collected by filtration through a filter paper and washed with chilled acetone (50 mL). This precipitate is highly hygroscopic and thus was immediately subjected to the next procedure. The collected precipitate was dissolved in methanol (50 mL) and the solution was concentrated. The resulting oily material was co-evaporated with toluene (50 mL×3). The residue was suspended in THF (200 mL) and to this mixture were successively added *N*-methylimidazole (0.30 mL, 287 mg, 3.50 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (1.06 g, 3.50 mmol). The resulting solution was stirred at 25 °C for 36 h. To the reaction mixture was added water (50 mL) and stirring was continued for an additional 1 h. The reaction mixture was extracted with dichloromethane (50 mL×3) and the organic layer was concentrated. The resulting residual material was subjected to column chromatography on silica gel (50 g). Elution with a 1:20 methanol/dichloromethane mixture and then a 1:10 methanol/dichloromethane mixture afforded **4** (836 mg, a 76% overall yield from **3**) as an amorphous solid: ^{1}H NMR (CD_3OD) −0.14 (s, 6H), 0.09 (s, 6H), 0.76 (s, 18H), 2.95 (t, J=6.0 Hz, 4H), 3.14 (s, 6H), 3.31 (s, 6H), 4.13–4.21 (m, 2H), 4.35–4.68 (m, 10H), 5.36, 5.38 (2d, J=5.0 Hz, 2H), 5.31–5.44 (m, 2H), 5.91–5.96 (m, 4H), 7.08 (s, 2H), 7.94 (s, 2H), 8.69 (s, 2H); ^{31}P NMR (CD_3OD) −0.97, −0.75, 66.91, 67.75; HRMS (ESI^+) calcd for $C_{44}H_{69}N_{14}O_{13}P_2SSi_2Na^+$ ($M+Na^+$) *m/z* 1173.3717, found *m/z* 1173.4057.

4.2.3. Preparation of *c*-GpGps (5) by deprotection of 4. To a suspension of **4** (155 mg, 0.13 mmol) in methanol (10 mL) was added a concd aqueous ammonia solution (10 mL), and the resulting mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated and the residue was dried under reduced pressure using a vacuum oil pump. The resulting product was mixed with $(C_2H_5)_3N\cdot 3HF$ (6.0 mL, 5.93 g, 37 mmol) and the mixture was stirred for 12 h. To the reaction mixture was added a 1 M (1 mol dm^{-3}) ammonium acetate buffer solution (30 mL) and the mixture was vigorously stirred at 30–40 °C for 10 min. After removing the resulting pale yellow precipitate by filtration, the aqueous filtrate was subjected to preparative HPLC using a COSMOSIL 5C_{18}-AR-300 column [25 (diameter)×200 (height) mm]. Elution carried out under the following conditions [A=a 1.0 mM ammonium acetate buffer solution, B=a 0.2 mM ammonium acetate solution in a 20:80 mixture of H_2O and acetonitrile; gradient: 0–8 min A 100%, 8–55 min linear gradient A 100% to A 40%/B 60%, 55–63 min B 100%; detection 254 nm; flow rate 10 mL/min] gave rise to the diammonium salt of **5** (64 mg, a 64% overall yield from **4**, a mixture of two diastereomers): UV (a 50 mM solution of ammonium acetate in water) λ_{max} 254 nm (ε 23,700); ^{1}H NMR (DMSO-d_6) 3.76–4.15 (m, 6H), 4.35–4.92 (m, 4H), 5.67–5.72 (m, 2H), 6.54 (br, 2H), 7.92, 7.94 (2s, 2H); ^{31}P NMR (DMSO-d_6) 1.27, 54.21; HRMS (ESI^-) calcd for $C_{20}H_{23}N_{10}O_{17}P_2S^-$ ($M-H^-$) *m/z* 705.0648, found *m/z* 705.0804.

4.2.4. Preparation of the adenylyl(3′-5′)guanosine 3′-phosphate 7. The phosphoramidite **6** (916 mg, 0.90 mmol) and the 5′-*O*-free nucleoside phosphate **2** (378 mg, 0.60 mmol) were mixed in acetonitrile (3 mL) containing powdery MS 3 Å (200 mg) and stirred at 25 °C for 30 min. The mixture was added IMP (207 mg, 1.20 mmol) and stirred for additional 30 min. To the resulting mixture was added a 3.30 M solution of TBHP in toluene (0.30 mL, 0.90 mmol of the peroxide). The mixture was left at 25 °C with stirring for 30 min and then passed through a Celite 545 pad for removing MS 3 Å. The filtrate was concentrated to afford oily material, which was dissolved in dichloromethane (20 mL). To this solution was added dichloroacetic acid (1.10 mL, 1.70 g, 15.6 mmol) at 0 °C. After stirring for 20 min at 25 °C, the reaction mixture was poured into an aqueous sodium hydrogen carbonate solution (100 mL).

The organic layer was separated and the aqueous layer was extracted with dichloromethane (100 mL, 50 mL×2). The combined organic layers were dried and concentrated. The resulting material was subjected to silica gel (50 g) column chromatography using a 1:30 methanol/dichloromethane mixture, a 1:20 methanol/dichloromethane mixture and then a 1:10 methanol/dichloromethane mixture as an eluent to afford **7** (660 mg, an 88% overall yield; a mixture of four diastereomers) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) −0.37–0.09 (m, 12H), 0.70–0.87 (m, 18H), 2.77–2.82 (m, 4H), 3.11 (s, 3H), 3.21, 3.22 (2s, 3H), 3.63–3.90 (m, 3H), 4.32–5.46 (m, 16H), 5.93–6.24 (m, 3H), 7.06–7.08 (m, 3H), 7.36 (t, J=7.4 Hz, 2H), 7.85–7.92 (m, 1H), 8.55–8.66, (m, 1H), 8.77 (br, 2H), 9.72 (br, 1H); ^{31}P NMR ($CDCl_3$) −3.08, −2.86, −2.71, −2.64, −2.52, −2.46, −2.34, −2.27; HRMS (ESI^+) calcd for $C_{52}H_{76}N_{13}O_{16}P_2Si_2^+$ ($M+H^+$) m/z 1256.4541, found m/z 1256.4742.

4.2.5. Transformation of 7 to the protected cyclic (3′-5′)adenylic-guanylic acid 8. A mixture of **7** (660 mg, 0.53 mmol) and sodium iodide (566 mg, 5.30 mmol) in acetone (30 mL) was refluxed with stirring for 2 h. The occurring yellow precipitate was collected by filtration and washed with chilled acetone (50 mL). This solid was suspended in THF (120 mL) and to this heterogeneous mixture were successively added *N*-methylimidazole (0.211 mL, 218 mg, 2.65 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (803 mg, 2.65 mmol). The resulting mixture was stirred at 25 °C for 30 h. The reaction was quenched by addition of water (50 mL) at 25 °C and the resulting aqueous mixture was stirred at the same temperature for additional 1 h. The reaction mixture was extracted with dichloromethane (50 mL×3) and the organic layer was separated and concentrated. The residue was subjected to column chromatography on silica gel (50 g) eluted with a 1:20 mixture of methanol and dichloromethane and then a 1:10 mixture of methanol and dichloromethane to provide **8** (180 mg, a 40% overall yield from **7**) as an amorphous solid: ^{1}H NMR (CD_3OD) −0.23 (s, 3H), −0.09 (s, 3H), 0.10 (s, 6H), 0.74, 0.79 (2s, 18H), 2.46–2.48 (m, 2H), 2.65, 2.67 (2s, 6H), 3.12–3.22 (m, 4H), 3.47–3.48 (m, 2H), 3.76 (s, 2H), 4.05–5.00 (m, 4H), 5.34–5.43 (m, 2H), 5.91–5.99 (m, 3H), 6.13–6.19 (m, 1H), 6.96–7.16 (m, 3H), 7.33–7.45 (m, 2H), 7.95–7.99 (m, 1H), 8.27–8.32 (m, 1H), 8.54–8.61 (m, 1H), 8.67–8.78 (m, 2H); NMR (CD_3OD) −0.66, 0.00; HRMS (ESI^+) calcd for $C_{49}H_{70}N_{13}O_{15}P_2Si_2^+$ ($M+H^+$) m/z 1198.4123, found m/z 1198.4466.

4.2.6. Preparation of *c*-GpAp (9) from 8. A suspension of **8** (180 mg, 0.21 mmol) in methanol (5 mL) was mixed with a concd aqueous ammonia solution (10 mL) and the resulting mixture was stirred at 50 °C for 14 h. The reaction mixture was concentrated and the resulting residue was dried in vacuo. The dried material was mixed with $(C_2H_5)_3N\cdot 3HF$ (4.0 mL, 3.96 g, 25 mmol) and stirred at 25 °C for 14 h. To this mixture was added a 1 M (1 mol dm^{-3}) ammonium acetate buffer solution (30 mL) and the mixture was vigorously stirred at 30–40 °C for 10 min. The resulting precipitate was removed by passage of the reaction mixture through a column packed with Celite 545 and the filtrate was subjected to preparative HPLC using a COSMOSIL 5C_{18}-AR-300 column [25 (diameter)×200 (height) mm] eluted under the following conditions [A=a 1.0 mM ammonium acetate buffer solution, B=a 0.2 mM ammonium acetate solution in a 20:80 mixture of H_2O and acetonitrile; gradient: 0–8 min A 100%, 8–55 min linear gradient A 100% to A 40%/B 60%, 55–63 min B 100%; detection 254 nm; flow rate 10 mL/min] to afford the diammonium salt of **9** (80 mg, an 81% overall yield from **8**): ^{1}H NMR (DMSO-d_6) 3.77–3.96 (m, 4H), 4.12–4.19 (m, 2H), 4.58–4.63 (m, 3H), 4.89–4.91 (m, 1H), 5.73 (d, J=8.1 Hz, 1H), 5.84 (d, J=8.0 Hz, 1H), 6.57 (br, 2H), 7.23 (br, 2H), 7.92 (s, 1H), 8.12 (s, 1H), 8.38 (s, 1H); ^{31}P NMR (DMSO-d_6) 1.16; HRMS (ESI^-) calcd for $C_{20}H_{23}N_{10}O_{13}P_2^-$ ($M-H^-$) m/z 673.0927, found m/z 673.1104.

4.2.7. Preparation of the inosinylyl(3′-5′)guanosine 3′-phosphate 11. A mixture of the phosphoramidite **10** (620 mg, 0.60 mmol) and the 5′-*O*-free nucleoside phosphate **2** (313 mg, 0.50 mmol) in acetonitrile (1 mL) containing powdery MS 3 Å (200 mg) was stirred at 25 °C for 30 min. To this mixture was added IMP (168 mg, 1.00 mmol). After stirring at the same temperature for 30 min, to the reaction mixture was added a 6.7% solution of 2-butanone peroxide/dimethyl phthalate in toluene (1.00 mL, 1.0 mmol of the peroxide) and the mixture was stirred for additional 30 min. The reaction mixture was passed through a column packed with Celite 545 pad to remove MS 3 Å. Concentration of the filtrate afforded a viscous oil, which was dissolved in dichloromethane (20 mL). To this solution was added dichloroacetic acid (0.50 mL, 0.77 g, 6.00 mmol) at 0 °C. After stirring for 30 min at 25 °C, the reaction mixture was poured into an aqueous sodium hydrogen carbonate solution (100 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (100 mL, 50 mL×2). The organic solutions were collected and concentrated to give an oily material. This crude product was chromatographed on a silica gel (50 g) column using a 1:30 methanol/dichloromethane mixture, a 1:20 methanol/dichloromethane mixture, and then a 1:10 methanol/dichloromethane mixture as eluents to afford **11** (579 mg, a 75% overall yield from **10**; a mixture of four diastereomers) as a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) −0.39–0.22 (m, 12H), 0.68–0.91 (m, 18H), 2.73–2.82 (m, 4H), 3.12–3.23 (m, 6H), 3.33 (t, J=6.8 Hz, 2H), 3.75–3.90 (m, 2H), 4.24–4.62 (m, 10H), 4.82–5.45 (m, 8H), 5.68–6.17 (m, 4H), 7.48–7.51 (m, 2H), 7.75–7.86 (m, 1H), 8.15 (d, J=8.8 Hz, 2H), 8.27–8.33 (m, 1H), 8.47–8.48 (m, 1H), 8.53–8.62 (m, 1H) 9.38–9.46 (m, 1H); ^{31}P NMR ($CDCl_3$) −2.93, −2.82, −2.64, −2.53, −2.38, −2.27; HRMS (ESI^+) calcd for $C_{52}H_{75}N_{13}O_{17}P_2Si_2Na^+$ ($M+Na^+$) m/z 1294.4310, found m/z 1294.4623.

4.2.8. Conversion of 11 to the fully protected cyclic (3′-5′)guanylic/inosinic acid 12. To a solution of **11** (398 mg, 0.30 mmol) in acetone (10 mL) was added sodium iodide (420 mg, 3.00 mmol) and the resulting solution was stirred at the reflux temperature for 2 h. The reaction mixture was poured into a 10 mM of triethylammonium carbonate solution in water (100 mL) and extracted with dichloromethane (100 mL, 50 mL×2). The collected organic solutions were concentrated. The resulting residue was mixed with THF (100 mL) and to this mixture were successively added *N*-methylimidazole (0.11 mL, 123 mg,

1.50 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (460 mg, 1.50 mmol). The resulting solution was stirred at 25 °C for 55 h. To the reaction mixture was added water (50 mL) at 25 °C and stirring was continued at the same temperature for an additional 1 h. The reaction mixture was extracted with dichloromethane (50 mL×3) and the organic layer was concentrated. The resulting residual material was subjected to column chromatography on silica gel (50 g) and eluted with a 1:20 mixture of methanol and dichloromethane and then a 1:10 mixture of methanol and dichloromethane. The desired product **12** was obtained as an amorphous solid (324 mg, an 87% overall yield from **11**): ^{1}H NMR (CD_3OD) −0.13–0.20 (6s, 12H), 0.80–0.97 (3s, 18H), 2.89–3.06 (m, 2H), 3.17–3.50 (m, 10H), 3.90 (d, J= 1.5 Hz, 2H), 4.21–5.02 (m, 12H), 5.42–5.66 (m, 2H), 5.95 (s, 1H), 6.11–6.12 (m, 1H), 6.93–6.95 (m, 2H), 7.66–7.69 (m, 2H), 7.87–7.99 (m, 1H), 8.28–8.32 (m, 2H), 8.64–8.78 (m, 2H); ^{31}P NMR (CD_3OD) 4.47, 5.33; HRMS (ESI^+) calcd for $C_{49}H_{70}N_{13}O_{16}P_2Si_2^+$ ($M+H^+$) m/z 1214.4072, found m/z 1214.5455.

4.2.9. Deprotection of 12 giving *c*-GpIp (13). To a solution of **12** (296 mg, 0.23 mmol) in pyridine (10 mL) was added DBU (0.4 mL, 407 mg, 2.7 mmol) and the mixture was stirred at 25 °C for 3 h. To this mixture was added an aqueous solution concentrated with ammonia (10 mL) and the mixture was stirred at 50 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the obtained residue was dried in vacuo. The resulting product was mixed with $(C_2H_5)_3N\cdot 3HF$ (4.4 mL, 4.35 g, 27 mmol) and the mixture was stirred at 25 °C for 12 h. The reaction mixture was added a 1 M (1 mol dm^{-3}) ammonium acetate buffer solution (30 mL) and vigorously stirred at 30–40 °C for 10 min to precipitate a pale yellow solid. After removal of the resulting precipitate by filtration by passing through a Celite 545 pad, the aqueous filtrate was subjected to preparative HPLC using a COSMOSIL 5C_{18}-AR-300 column [25 (diameter)×200 (height) mm]. Elution was performed under the following conditions [A=a 1.0 mM ammonium acetate buffer solution, B=a 0.2 mM ammonium acetate solution in a 20:80 mixture of water and acetonitrile; gradient: 0–8 min A 100%, 8–55 min linear gradient A 100% to A 40%/B 60%, 55–63 min B 100%; detection 254 nm; flow rate 10 mL/min] to give the diammonium salt of **13** (125 mg, an 80% overall yield from **12**, a mixture of two diastereomers): ^{1}H NMR (DMSO-d_6) 3.73–3.99 (m, 4H), 4.11–4.21 (m, 2H), 4.57–4.87 (m, 4H), 5.72 (d, J=8.0 Hz, 1H), 5.82 (d, J=8.0 Hz, 1H), 6.75 (br, 2H), 7.91 (s, 1H), 8.03 (br, 1H), 8.32 (s, 1H); ^{31}P NMR (DMSO-d_6) 1.02, 1.16; HRMS (ESI^-) calcd for $C_{20}H_{23}N_9O_{14}P_2^-$ ($M-H^-$) m/z 674.0767, found m/z 674.1057.

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Diels–Alder cycloaddition of electrophilic 2*H*-azirines with 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl) oxazolidin-2-ones. Treatment of the cycloadducts under acidic conditions

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Abstract—3-(3-(*tert*-Butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one was reacted with several electrophilic 2*H*-azirines to give the expected cycloadducts in moderate to good yields. Treatment of the cycloadducts under acidic conditions gave six-membered ring aminoenones and aziridine derivatives. In the case where anilinium fluoride was used an inversion at the C-2 stereogenic center was observed forming an isomer of the former cycloadduct. The chiral (*R*)-3-(3-(*tert*-butyldimethylsiloxy)buta-1,3-dienyl)-4-phenyloxazolidin-2-one was also reacted with an electrophilic 2*H*-azirine. The reaction showed no diastereoselectivity, but both diastereoisomers were fully isolated by chromatography.

1. Introduction

Diels–Alder cycloadditions of 3-(3-(trialkylsilyloxy)buta-1,3-dienyl)oxazolidin-2-ones in general have proved to be extremely interesting due to their high *endo* selectivity with a number of carbodienophiles, opening the possibility of generating cyclohexanones by hydrolysis of the cycloadducts.[1] Reactions with imines gave a no less interesting type of compounds: dihydro-4-pyridones, that are memory enhancers when functioning as ligands for acetylcholine receptors and are building blocks to a wide range of natural products of biological interest.[2,3] 2*H*-Azirines are special imines that have proved to be excellent partners in aza-Diels–Alder reactions that occur at rt when the C=N bond is activated with a conjugated oxo,[4] alkoxycarbonyl[5] or heteroaromatic group.[6]

2. Results and discussion

In order to exploit the potential of both 2*H*-azirines and the dienes quoted above, we combined the 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** with the azirines **2a–e** in toluene and left the solution stirring at rt for 4–5 days. Cycloadducts were obtained after dry flash chromatography in moderate to good yields. In cases where the 2*H*-azirine could not be isolated (**2a**, **2d**) the cycloaddition was preceded by the pyrolysis of the α-azido precursor **1a**, **1d**, then the reaction solution was cooled and the diene added (Scheme 1).

Products are assumed to be formed by an *endo* process, as generally occurs in reactions of electrophilic 2*H*-azirines with 1,3-conjugated dienes, in particular with Danishefsky's diene and other similar types of dienes.[5b,j,k] The chemical shift of H-7 has been recognized as indicative of the stereochemistry of the cycloadducts. Figure 1 shows a good equivalence for the chemical shifts of H-7 protons in compounds **6**[5b]**/5c**, and **7**[5c]**/5d**.

The exceptions to the *endo* rule in Diels–Alder cycloadditions envolving 2*H*-azirines occur with furan and its derivatives, where the easy retro Diels–Alder favors the thermodynamic product resulting from the *exo* approach.[5g]

After having succeeded with achiral reagents we chose to use the known chiral diene **4**[1] to test a possible diastereoselectivity in these reactions. It is well established that the carbonyl group on the imide nitrogen preferentially adopts the anti conformation, away from the dienyl moiety, as represented in structure **4**. Due to this fixed conformation

Keywords: 2*H*-Azirines; Aza-Diels–Alder; 3-(3-(Trialkylsilyloxy)buta-1,3-dienyl)oxazolidin-2-ones; Aminoenones; Aziridines.
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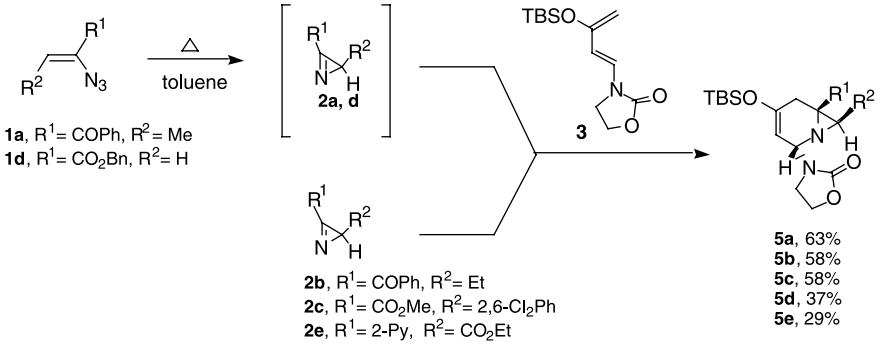


Scheme 1.

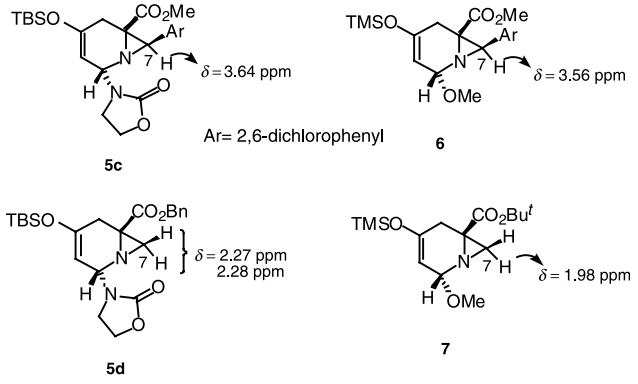


Figure 1.

the differentiation of the two faces of the diene made by the dienophile it is generally high. But this did not occur with the 2*H*-azirine **2d**. The small volume of the methylene group of the azirine is most probably responsible for the observed lack of selectivity. Figure 2 shows the two possible approaches of diene–azirine giving two diastereoisomers, compounds **8d** and **9d**.

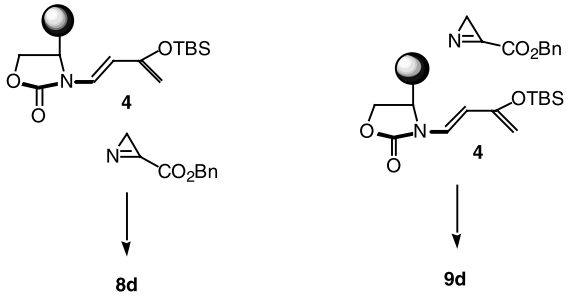
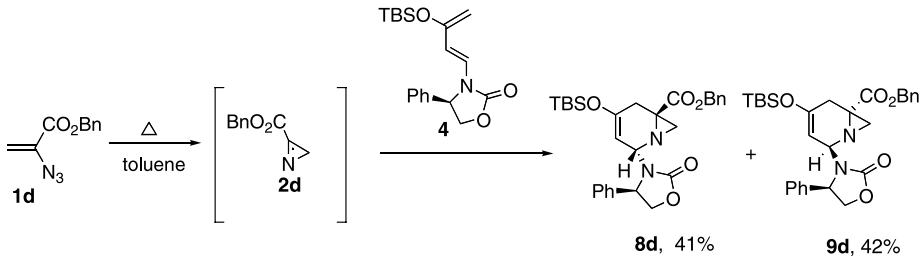


Figure 2.

Both products were effectively obtained from the reaction of the chiral diene **4** with 2*H*-azirine **2d**, prepared 'in situ' by pyrolysis of the α-azido compound **1d**. ^{1}H NMR of the crude product showed two diastereoisomers in approximately 1:1 ratio (Scheme 2). Compounds **8d** and **9d** were completely separated by dry flash chromatography (**8d**, 41% yield; **9d**, 42% yield).

Based on the ^{1}H NMR analysis both products **8d** and **9d** would be formed by an *endo* approach of reactants. The chemical shifts of the two H-7 protons are quite close to each other in both products (δ_H 2.10/2.27 ppm in compound **8d** and δ_H 2.00/2.48 ppm in compound **9d**) and in the other products obtained from *endo* approach, as those shown in Figure 1. The main spectroscopic difference between the two diastereoisomeric compounds **8d** and **9d**, is the chemical shift of H-2. Compound **8d** shows H-2 at δ_H 5.87 ppm, quite near the values of compounds **5a–e** (δ_H 5.67–5.90 ppm) and compound **9d** at δ_H 4.84 ppm, around 1 ppm upfield. This difference can be explained by the effect of the carbonyl of the oxazolidinone group over H-2 in one case that fails in the other. This is sustained by the chemical shift of H-2 in compound **7** at δ_H 4.91 ppm, also 1 ppm upfield. The methoxy group (in compound **7**) cannot display a similar effect to the carbonyl through space since the oxygen atom is away from H-2. ^{13}C spectrum shows that the inductive effect of the methoxy group (in compound **7**)[5c] is higher than the effect of the oxazolidinyl group (in compounds **5**, **8d** and **9d**). The C-2 chemical shift in compounds **5**, **8d** and **9d** are very near to each other ($\delta_C \sim 66$ ppm), but compound **7** shows C-2 around 20 ppm downfield, at δ_C 87.8 ppm. It is so clear that in compound **9d**, formed by approach of the azirine to the bulky face of the diene, the phenyl group in the oxazolidinone moiety will tend to move away from the methylene group of the aziridine to avoid a steric interaction between the two moieties of the molecule. The arrangement of groups in



Scheme 2.

conformer **I** is certainly less stable than in conformer **II**. Due to the absence of interaction between the carbonyl group and H-2 in conformer **II**, the effect disappears resulting in a drop of the chemical shift of H-2 in ca. 1 ppm (Fig. 3).

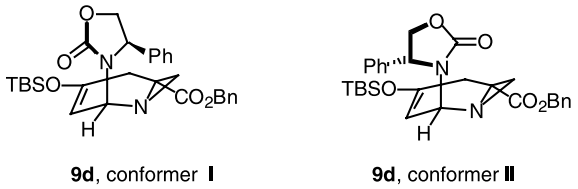


Figure 3.

Cycloadducts **5a–e** were then reacted under acidic conditions. The nature of the acid seems to play a decisive role in the outcome of reactions. It is to be expected that any reaction would begin with protonation either on the nitrogen atom of the aziridine ring, forming **5I**, or on the oxygen atom of the carbonyl group, forming **5II** (Fig. 4).

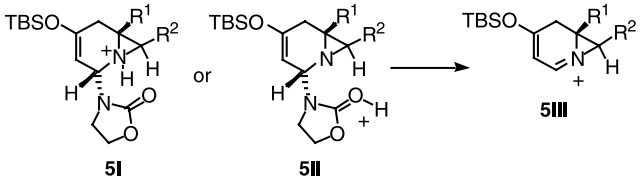


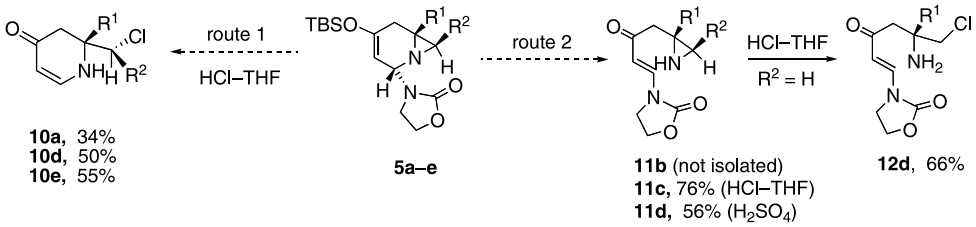
Figure 4.

Reaction of cycloadducts **5a**, **5d**, **5e** with 1 equiv of HCl in THF (15 min–1 h at rt) produced compounds **10a**, **10d**, **10e**. Either **5I**, **5II** or **5III** could have been the precursors in these reactions. The loss of the oxazolidinone from **5II** would form **5III**. Of course, the nucleophilic attack at C-7 is specially enhanced in structures **5I** and **5III**. After the three-membered ring opening, the oxazolidinone would be eliminated together with the silyl group. Reactions of cycloadducts **5b**, **5d** with 1 equiv of H_2SO_4/H_2O in THF formed a different type of product. The absence of a good nucleophilic species preserves the aziridine ring and the products are compounds **11b**, **11d** (Scheme 3). Since the oxazolidinone group is present in the molecule, the initial protonated species should be **5I** to avoid elimination of the oxazolidinone that would be converted into a very good leaving group if the carbonyl was protonated. And so it is reasonable to conclude that the same protonated species **5I**, could be the precursor of both compounds **10** and **11**.

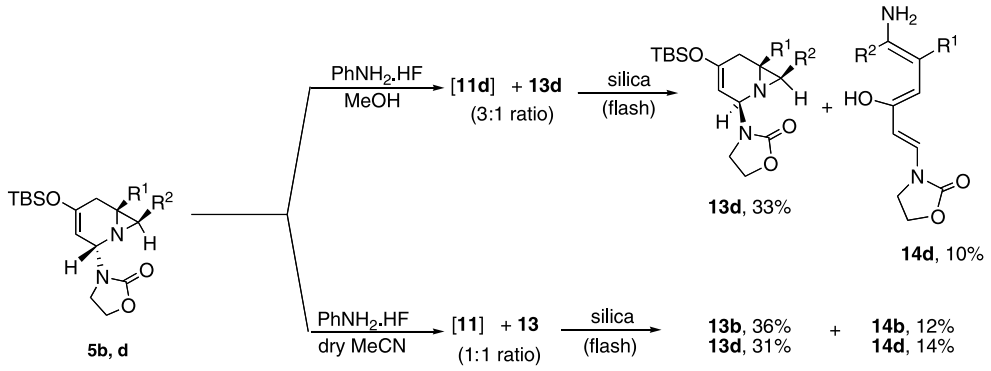
It was proved that compounds **11** are not intermediates in the formation of compounds **10**. When compound **11d** was re-dissolved in THF and treated with HCl in THF, under the same conditions used in route 1 in the formation of compounds **10**, a new compound was formed, isolated and identified as compound **12d**.

Interestingly, reaction of compound **5c** with HCl–THF gives compound **11c** and not the expected structure **10**. The 2,6-dichlorophenyl group attached to C-7 makes the nucleophilic attack of the chloride ion difficult for steric reasons and so route 2 prevails over route 1 giving compound **11c** in 76% yield. Reaction of cycloadduct **5d** with anilinium fluoride in MeOH gave a 3:1 mixture of compounds **11d** and **13d**, according to the ^{1}H NMR spectrum. A long exposure (5–6 h) of this mixture to silica, during flash chromatography in order to separate the two products, showed decomposition of compound **11d**. Compound **13d** was obtained pure in 33% yield together with **14d** (10% yield) after flash chromatography. Compound **14d** is a decomposition product of **11d**. It was confirmed that **11d** is totally converted into **14d**, by treatment of a mixture of **11d** and **13d** with silica, giving **13d** and **14d**. A plausible explanation for the formation of compound **11d** is that being fluoride ion a much worst nucleophile than chloride ion, it fails to attack the aziridine and the alternative process of the six-membered ring opening prevails (route 2, Scheme 3). Product **13d** was formed by treatment of **5d** with anilinium fluoride either in methanol or acetonitrile. A conversion of **5d** into **13d** was also observed in the NMR tube. After 1 h at rt, a solution of **5d** in $CDCl_3$ showed **13d** together with traces of **5d**. Comparing the ^{1}H NMR spectra of crude products in reactions starting from **5d** in dry acetonitrile or **5d** in methanol, it is apparent that the silyl group was preserved to a larger extent in the case of acetonitrile as solvent. This is possibly due to the nucleophilic power of MeOH, towards silicon when used as solvent. Treatment of a solution of **5b** in acetonitrile with anilinium fluoride at rt gave **13b** and **14b** after dry flash chromatography (Scheme 4).

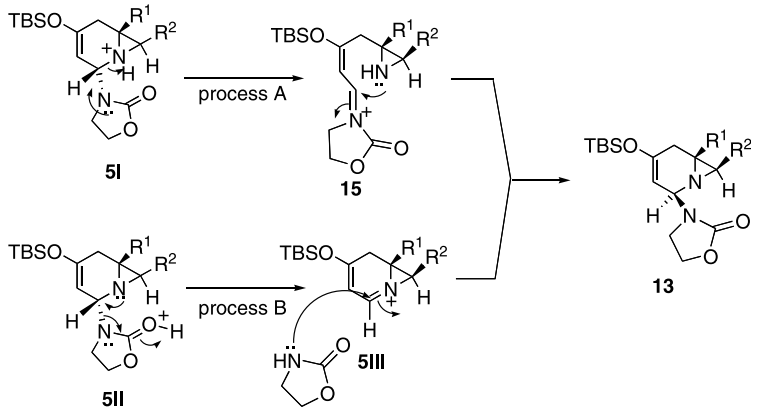
Two mechanistic processes can be envisaged for the inversion of the C-2 stereogenic center that occurred in formation of compounds **13** from adducts **5**: (1) the opening of the six-membered ring by conjugation of the electron pair on the nitrogen atom of the oxazolidinone ring, passing through the intermediate **15** (Scheme 5, process A), followed by an attack of the nitrogen lone pair of electrons in the aziridine to the other face to close the six-membered ring; (2) the elimination of the oxazolidinone followed by its attack from the other side of the six-membered ring (Scheme 5, process B). Indeed process A is more plausible considering either enthalpic (three-membered ring strain would be greater in intermediate **5III** than in **15**) and entropic factors.



Scheme 3.



Scheme 4.



Scheme 5.

An interesting mechanistic point that follows from these reactions is that the desilylation does not have to be concerted with the cleavage of C–N bond. In fact desilylation does not occur in the process of synthesis of compounds **13**. So in the mechanism that assists formation of compound **11** it is also possible that the cleavage of the silyl group occurs after cleavage of the C–N bond in the six-membered ring, being structure **15** the intermediate.

Major features of compounds **10** in ^{1}H NMR spectra are H-6 at $\delta_H \sim 7.0$ ppm and H-5 at $\delta_H \sim 5.0$ ppm with a geminal coupling of 7.2 or 7.8 Hz. The coupling of H-6 to NH is visible in the spectra of compounds **10a** and **10d** (6.9 Hz).

Compounds **11** showed the two ethylenic protons as doublets with a typical vicinal coupling (14.1 or 14.4 Hz), at δ 7.91–7.72 and 5.42–5.80 ppm. The two geminal protons of aziridine ring in compound **11d** are singlets at δ 1.79 and 2.22 ppm. ^{1}H NMR absorptions of compound **12d** are similar to those registered for compound **11d**, except for the new chloromethyl protons at δ 2.90 and 3.25 ppm with a coupling constant of 17.1 Hz that substituted the aziridine protons described as singlets.

^{1}H and ^{13}C NMR spectra of compounds **13** are virtually superimposable on those of their isomers **5**. The major difference is registered in the ^{1}H spectra: the coupling constant of H-2 to H-3 is 4.8–5.1 Hz in compounds **13** and 1.8–2.1 Hz in compounds **5**.

Compounds **14** showed a proton attached to the oxygen atom in the enol moiety at δ_H 10.00 ppm and a trans coupling of the vicinal ethylenic protons ($J=15$ Hz) at δ_H 5.50 and 7.44 ppm.

3. Conclusion

Methods of generating a new type of six-membered ring aminoenones and open chain aminoenones attached to aziridines have been devised. The chiral version of these compounds (both enantiomers) can be envisaged in the future once the parent cycloadducts have been formed and isolated. In reactions between the primary Diels–Alder cycloadducts and anilinium fluoride an interesting phenomenon has been observed: the inversion of C-2 stereogenic center with formation of a new isomer.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), doublets of doublets (dd), quartets (q) and multiplets (m). J values are recorded in Hz. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Solid samples

were run as DCM mulls, and oils as thin films. Mass spectra were recorded on a VG Autospec M. spectrometer. Microanalyses were performed in a LECO-CHNS-932 analyser. Melting points (mp) were determined on a Gallenkamp block. Dry flash chromatography was performed on silica gel 60<0.063 mm for column chromatography. Petroleum ether 40–60 °C was distilled before use. Toluene was distilled over sodium.

4.2. Synthesis of cycloadducts

4.2.1. 3-(6-Benzoyl-4-(*tert*-butyldimethylsilyloxy)-7-methyl-1-aza-bicyclo[4.1.0]hept-3-en-2-yl)oxazolidin-2-one 5a. The α-azide **1a** (0.25 g; 1.33 mmol) was dissolved in toluene (10 mL) and the solution refluxed for 2.5 h. After cooling the solution to rt 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** (0.34 g; 1.26 mmol) in toluene (10 mL) was added. The reaction mixture was stirred under N_2 at rt for 5 days. After that the solvent was evaporated leaving an oil that was subjected to dry flash chromatography (pet. ether/ether; 2:5). A white solid was obtained and recrystallized from ether/pet. ether (mp 152.5–154.0 °C) to give compound **5a**. Yield (304 mg; 0.71 mmol, 63%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.16 (s, 3H, Me), 0.18 (s, 3H, Me), 0.91 (s, 9H, 3×Me), 1.12 (d, *J*=5.7 Hz, 3H, Me), 2.44 (dm, *J*=17.7 Hz, 1H, H-5), 2.52 (q, *J*=5.7 Hz, 1H, H-7), 2.82 (d, *J*=17.7 Hz, 1H, H-5), 3.64 (t, *J*=8.1 Hz, 2H, ox), 4.63 (t, *J*=2.1 Hz, 1H, H-3), 4.37 (dt, *J*=8.1 Hz, 3.3, 2H, ox), 5.90 (br s, 1H, H-2), 7.46–7.63 (m, 3H, Ar), 7.98–8.06 (m, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.6 (Me), −4.4 (Me), 15.2 (Me), 17.8 (C), 25.4 (Me), 29.3 (C-5), 34.4 (C-7), 41.4 (ox), 47.3 (C-6), 62.1 (ox), 65.6 (C-2), 98.2 (C-3), 128.6, 129.4, 133.4, 135.2, 149.4 (C-4), 157.4 (CO, ox), 197.4 (CO). $C_{23}H_{32}N_2O_4Si$ (428.05): calcd C 64.47, H 7.47, N 6.54; found C 64.20, H 7.56, N 6.47.

4.2.2. 3-(6-Benzoyl-4-(*tert*-butyldimethylsilyloxy)-7-ethyl-1-aza-bicyclo[4.1.0]hept-3-en-2-yl)oxazolidin-2-one 5b. To a solution of 2*H*-azirine **2b** (420 mg; 2.42 mmol) in toluene (10 mL) was added 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** (0.45 g; 1.68 mmol) dissolved in toluene (10 mL). The reaction mixture was stirred under N_2 at rt for 4 days. After that the solvent was evaporated and the crude subjected to dry flash chromatography (pet. ether/diethyl ether; 1:2). A white solid **5b** was obtained (mp 141.0–143.5 °C). Yield (434 mg; 0.98 mmol; 58%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.15 (s, 3H, Me), 0.18 (s, 3H, Me), 0.90 (s, 9H, 3×Me), 0.97 (t, *J*=7.2 Hz, 3H, Me), 1.17–1.30 (m, 1H, C*H*H), 1.37–1.48 (m, 1H, CH*H*), 2.36–2.44 (m, 2H, H-5+H-7), 2.84 (d, *J*=18.0 Hz, 1H, H-5), 3.70 (m, 2H, ox), 4.34 (t, *J*=7.5 Hz, 2H, ox), 4.69 (t, *J*=1.8 Hz, 1H, H-3), 5.79 (br s, 1H, H-2), 7.43–7.57 (m, 3H, Ar), 8.03 (d, *J*=7.2 Hz, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.6 (Me), −4.5 (Me), 11.4 (Me), 17.8 (C), 23.5 (Me), 25.4 (Me), 29.3 (C-5), 40.9 (C-7), 42.1 (ox), 47.5 (C-6), 62.0 (ox), 65.7 (C-2), 98.2 (C-3), 128.5, 129.4, 133.3, 135.3, 149.0 (C-4), 157.3 (CO, ox), 197.7 (CO). $C_{24}H_{34}N_2O_4Si$ (442.62): calculated C 65.12, H 7.74, N 6.33; found C 64.78, H 7.63, N 6.39.

4.2.3. Methyl 4-(*tert*-butyldimethylsilyloxy)-7-(2,6-dichlorophenyl)-2-(2-oxooxazolidin-3-yl)-1-azabicyclo[4.1.0]hept-3-en-6-carboxylate 5c. To a solution of 2*H*-azirine **2c** (420 mg, 1.72 mmol) in toluene (10 mL) was added 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)-oxazolidin-2-one **3** (0.85 g; 3.16 mmol) dissolved in toluene (10 mL). The reaction mixture was stirred under N_2 at rt over 4 days. After that the solvent was evaporated and a white solid **5c** was formed (mp 190.5–191.0 °C). Yield (865 mg; 1.69 mmol, 58%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.22 (s, 3H, Me), 0.23 (s, 3H, Me), 0.96 (s, 9H, 3× Me), 2.85 (dt, *J*=18.6, 2.1 Hz, 1H, H-5), 3.00 (dd, *J*=18.6, 1.2 Hz, 1H, H-5), 3.38 (s, 3H, OMe), 3.64 (s, 1H, H-7), 3.77 (t, *J*=8.1 Hz, 2H, ox), 4.37 (m, 2H, ox), 4.61 (t, *J*=2.1 Hz, 1H, H-3), 5.80 (br s, 1H, H-2), 7.08–7.15 (m, 1H, Ar), 7.25–7.30 (m, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.3 (Me), −4.4 (Me), 17.9 (C), 25.5 (Me), 27.7 (C-5), 41.9 (C-7), 42.3 (ox), 43.5 (C-6), 52.2 (Me), 61.9 (ox), 66.5 (C-2), 96.9 (C-3), 128.4, 128.9, 130.8, 135.6, 150.3 (C-4), 157.4 (CO, ox), 170.1 (CO). $C_{23}H_{28}Cl_2N_2O_5Si$ (511.09): calculated C 54.00, H 5.48, N 5.48; found C 53.80, H 5.85, N 5.66.

4.2.4. Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxooxazolidin-3-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 5d. The α-azide **1d** (1.80 g; 8.86 mmol) was dissolved in toluene (200 mL) and heated under reflux for 5 h. After cooling the solution to rt 3-(3-(*tert*-butyldimethylsilyloxy)-buta-1,3-dienyl)oxazolidin-2-one **3** (1.25 g; 4.64 mmol) was added, dissolved in toluene (15 mL). The reaction mixture was stirred under N_2 at rt, for 4.5 days. After that the solvent was evaporated to give a brown oil that was purified by dry flash chromatography (pet. ether/ether; gradient polarity). The product **5d** was obtained as an oil. Yield (768 mg; 1.73 mmol; 37%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.19 (s, 6H, 2×Me); 0.94 (s, 9H, 3×Me); 2.27 (s, 1H, H-7); 2.28 (s, 1H, H-7); 2.60 (d, *J*=18.0 Hz, 1H, H-5); 2.85 (br d, *J*=18.0 Hz, 1H, H-5), 3.60 (q, *J*=8.4 Hz, 1H, ox), 3.75 (q, *J*=8.4 Hz, 1H, ox), 4.35–4.42 (m, 2H, ox), 4.50 (t, *J*=2.1 Hz, 1H, H-3), 5.14 (d, *J*=12.3 Hz, 1H, OCH_2), 5.31 (d, *J*=12.3 Hz, 1H, OCH_2), 5.67 (br s, 1H, H-2), 7.39 (br s, 5H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.6 (Me), −4.4 (Me), 17.8 (C), 25.4 (Me), 27.3 (C-5), 29.5 (C-7), 36.7 (C-6), 41.1 (ox), 62.0 (ox), 65.8 (C-2), 67.2 (CH_2), 96.7 (C-3), 128.3, 128.32, 128.5, 135.5, 150.1 (C-4), 157.3 (CO, ox), 171.2 (CO). HRMS (FAB): calcd 445.2159 [M+1]; found 445.2158.

4.2.5. Ethyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxooxazolidin-3-yl)-6-(pyridin-2-yl)-1-aza-bicyclo[4.1.0]hept-3-en-7-carboxylate 5e. To the 2*H*-azirine **2e** (0.36 g; 1.87 mmol) solubilized in toluene (10 mL) was added 3-(3-(*tert*-butyldimethylsilyloxy)buta-1,3-dienyl)oxazolidin-2-one **3** (0.35 g; 1.87 mmol) solubilized in toluene (10 mL). The reaction mixture was stirred under N_2 at 75–80 °C for 2.5 days. After that the solvent was evaporated and the crude obtained was purified by dry flash-cromatography (pet. ether/diethyl ether; gradient polarity), to give compound **5e** as an oil. Yield (248 mg; 0.54 mmol; 29%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.15 (s, 3H, Me), 0.18 (s, 3H, Me), 0.91 (s, 9H, 3×Me), 2.46 (dt, *J*=18.0, 2.4 Hz, 1H, H-5), 3.27 (dd, *J*=18.0, 0.9 Hz, 1H, H-5), 3.27 (s, 1H, H-7), 3.60–3.75 (m, 2H, ox), 3.88–4.00 (m, 2H, CH_2), 4.33–4.41 (m, 2H, ox), 4.58 (t, *J*=2.1 Hz, 1H, H-3), 5.82 (br s, 1H, H-2), 7.14–7.19 (m, 1H, Ar), 7.62–7.66 (m, 2H, Ar), 8.48–8.51 (m, 1H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=−4.7 (Me), −4.4 (Me), 13.8 (Me), 17.8 (C), 25.4 (Me), 31.2 (C-5), 40.1

(C-7), 40.9 (ox), 47.2 (C-6), 60.9 (CH_2), 62.2 (ox), 65.9 (C-2), 97.1 (C-3), 122.4, 122.5, 136.3, 148.7, 150.5 (C-4), 157.4, 157.8, 168.1 (CO). HRMS (FAB): calcd 440.2268 [M+1]; found 440.2279.

4.2.6. Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 8d and 9d. The α-azide **1d** (0.71 g; 3.46 mmol) was dissolved in toluene (100 mL) and heated under reflux for 5 h. (*R*)-3-(3-(*tert*-Butyldimethylsiloxy)-buta-1,3-dienyl)-4-phenyloxazolidin-2-one **4** (0.60 g; 1.73 mmol) was added after cooling the solution to rt. The reaction mixture was stirred under N_2 at rt, for 5 days. After that the solvent was evaporated to give a brown oil that was purified by dry flash chromatography (pet. ether/ether; gradient polarity). A first fraction was obtained as a thick oil identified as compound **8d**. Yield (370 mg; 0.71 mmol; 41%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=-0.27$ (s, 3H, Me), −0.12 (s, 3H, Me), 0.78 (s, 9H, 3×Me), 2.10 (s, 1H, H-7), 2.27 (s, 1H, H-7), 2.42 (dd, $J=17.7$, 0.6 Hz, 1H, H-5), 2.71 (dd, $J=17.7$, 1.2 Hz, 1H, H-5), 4.07 (t, $J=2.2$ Hz, 1H, H-3), 4.10 (dd, $J=8.7$, 6.3 Hz, 1H, ox), 4.67 (t, $J=8.7$ Hz, 1H, ox), 5.06 (dd, $J=8.7$, 6.3 Hz, 1H, ox), 5.12 (d, $J=12.6$ Hz, 1H, OCH_2), 5.28 (d, $J=12.6$ Hz, 1H, OCH_2), 5.78 (br s, 1H, H-2), 7.36 (br s, 10H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=-5.0$ (Me), −4.8 (Me), 17.6 (C), 25.3 (Me), 27.4 (C-5), 29.6 (C-7), 36.6 (C-6), 57.4 (ox), 67.0 (C-2), 67.2 (OCH_2), 70.9 (ox), 97.4 (C-3), 126.9, 128.2, 128.3, 128.5, 129.0, 129.2, 135.4, 139.6, 148.4 (C-4), 158.4 (CO, ox), 171.1 (CO). HRMS (FAB): calcd 521.24717 [M+1]; found 521.24812.

A second fraction was obtained pure, as thick oil identified as compound **9d**. Yield (0.375 g; 0.72 mmol; 42%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=0.18$ (s, 3H, Me), 0.19 (s, 3H, Me), 0.92 (s, 9H, 3×Me), 2.00 (s, 1H, H-7), 2.48 (s, 1H, H-7), 2.52 (d, $J=17.7$ Hz, 1H, H-5), 2.70 (d, $J=17.7$ Hz, 1H, H-5), 4.10 (t, $J=8.4$ Hz, 1H, ox), 4.65 (t, $J=8.4$ Hz, 1H, ox), 4.79 (t, $J=2.1$ Hz, 1H, H-3), 4.84 (br s, 1H, H-2), 5.27 (t, $J=8.4$ Hz, 1H, ox), 5.13 (d, $J=12.6$ Hz, 1H, OCH_2), 5.20 (d, $J=12.6$ Hz, 1H, OCH_2), 7.30–7.41 (m, 10H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=-4.7$ (Me), −4.4 (Me), 17.8 (C), 25.5 (Me), 27.4 (C-5), 30.4 (C-7), 37.7 (C-6), 60.0 (ox), 66.6 (C-2), 66.9 (OCH_2), 70.0 (ox), 98.2 (C-3), 127.2, 127.9, 128.1, 128.2, 128.5, 128.6, 129.0, 129.2, 135.6, 138.3, 148.0 (C-4), 157.5 (CO, ox), 171.6 (CO). HRMS (ESI): calcd 543.2291 [M+Na]; found 543.2292.

4.3. Synthesis of hydrolysis products

4.3.1. 2-Benzoyl-2-(1-chloroethyl)-2,3-dihydropyridin-4-(1*H*)-one 10a. To a solution of the adduct **5a** (228 mg; 0.53 mmol) in THF (5 mL) was added dropwise a solution of HCl (45 μL; 0.53 mmol) in THF (3 mL) at 0 °C and left at rt for 15 min. The solvent was removed and the residue re-dissolved in DCM (25 mL). The solution was washed with water (25 mL) and the organic phase dried over $MgSO_4$ and evaporated. The crude material was subjected to dry flash chromatography (ether) to give a pale yellow oil identified as compound **10a**. Yield (68 mg; 0.18 mmol; 34%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.64$ (d, $J=6.6$ Hz, 3H, Me), 2.85 (d, $J=17.1$ Hz, 1H, H-3), 3.08 (d, $J=17.1$ Hz, 1H, H-3), 4.69 (q, $J=6.6$ Hz, 1H, H-1′), 5.07 (dd, $J=7.8$, 0.9 Hz, H-5), 5.95 (br d, $J=5.1$ Hz, 1H, NH), 7.32 (dd, $J=7.8$, 6.3 Hz, 1H, H-6), 7.40–7.80 (m, 5H, Ar). ^{13}C (75.5 MHz, $CDCl_3$), $\delta=19.7$ (Me), 41.6 (C-3), 61.9 (C-1′), 71.5 (C-2), 99.0 (C-5), 128.2, 128.5, 132.5, 135.5, 150.6 (C-6), 187.9 (CO), 200.3 (CO). HRMS (FAB): calcd 266.0762 [M+1]; found 266.0755.

4.3.2. Benzyl 2-(chloromethyl)-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate 10d. To a solution of the adduct **5d** (230 mg; 0.52 mmol) in THF (5 mL) was added dropwise a solution of HCl (43 μL; 0.52 mmol) in THF (3 mL) at 0 °C. Then the mixture was allowed to reach rt and was stirred for 1 h. After this time the solvent was partially evaporated, aqueous 10% $NaHCO_3$ (20 mL) was added and the mixture was stirred for 15 min at rt. The organic phase was separated and the aqueous phase washed with DCM (3×25 mL). The organic extracts were combined and washed with water (25 mL), dried over $MgSO_4$, and the solvent evaporated to give a brown oil. Dry flash chromatography (pet. ether/ether; polarity gradient) gave a white solid **10d** (mp 106–107 °C).Yield (67 mg; 25.5 mmol; 50%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=2.66$ (d, $J=16.5$ Hz, 1H, H-3), 2.94 (d, $J=16.5$ Hz, 1H, H-3), 3.81 (d, $J=11.1$ Hz, 1H, H-1′), 3.92 (d, $J=11.1$ Hz, 1H, H-1′), 5.08 (d, $J=7.8$ Hz, 1H, H-5), 5.23 (s, 2H, OCH_2), 5.85 (br s, 1H, NH), 7.21 (dd, $J=7.8$, 6.3 Hz, 1H, H-6), 7.34–7.37 (m, 5H, Ar). ^{13}C (75.5 MHz, $CDCl_3$), $\delta=42.1$ (C-3), 46.6 (C-1′), 64.2 (C-2), 68.4 (OCH_2), 99.9 (C-5), 128.3, 128.7, 128.72, 134.5, 149.3 (C-6), 169.76 (CO), 188.5 (CO). HRMS (FAB): calcd 280.0740 [M+1]; found 280.0745.

4.3.3. Ethyl 2′-chloro-2-(4-oxo-2-(pyridin-2-yl)-1,2,3,4-tetrahydropyridin-2-yl)acetate 10e. To a solution of **5e** (248 mg; 0.54 mmol) in THF (2 mL) was added dropwise at 0 °C HCl (45 μL; 0.54 mmol) dissolved in THF (3 mL). Then the mixture was allowed to reach rt and was stirred for 1 h. After this time the solvent was partially evaporated, 10% aqueous $NaHCO_3$ (20 mL) was added and stirred for 15 min at rt. The organic phase was separated and the aqueous phase washed with DCM (3×25 mL). The organic extracts were combined and washed with water (25 mL), dried over $MgSO_4$ and the solvent was evaporated to give a yellow oil that was purified by dry flash chromatography (ether) to afford an oil identified as compound **10e**. Yield (87 mg; 0.29 mmol; 55%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.22$ (t, $J=7.5$ Hz, 3H, Me), 3.10 (d, $J=16.5$ Hz, 1H, H-3), 3.22 (d, $J=16.5$ Hz, 1H, H-3), 4.15 (m, 2H, OCH_2), 5.09 (dd, $J=7.8$, 0.9 Hz, 1H, H-5), 5.09 (s, 1H, H-1′), 6.54 (br d, $J=6.0$ Hz, 1H, NH), 7.24–7.32 (m, 2H, Ar), 7.43 (dd, $J=7.8$, 0.9 Hz, 1H, H-6), 7.73 (dt, $J=7.5$, 1.8 Hz, 1H, Ar), 8.57 (dm, $J=4.5$ Hz, 1H, Ar). ^{13}C (75.5 MHz, $CDCl_3$), $\delta=13.8$ (Me), 43.2 (C-3), 61.6 (C-1′), 62.5 (OCH_2), 64.4 (C-2), 99.9 (C-5), 121.1 (CH), 123.3 (CH), 136.8 (CH), 149.0 (C), 149.1 (C-6), 156.6 (C), 166.8 (CO), 189.6 (CO). HRMS (FAB): calcd 295.0849 [M+1]; found 295.0853.

4.3.4. Attempt to the synthesis of (*E*)-3-(4-(2-benzoyl-3-ethylaziridin-2-yl)-3-oxobut-1-enyl)oxazolidin-2-one 11b. To a solution of the adduct **5b** (0.13 g; 0.29 mmol) in THF (5 mL) was added dropwise at 0 °C H_2SO_4 (16 μL; 0.29 mmol) and water (3 equiv; 25 μL). The mixture was

stirred for 30 min at 0 °C and another 30 min at rt. The solvent was removed, the residue re-dissolved in DCM, washed with 10% $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$ and the solvent evaporated to give a yellow solid. The crude product showed to be mainly compound **11b** by ^1H NMR. ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.03$ (t, $J=7.2$ Hz, 3H, Me), 1.25 (m, 1H, CH_2), 1.52 (m, 1H, CH_2), 1.95 (br s, 1H, NH), 2.33 (t, $J=5.7$ Hz, 1H, H-3), 2.75 (d, $J=16.8$ Hz, 1H, H-1′), 3.60 (d, $J=16.8$ Hz, 1H, H-1′), 3.70 (t, $J=7.2$ Hz, 2H, CH_2, ox), 4.50 (t, $J=7.2$ Hz, 2H, CH_2, ox), 5.37 (d, $J=14.1$ Hz, 1H, H-3′), 7.41–7.54 (m, 3H, Ar), 7.72 (d, $J=14.1$ Hz, 1H, H-4′), 7.89 (d, $J=6.9$ Hz, 2H, Ar). HRMS (FAB): calcd 328.1423 [M^+]; found 328.1434.

Dry flash chromatography (ether/DCM) gave a pure yellow solid, compound **14b** [mp 160 °C (dec)]. Yield (22 mg; 0.07 mmol; 23%). A second chromatography fraction was a mixture of at least three compounds, the original **5b**, compound **11b** and an unknown product. Re-dissolution of a portion of this fraction (20 mg) in DCM (5 mL) and treatment with silica for 1 h gave a mixture of compounds **11b** and **14b** as an oil after removal of silica and evaporation to dryness. Yield (15 mg). Compound **14b**: ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.31$ (3H, Me), 3.05 (q, 2H, $J=7.2$ Hz), 3.82 (t, 2H, $J=7.8$ Hz, ox), 4.53 (t, 2H, $J=8.4$ Hz, ox), 5.50 (d, 1H, $J=15.0$ Hz), 6.25 (d, 1H, $J=2.7$ Hz), 7.44 (d, 1H, $J=15.0$ Hz), 7.44–7.51 (m, 3H, Ar), 7.80 (m, 2H, Ar), 10.00 (br s, 1H, OH). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=13.9$ (Me), 20.9 (CH_2), 42.4 (CH_2), 62.6 (CH_2), 102.7 (CH), 111.6 (CH), 119.5 (C), 120.3 (CH), 125.9 (C), 127.9 (CH), 129.0 (CH), 131.0 (CH), 140.8 (C), 144.0 (C), 155.9 (CO, ox), 191.8 (CO).

4.3.5. (*E*)-Methyl 3-(2,6-dichlorophenyl)-2-(2-oxo-4-(2-oxooxazolidin-3-yl)but-3-enyl)aziridine-2-carboxylate 11c. To a solution of the adduct **5c** (250 mg; 0.53 mmol) in THF (5 mL) was added dropwise at 0 °C HCl (44 μL; 0.53 mmol) diluted in THF (3 mL). The mixture was allowed to reach rt and stirred for 1 h. The solvent was partially evaporated and 10% aqueous $NaHCO_3$ (20 mL) was added. The mixture was stirred for 15 min and then extracted with DCM (3×25 mL). The organic extracts were combined and washed with water (25 mL), dried over $MgSO_4$ and evaporated to give an oil that was purified recrystalization (DCM/pet. ether) to give a colorless solid (mp 162.5—164.5 °C) identified as compound **11c**. Yield (142 mg; 0.40 mmol; 76%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=2.65$ (d, $J=17.4$ Hz, 1H, H-1′), 2.95 (br s, 1H, NH), 3.16 (s, 1H, H-3), 3.51 (s, 3H, OMe), 3.82 (t, $J=7.8$ Hz, 2H, ox), 3.94 (d, $J=17.4$ Hz, 1H, H-1′), 4.56 (t, $J=7.8$ Hz, 2H, ox), 5.57 (d, $J=14.4$ Hz, 1H, H-3′), 7.17 (d, $J=8.1$ Hz, 1H, Ar), 7.28 (m, 2H, Ar), 7.92 (d, $J=14.4$ Hz, 1H, H-4′). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=42.1$ (ox), 42.8 (C-2), 43.4 (C-1′), 44.8 (C-3), 52.7 (OMe), 62.6 (ox), 109.6 (C-3′), 128.0, 129.3, 131.3 (C), 135.7 (C) 137.6 (C-4′), 154.7 (CO, ox), 170.9 (CO), 195.0 (CO). HRMS (FAB): calcd 399.0515 [M+1]; found 399.0514.

4.3.6. (*E*)-Benzyl 3-(2,6-dichlorophenyl)-2-(2-oxo-4-(2-oxooxazolidin-3-yl)but-3-enyl)aziridine-2-carboxylate 11d. To a solution of the adduct **5d** (0.25 g; 0.55 mmol) in THF (5 mL), H_2SO_4 (30 μL; 0.55 mmol) and water (3 equiv; 27 μL) were added dropwise at 0 °C. The mixture was stirred at rt for 1 h. The solvent was removed, the residue re-dissolved in DCM, washed with 10% aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$ and the solvent evaporated to give an oil. A fast dry flash chromatography (MeCN) gave a yellow oil identified as compound **11d**. Yield (101 mg; 0.31 mmol; 56%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=1.79$ (s, 1H, H-3), 2.22 (s, 1H, H-3), 2.75 (d, $J=17.1$ Hz, 1H, H-1′), 3.23 (d, $J=17.1$ Hz, 1H, H-1′), 3.66 (dt, 2H, $J=8.1$, 2.4 Hz, ox), 4.47 (t, $J=8.1$ Hz, 2H, ox), 5.12 (s, 2H, OCH_2), 5.45 (d, 1H, $J=14.1$ Hz, H-3′), 7.27–7.32 (m, 5H, Ar), 7.79 (d, $J=14.1$ Hz, 1H, H-4′). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=32.9$ (C-3), 35.1 (C-2), 41.9 (ox), 42.9 (C-1′), 62.5 (ox), 67.5 (OCH_2), 109.1 (C-3′), 128.1, 128.2, 128.4, 135.1 (C), 137.4 (C-4′), 154.5 (CO, ox), 172.7 (CO) 195.1 (CO). HRMS (FAB): calcd 331.1294 [M+1]; found 331.1298.

4.3.7. (*E*)-Benzyl 2-amino-2-(chloromethyl)-4-oxo-6-(2-oxooxazolidin-3-yl)hex-5-enoate 12d. To a solution of the adduct **11d** (45 mg; 0.14 mmol) in THF (2 mL) was added dropwise at 0 °C HCl (11.5 μL; 0.14 mmol) diluted in THF (1 mL). The mixture was allowed to reach rt and stirred for 1 h. The solvent was partially evaporated and 10% aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with DCM (3×5 mL). The organic extracts were combined and washed with water (10 mL), dried over $MgSO_4$ and evaporated to give a clean yellow oil that was identified as compound **12d**. Yield (33 mg; 0.90 mmol; 66%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=2.41$ (br s, 2H, NH_2), 2.91 (d, $J=17.1$ Hz, 1H, H-3), 3.26 (d, $J=17.1$ Hz, 1H, H-3), 3.67–3.75 (m, 4H, ox +H-1), 4.53 (t, $J=8.1$ Hz, 2H, ox), 5.17 (s, 2H, OCH_2), 5.44 (d, 1H, $J=14.1$ Hz, H-5), 7.31–7.36 (m, 5H, Ar), 7.84 (d, $J=14.1$ Hz, 1H, H-6). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=41.9$ (ox), 46.3 (C-3), 50.9 (CH_2Cl), 60.4 (C), 62.6 (ox), 67.6 (OCH_2), 109.1 (C-5), 128.3, 128.5, 128.6, 135.3 (C), 138.1 (C-6), 154.5 (CO, ox), 173.4 (CO) 195.3 (CO). HRMS (ESI): calcd 389.0889 [M+Na]; found 389.0875.

4.3.8. 3-(6-Benzoyl-4-(*tert*-butyldimethylsilyloxy)-7-ethyl-1-aza-bicyclo[4.1.0]hept-3-en-2-yl)oxazolidin-2-one 13b. To a solution of the adduct **5b** (260 mg, 0.59 mmol) in dry CH_3CN (10 mL) was added anilinium fluoride in one portion at 0 °C. The reaction mixture was stirred for 45 min at rt. The solvent was removed and the residue re-dissolved in DCM (30 mL). The organic phase was washed with 10% aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, and the solvent evaporated to give a crude material. This product was subjected to dry flash chromatography (pet. ether/ether; 1:3) giving a pure solid (130.5–131.5 °C) identified as compound **13b**. Yield (95 mg; 0.21 mmol, 36%). ^1H NMR, (300 MHz, $CDCl_3$, *J* Hz), $\delta=0.13$ (s, 3H, Me), 0.17 (s, 3H, Me), 0.89 (s, 9H, 3× Me), 0.98–1.06 (m, 4H, Me+C*H*H), 1.55–1.63 (m, 1H, CH*H*), 2.25 (dd, $J=8.4$, 3.0 Hz, 1H, H-7), 2.36 (dt, $J=18.0$, 2.1 Hz, 1H, H-5), 2.81 (dd, $J=18.0$, 2.1 Hz, 1H, H-5), 3.37 (q, $J=7.8$ Hz, 1H, ox), 4.05–4.14 (m, 1H, ox), 4.29–4.38 (m, 1H, ox), 4.43–4.52 (m, 1H, ox), 4.64–4.66 (m, 1H, H-3), 5.59–5.62 (m, 1H, H-2), 7.56–7.61 (m, 2H, Ar), 7.65–7.71 (m, 1H, Ar), 7.99–8.02 (m, 2H, Ar). ^{13}C NMR, (75.5 MHz, $CDCl_3$), $\delta=-4.6$ (Me), −4.4 (Me), 11.7 (Me), 17.9 (C), 24.0 (Me), 25.4 (Me), 29.8 (C-5), 39.5 (ox), 44.2 (C-7), 51.5

(C-6), 62.3 (ox), 67.4 (C-2), 96.4 (C-3), 128.8, 129.2, 133.7, 134.9, 149.0 (C-4), 157.7 (CO, ox), 196.6 (CO). HRMS (FAB): calcd 443.2366 [M+1]; found 443.2361.

A second fraction (ether) gave a white solid (mp>160 °C (dec)) identified as compound **14b**. Yield (22 mg; 0.067 mmol; 12%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=1.31 (t, *J*=7.2 Hz, 3H, Me), 3.05 (q, *J*=7.2 Hz, 2H, CH_2), 3.82 (t, *J*=7.8 Hz, 2H, ox), 4.53 (t, *J*=8.4 Hz, 2H, ox), 5.50 (d, *J*=15.0 Hz, 1H), 6.25 (d, *J*=2.7 Hz, 1H), 7.44 (d, *J*=15.0 Hz, 1H), 7.44–7.51 (m, 3H, Ar), 7.80 (m, 2H, Ar), 10.00 (br s, 1H, OH). ^{13}C NMR, (75.5 MHz, $CDCl_3$), δ=13.9 (Me), 20.9 (CH_2), 42.4 (CH_2 ox), 62.6 (CH_2 ox), 102.7 (CH), 11.6 (CH), 119.5 (C), 120.3 (CH), 125.9 (C), 127.9 (CH), 129.0 (CH), 131.0 (CH), 140.8 (C), 144.0 (C), 155.9 (CO, ox), 191.8 (CO). HRMS (FAB): calcd 329.1501 [M+1]; found 329.1492.

4.3.9. Benzyl 4-(*tert*-butyldimethylsilyloxy)-2-(2-oxooxazolidin-3-yl)-1-aza-bicyclo[4.1.0]hept-3-ene-6-carboxylate 13d. *Method 1*. To a solution of the adduct **5d** (488 mg; 1.09 mmol) in dry MeCN (10 mL) was added anilinium fluoride (125 mg, 1.1 mmol) in one portion at 0 °C. The reaction mixture was stirred at rt for 45 min. The solvent was then removed and the residue re-dissolved in DCM (25 mL). The organic phase was washed with 10% $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, and the solvent evaporated. A yellow solid was obtained and subjected to dry flash chromatography (ether) to give a pure solid (mp 104–106 °C), identified as compound **13d**. Yield (0.15 g; 0.34 mmol; 31%). ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=0.15 (s, 3H, Me), 0.16 (s, 3H, Me), 0.92 (s, 9H, 3×Me), 1.91 (s, 1H, H-7), 2.40 (s, 1H, H-7), 2.56 (dd, *J*=18.3, 1.8 Hz, 1H, H-5), 2.94 (d, *J*=18.3 Hz, 1H, H-5), 3.40 (m, 2H, ox), 4.26 (t, *J*=7.8 Hz, 2H, ox), 4.60 (dd, *J*=5.1, 2.7 Hz, 1H, H-3), 5.13 (d, *J*=12.6 Hz, 1H, OCH_2), 5.51 (dt, *J*=5.1, 1.5 Hz, 1H, H-2), 5.62 (d, *J*=12.6 Hz, 1H, OCH_2), 7.35–7.55 (m, 5H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ=−4.56 (Me), −4.58 (Me), 17.9 (C), 25.4 (Me), 26.8 (C-5), 31.1 (C-7), 49.8 (ox), 40.6 (C-6), 62.0 (ox), 67.0 (OCH_2), 67.2 (C-2), 95.0 (C-3), 128.0, 128.3, 128.5, 135.5 (C), 149.6 (C-4), 157.5 (CO, ox), 171.0 (CO). HRMS (FAB): calcd 445.2159 [M+1]; found 445.2158. An impure sample of compound **14d** was also obtained. Some peaks of its ^{1}H NMR spectrum are registered: ^{1}H NMR, (300 MHz, $CDCl_3$, *J* Hz), δ=3.82 (t, 2H, *J*=8.4 Hz, ox), 4.53 (t, 2H, *J*=8.4 Hz, ox), 5.29 (s, 2H), 5.70 (d, 1H, *J*=15.0 Hz), 6.99 (s, 1H), 7.19 (d, 1H, *J*=15.0 Hz), 7.32–7.44 (m, 5H, Ar), 8.95 (br s, 1H, OH). HRMS (ESI): calcd 353.1114 [M+Na]; found 353.1115.

Method 2. To a solution of the adduct **5d** (100 mg; 0.23 mmol) in MeOH (5 mL), anilinium fluoride (26 mg; 0.23 mmol) was added in one portion at 0 °C. The reaction mixture was stirred at rt for 45 min. The solvent was then removed and the mixture re-dissolved in DCM (30 mL), washed with 10% $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, and the solvent evaporated giving a yellow oil. Dry flash chromatography (ether) gave a pure solid, compound **13d**, by comparation with product obtained in method 1. Yield (33 mg; 0.08 mmol; 33%). A second fraction (ether/DCM; 9:1) was obtained and identified by ^{1}H NMR as compound **14d** (10 mg; 0.02 mmol; 10%).

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Mg-promoted reductive coupling of aromatic carbonyl compounds with trimethylsilyl chloride and bis(chlorodimethylsilyl) compounds☆

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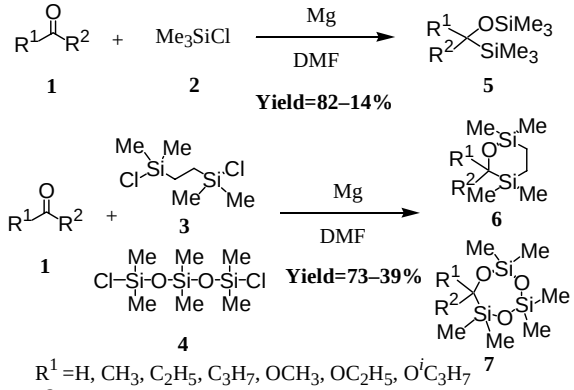
Abstract—Mg-promoted reductive coupling of aromatic carbonyl compounds (**1**) with chlorosilanes, such as trimethylsilyl chloride (TMSCl:**2**), 1,2-bis(chlorodimethylsilyl)ethane (**3**) and 1,5-dichlorohexamethyltrisiloxane (**4**), in *N*,*N*-dimethylformamide (DMF) at room temperature brought about selective and facile reductive formation of both of carbon–silicon and oxygen–silicon bonds to give the corresponding α-trimethylsilylalkyl trimethylsilyl ethers (**5**) and cyclic siloxanes (**6**), (**7**) in moderate to good yields, respectively. The present facile and selective coupling may be initiated through electron transfer from Mg metal to aromatic carbonyl compounds (**1**).

1. Introduction

Effective formation of a carbon–silicon bond is one of the most attractive subjects in organic synthesis[2] because of much usefulness and important functions of organosilicon compounds. It have been reported[3] that carbon–silicon bond formation was accomplished by treatment of carbonyl compounds and activated olefins with an alkali metal such as Li or Na in THF or DME as the solvent in the presence of trimethylsilyl chloride (TMSCl), although selectivity and/or yield of *C*-silylated products were not always satisfactory and special caution was generally needed for treatment of these alkali metals.

On the other hand, a variety of Mg-promoted carbon-silylation of carbonyl compounds and activated olefins were reported by Calas et al.,[4] although carcinogenic hexamethylphosphoric triamide (HMPA)[5,6] was necessary to use as the solvent.

We now wish to report a facile method for selective and effective carbon–silicon bond formation through Mg-promoted reductive coupling of carbonyl compounds (**1**) with TMSCl (**2**) in DMF at room temperature to give the corresponding α-trimethylsilylalkyl trimethylsilyl ethers (**5**) in good yields. Furthermore, Mg-promoted one-pot cyclization of aromatic carbonyl compounds (**1**), including ketones, and esters, with bis(chlorodimethylsilyl) compounds, such as 1,2-bis(chlorodimethylsilyl)ethane (**3**) or 1,5-dichlorohexamethyltrisiloxane (**4**), to give the corresponding cyclic siloxane compounds (**6**, **7**) in good yields, respectively (Scheme 1).



Scheme 1.

☆ See, Ref. 1.

Keywords: Silylation; Electron transfer; Aromatic carbonyl compounds; Magnesium.
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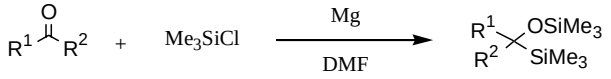
2. Result and discussion

2.1. Mg-promoted reductive coupling of carbonyl compounds with TMSCl

It was found that treatment of benzaldehyde (**1a**) with TMSCl in the presence of commercially available magnesium turnings for Grignard reagents in DMF at room temperature brought about facile and selective reductive formation of carbon–silicon and oxygen–silicon bonds to give α-trimethylsilyloxyl benzyltrimethylsilane (**5a**) in a 82% yield. Among a variety of reactive metals such as Zn, Al, and Mg, Mg showed the best result in present reaction, and no or little formation of **5a** was observed when Zn or Al was employed instead of Mg. It may be noteworthy that any reactions did not occur to recover **1a** quantitatively when TMSCl was absent in the reaction system. This reductive coupling reaction was also considerably influenced by a relative ratio of Mg, **2**, and **1a**. The best result for formation of **3a** was obtained when the relative proportion of Mg/**2**/**1a** was 3:8:1.[7] Employment of DMF as a solvent gave the best result among acetonitrile, tetrahydrofuran, dimethoxyethane and *N*,*N*-dimethyl-acetoamide.

Under the similar optimized reaction conditions, a variety of trimethylsilylated adducts **5a–l** were efficiently obtained in good to excellent yields, as shown in Table 1. It was quite interesting that the present reaction readily proceeded with not only aromatic aldehydes (**1a–g**) but also aromatic ketones (**1h–k**) and ester (**1l**). The α-trimethylsilylalkyl trimethylsilyl ethers (**5**) were readily hydrolyzed with an acidic aqueous solution to the corresponding α-trimethylsilyl alcohols.

Table 1. Mg-promoted silylation of aldehydes, ketones and esters with TMSCl (**2**)[a]

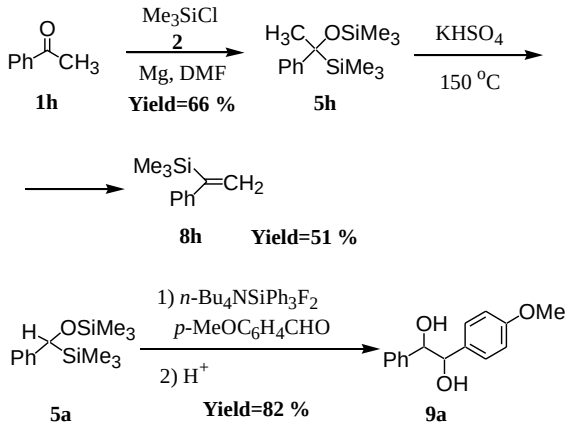


1 **2** **5**

Entry	R^1 in **1**	R^2 in **1**		Yield of **5** (%)[b]
1	H	C_6H_5	(**1a**)	82 (**5a**)
2	H	*o*-ClC_6H_4	(**1b**)	79 (**5b**)
3	H	*m*-ClC_6H_4	(**1c**)	75 (**5c**)
4	H	*p*-ClC_6H_4	(**1d**)	73 (**5d**)
5	H	*p*-$CF_3C_6H_4$	(**1e**)	54 (**5e**)
6	H	*o*-$CH_3OC_6H_4$	(**1f**)	78 (**5f**)
7	H	2-Thienyl	(**1g**)	52 (**5g**)
8	CH_3	C_6H_5	(**1h**)	74 (**5h**)
9	C_2H_5	C_6H_5	(**1i**)	14 (**5i**)[c]
10	C_6H_5	C_6H_5	(**1j**)	68 (**5j**)
11	CH_3	2-Thienyl	(**1k**)	42 (**5k**)
12	OC_2H_5	C_6H_5	(**1l**)	56 (**5l**)

[a] Reaction condition: substrate (5 mmol), trimethysilylchloride (**2**) (8.0 equiv per mol), magnesium (3.0 equiv per mol), DMF (60 mL), 20 h, room temperature, under N_2 atmosphere.
[b] Isolated yield.
[c] 4-Trimethylsilylpropiophenone was obtained in 20% yield.

The product **5a–l** can be easily transformed to many useful compounds such as esters, aldehydes, ketones, alcohols, and ethers.[8] For example, treatment of the product **5h** with $KHSO_4$, and that of the product **5a** with *n*-$Bu_4NSiPh_3F_2$/*p*-methoxybenzaldehyde gave α-silylstyrene (**8h**) and the mixed diarylethanediol (**9a**) in good yields, respectively (Scheme 2).



1h **Yield=66 %** **5h** **8h** **Yield=51 %** **5a** **Yield=82 %** **9a**

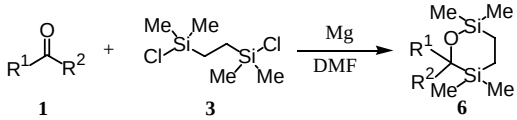
Scheme 2.

2.2. Mg-promoted one-pot cyclization of aromatic carbonyl compounds with bis(chlorodimethylsilyl) compounds (3, 4)

At the next step, use of bis(chlorodimethylsilyl) compounds (**3**, **4**) instead of TMSCl in the present cross coupling brought about efficient and selective one-pot cyclization of aromatic carbonyl compounds (**1**) to give the corresponding cyclic siloxanes (**6h–v**, **7h–t**) successfully.

Generally the reaction was carried out in anhydrous DMF at room temperature with magnetically stirring under nitrogen atmosphere for 20 h. Commercially available magnesium turnings for Grignard reaction was also used without any pre-treatment in the present cyclization. After usual work-up of the reaction mixture, column chromatography of the crude products gave the corresponding cyclic siloxanes (**6h–v**, **7h–t**) in 39–73% yields, as shown in Tables 2 and 3.

Table 2. Cyclization of aromatic carbonyl compounds in the presence of 1,2-bis(chlorodimethylsilyl)ethane (**3**)[a]

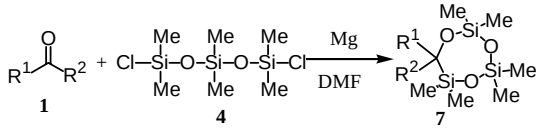


1 **3** **6**

Entry	R^1 in **1**	R^2 in **1**		Yield of **6** (%)[b]
1	CH_3	C_6H_5	(**1h**)	43 (**6h**)
2	CH_3	*m*-$MeOC_6H_4$	(**1m**)	43 (**6m**)
3	CH_3	*p*-$MeOC_6H_4$	(**1n**)	43 (**6n**)
4	CH_3	*m*-ClC_6H_4	(**1o**)	47 (**6o**)
5	CH_3	*p*-ClC_6H_4	(**1p**)	49 (**6p**)
6	C_2H_5	C_6H_5	(**1i**)	53 (**6i**)
7	C_3H_7	C_6H_5	(**1q**)	48 (**6q**)
8	OC_2H_5	C_6H_5	(**1l**)	54 (**6l**)
9	OC_2H_5	*m*-$MeOC_6H_4$	(**1r**)	73 (**6r**)
10	OC_2H_5	*p*-MeC_6H_4	(**1s**)	60 (**6s**)
11	OC_2H_5	*m*-ClC_6H_4	(**1t**)	69 (**6t**)
12	OCH_3	C_6H_5	(**1u**)	66 (**6u**)
13	$O^iC_3H_7$	C_6H_5	(**1v**)	73 (**6v**)

[a] Reaction condition: substrate (5 mmol), 1,2-bis(chlorodimethylsilyl)-ethene (**3**) (4.5 equiv per mol), magnesium (6.0 equiv per mol), DMF (60 mL), 20 h, room temperature, under N_2 atmosphere.
[b] GC yield.

Table 3. Cyclization of aromatic carbonyl compounds in the presence of 1,5-dichlorohexamethyltrisiloxane (**4**)[a]



1 **4** **7**

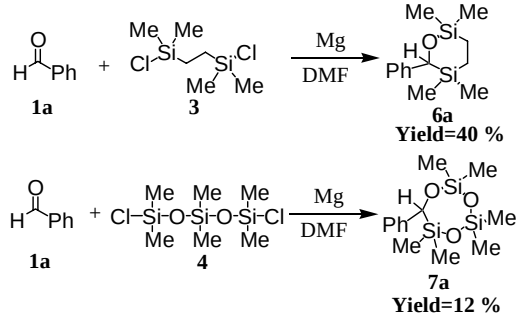
Entry	R^1 in **1**	R^2 in **1**		Yield of **7** (%)[b]
1	CH_3	C_6H_5	(**1h**)	43 (**7h**)
2	CH_3	*m*-$MeOC_6H_4$	(**1m**)	43 (**7m**)
3	CH_3	*p*-MeC_6H_4	(**1n**)	43 (**7n**)
4	CH_3	*p*-MeC_6H_4	(**1w**)	47 (**7w**)
5	CH_3	*p*-ClC_6H_4	(**1p**)	49 (**7p**)
6	OC_2H_5	C_6H_5	(**1l**)	54 (**7l**)
7	OC_2H_5	*m*-$MeOC_6H_4$	(**1r**)	73 (**7r**)
8	OC_2H_5	*p*-MeC_6H_4	(**1s**)	60 (**7s**)
9	OC_2H_5	*m*-ClC_6H_4	(**1t**)	69 (**7t**)

[a] Reaction condition: substrate (5 mmol), 1,5-dichlorohexamethyltrisiloxane) (**4**) (4.5 equiv per mol), magnesium (6.0 equiv per mol), DMF (60 mL), 20 h, room temperature, under N_2 atmosphere.
[b] GC yield.

These cyclic siloxanes (**6l–v**, **7l–t**) as well as non-cyclic product **5l**, the reductive coupling products from aromatic esters, may be useful reagents in organic synthesis as masked acyl silanes.[9]

It may be noteworthy tendency in the present cyclization that the reaction of aromatic esters (**1l**, **1r–t**) with both of 1,2-bis(chlorodimethylsilyl)ethane (**3**) and 1,5-dichlorohexamethyltrisiloxane (**4**) gave the corresponding cyclic siloxanes (**6l**, **6r–t**, **7l**, **7r–t**) in moderate to good yields (entries 8–13 in Table 2 and entries 6–9 in Table 3) while the similar cyclic siloxanes (**6h–p**, **7h–w**) were obtained in relatively low yields from the reaction of aromatic ketones (**1h**, **1i**, **1m–p**, **1w**) with bis(chlorodimethylsilyl) compounds (**3**, **4**) (entries 1–7 in Table 2 and entries 1–5 in Table 3).[10]

Furthermore, similar treatment of benzaldehydes with bis(chlorodimethylsilyl) compounds (**3**, **4**) led to formation the corresponding cyclization products (**6a**, **7a**) in 40 and 12% yields, respectively (Scheme 3).



1a **3** **6a**

1a **4** **7a**

Scheme 3.

This tendency was unusual since the reaction of aromatic aldehydes with TMSCl gave better yields than the similar reductive coupling of aromatic esters with the same reagent, as shown above.

Also, reduction potential of aromatic esters (**1l**, **1r–v**) are generally more positive (less reducible) than that of aromatic aldehydes and ketones.

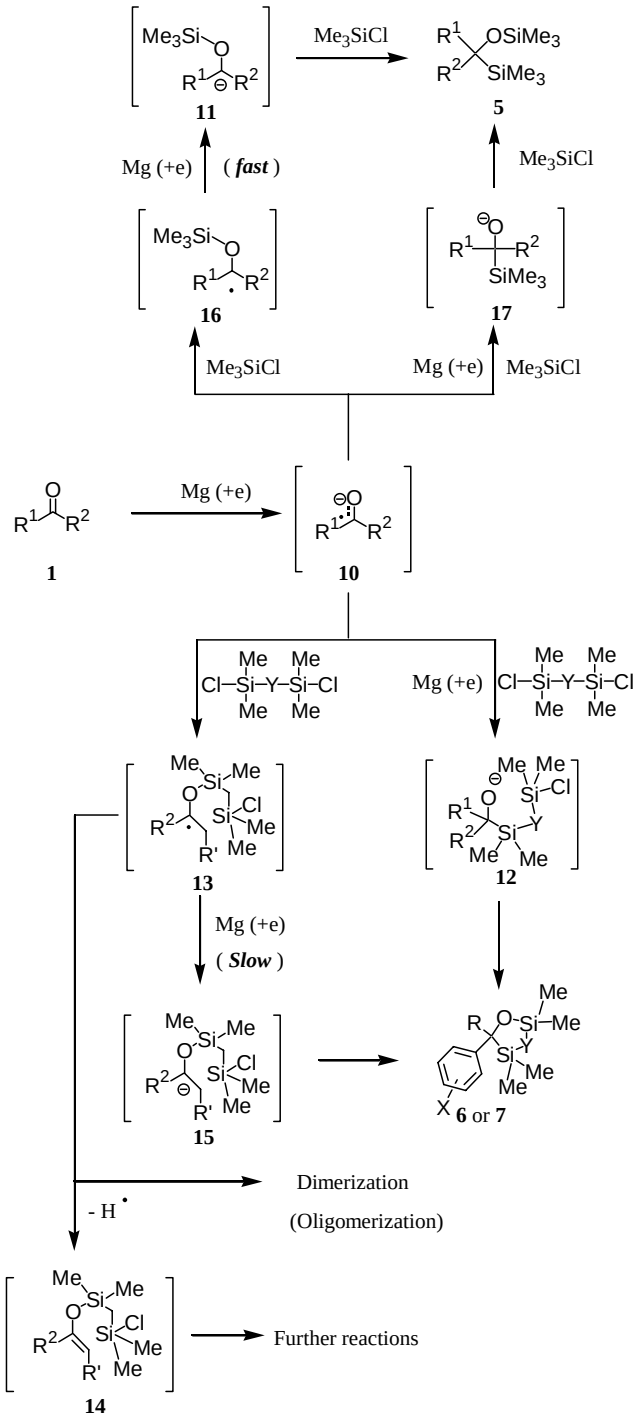
This unexpected phenomenon observed in this study may be probably attributed to some side-reactions[11] of aromatic aldehydes and ketones with bis(chlorodimethylsilyl) compounds (**3**, **4**), because our recent study[12] showed that Mg-promoted facile formation of enol trimethylsilyl ethers was observed in the reaction of aromatic ketones with trimethylsilyl choride under the similar conditions.

The reaction of aromatic aldehydes with bis(chlorodimethylsilyl) compounds (**3**, **4**) may be possibly accompanied with formation of pinacol type of complex dimeric product mixtures, because of lower electrophilicity of **3** and **4** in comparison with that of TMSCl as well as more stability (longer life-time) of the anion radical of aromatic aldehydes in comparison with that of aromatic esters.

It may be also interesting that the presence of an electron-withdrawing group on the phenyl ring of benzoic esters brought about some increase in the yield of the cyclic siloxanes (**6**, **7**) (entries 9 and 11 of Table 1), although similar substituent effect was not clearly observed in the reaction of acetophenone derivatives. The yield is not sensitive to a steric bulkiness of an alkoxy substituent of benzoic esters (entries 11–13 of Table 1).

Although the detailed role of TMSCl (**2**) and bis(chlorodimethylsilyl) compounds (**3** or **4**) in this reaction still remains ambiguous,[13] the following reaction mechanism may be proposed for the present Mg-promoted reductive coupling and cyclization from these experimental results as shown in Scheme 4. Cyclic voltammetry of the chlorosilanes, TMSCl (**2**), 1,2-bis(chlorodimethylsilyl)ethane (**3**) and 1,5-dichlorohexamethyltrisiloxane (**4**) do not give any reduction peak up to 3.0 V versus Ag/Ag^+ in DMF, while aromatic aldehydes, ketones and esters show their reduction peaks at -1.93, 2.10 and -2.36 V versus Ag/Ag^+ in DMF, respectively. Therefore, the first electron transfer from the Mg-metal to aromatic carbonyl compounds (**1**) may generate the corresponding anion radical, which may be subjected to the first electrophilic attack by TMSCl (**2**), 1,2-bis(chlorodimethylsilyl)ethane (**3**) or 1,5-dichlorohexamethyltrisiloxane (**4**) to the carbon atoms of carbonyl compounds followed by the fast second electron transfer giving the corresponding anionic intermediates (**12**). The second electrophilic attack to the oxygen atoms of the anonic intermediates (**12**) by TMSCl (**2**), 1,2-bis(chlorodimethylsilyl)ethane (**3**) or 1,5-dichlorohexamethyltrisiloxane (**4**) gave the α-trimethylsilylalkyl trimethylsilyl ethers (**5**) and final cyclic siloxane products (**6**, **7**), respectively (Scheme 2).

Electrophilic attack of bis(chlorodimethylsilyl) compounds (**3**, **4**) to the oxygen atoms of the carbonyl anion radicals (**10**) may generate α-silyloxy radicals (**13**), which may be subjected to the second slower electron transfer to the radical intermediate (**13**) giving the anion intermediate (**15**) in comparison with the faster electron transfer to the radical intermediate (**16**), giving the anion intermediate (**11**), because of steric effect in the electron transfer process



Scheme 4.

from Mg metal.[14] That may result in long-life time of the radical intermediate (**13**), to give various type of side-reactions such as dimerization, oligomerization, or elimination of hydrogen radicals in the case of aromatic ketones giving reactive silyloxy enol ethers (**14**) under the reaction conditions.

In conclusion, we have successfully developed one-pot selective formation of carbon–silicon and oxygen–silicon bonds and efficient novel cyclization, that are initiated by electron transfer from Mg metal. The present reactions may be characterized by simple procedure, unique reaction pattern, high selectivity, good yield and interesting functions of the products, which may possess high potentiality in organic chemistry.

3. Experimental

3.1. General

N,*N*-Dimethylformamide (DMF) was distilled from CaH_2. Unless otherwise mentioned, all the materials commercially obtained were used without further purification. Organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure by a rotary evaporator. Flash chromatography was carried out using Merck 60 (Mesh 230–400) silica gel. Reactants and chromatography fractions were analyzed using precoated silica gel 60 F_{254} plates (Merck). ^{1}H NMR spectra at 270 and 400 MHz were measured in the CCl_4 and $CDCl_3$ solutions. Chemical shifts are expressed in ppm downfield from internal dichloromethane (5.32 ppm). The apparatus of cyclic voltammetry was ASL model 600 (ASL).

3.2. Cyclic voltammetry analysis

Cyclic voltammetry was performed in a beaker-type cell equipped with Pt electrodes as the anode and the cathode, a reference electrode (Ag/AgCl) at room temperature. The solvent was DMF containing 1 wt% Bu_4NClO_4 as a supporting electrolyte. Sweep rate was 200 mV/s.

3.3. General procedure for synthesis of α-trimethylsilyl-alkyl trimethylsilyl ethers (5)

A typical procedure is as follows. A solution containing TMSCl (8 mmol) and Mg turnings (15 mmol) in 60 ml of dry DMF was stirred under nitrogen atmosphere. A DMF solution of benzaldehyde (**1a**) (10 mmol/5 ml) was dropwise added to the solution for 1 h at room temperature, which was then stirred for about 4 h. Then the reaction mixture was poured into 200 ml of a saturated aqueous ammonium chloride solution and was extracted by three 100 ml portions of ether. Usual work-up and subsequent column chromatography or distillation of the residue gave α-trimethylsilyl-α-trimethyl-siloxytoluene (**5a**) in a good yield with formation of a small amount of the homo-coupling by-product, 1,2-diphenyl-1,2-ethanediol.

3.3.1. α-Trimethylsilyl-α-trimethylsiloxytoluene (5a). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.07 (9H, s), 0.14 (9H, s), 4.56 (1H, d), 7.18–7.50 (5H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −4.13, 0.00, 70.29, 124.83, 125.09, 127.40, 144.38. IR (neat) ν (cm^{-1}): 1250, 1050. MS *m*/*z* 252 (M). Anal. Calcd for $C_{13}H_{24}OSi_2$: C, 61.84; H, 9.58. Found: C, 62.05; H, 9.41.

3.3.2. α-Trimethylsilyl-α-trimethylsiloxy-*o*-chlorotoluene (5b). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.03 (9H, s), 0.03 (9H, s), 4.99 (1H, s), 7.01–7.48 (4H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −3.74, −0.12, 66.04, 126.29, 126.45, 127.98, 128.81, 129.94, 142.32. IR (neat) ν (cm^{-1}): 1250, 1055. MS *m*/*z* 286 (M^+). Anal. Calcd for $C_{13}H_{23}ClOSi_2$: C, 54.41; H, 8.08. Found: C, 54.26; H, 8.25.

3.3.3. α-Trimethylsilyl-α-trimethylsiloxy-*m*-chrolotoluene (5c). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): −0.04 (9H, s), 0.03 (9H, s), 4.41 (1H, s), 6.98–7.26 (4H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −4.17, −0.03, 69.83, 122.86, 124.74, 125.27, 128.97, 133.82, 146.77. IR (neat) ν (cm^{-1}): 1250, 1055. MS *m/z* 286 (M). Anal. Calcd for $C_{13}H_{23}ClOSi_2$: C, 54.41; H, 8.08. Found: C, 54.11; H, 8.36.

3.3.4. α-Trimethylsilyl-α-trimethylsiloxy-*p*-chlorotoluene (5d). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): −0.03 (9H, s), 0.04 (9H, s), 4.43 (1H, s), 7.09 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −4.18, 0.02, 69.79, 126.07, 127.92, 130.67, 143.02. IR (neat) ν (cm^{-1}): 1245, 1050. MS *m/z* 286 (M^+). Anal. Calcd for $C_{13}H_{23}ClOSi_2$: C, 54.41; H, 8.08. Found: C, 54.36; H, 8.11.

3.3.5. α-Trimethylsilyl-α-trimethylsiloxy-*p*-trifluoromethyltoluene (5e). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): −0.04 (9H, s), 0.11 (9H, s), 4.61 (1H, s), 7.34 (2H, d, J=8.1 Hz), 7.59 (2H, d, J=8.1 Hz). IR (neat) ν (cm^{-1}): 1250, 1050. MS *m/z* 320 (M^+). Anal. Calcd for $C_{14}H_{23}F_3OSi_2$: C, 52.47; H, 7.23. Found: C, 54.26; H, 7.11.

3.3.6. α-Trimethylsilyl-α-trimethylsiloxy-*o*-methoxyltoluene (5f). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): −0.05 (9H, s), 0.02 (9H, s), 3.78 (3H, s), 4.94 (1H, s), 6.78 (1H, dd, J=1.0, 7.6 Hz), 6.93 (1H, ddd, J=7.6, 7.6, 1.0 Hz), 7.11 (1H, ddd, J=1.3, 6.0, 7.6 Hz), 7.34 (1H, dd, J=1.3, 7.6 Hz). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −3.88, −0.05, 54.72, 63.27, 109.08, 120.29, 125.57, 126.52, 133.10, 154.30. IR (neat) ν (cm^{-1}): 1250, 1050. MS *m/z* 267 ($M-Me)^+$). Anal. Calcd for $C_{14}H_{26}O_2Si_2$: C, 59.52; H, 9.28. Found: C, 59.80; H, 9.03.

3.3.7. α-Trimethylsilyl-α-trimethylsiloxy-2-methylthiophene (5g). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.03 (9H, s), 0.07 (9H, s), 4.71 (1H, s), 6.71 (1H, dd, J=1.0, 3.5 Hz), 6.93 (1H, dd, J=3.5, 4.6 Hz), 7.10 (1H, dd, J=1.0, 4.6 Hz). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −4.08, −0.02, 66.90, 120.59, 122.10, 126.36, 148.95. IR (neat) ν (cm^{-1}): 1250, 1050. MS *m/z* 258 (M^+). Anal. Calcd for $C_{11}H_{22}OSSi_2$: C, 51.10; H, 8.58. Found: C, 51.23; H, 8.62.

3.3.8. α-Trimethylsilyl-α-trimethylsiloxyethylbenzene (5h). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.03 (9H, s), 0.19 (9H, s), 1.82 (3H, s), 7.18–7.39 (5H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −4.36, 2.84, 24.08, 73.10, 124.87, 124.98, 127.57, 148.07. IR (neat) ν (cm^{-1}): 1250, 1050. MS *m/z* 209 ($(M-57)^+$). Anal. Calcd for $C_{14}H_{26}OSi_2$: C, 63.09; H, 9.83. Found: C, 63.20; H, 10.01.

3.3.9. α-Trimethylsilyl-α-trimethylsiloxypropylbenzene (5i). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): −0.39 (9H, s), −0.12 (9H, s), 0.55 (3H, d, J=7.3 Hz), 1.73–1.83 (2H, m), 6.78–7.00 (5H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −3.72, 2.19, 8.52, 18.23, 78.44, 124.60, 125.32, 127.44, 145.44. IR (neat) ν (cm^{-1}): 2940, 1250, 1120, 1050, 1020, 835. MS *m/z* 280 (M^+). Anal. Calcd for $C_{15}H_{28}OSi_2$: C, 64.22; H, 10.06. Found: C, 64.05; H, 11.0.

3.3.10. Diphenyl-trimethylsilyl-trimethyloxymethane (5j). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.04 (18H, s), 7.38–7.41 (10H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): 1.82, 86.84, 128.24, 128.33, 128.46, 140.79. IR (neat) ν (cm^{-1}): 2950, 1740, 1490, 1445, 1250, 895, 840, 700. MS *m/z* 328 (M^+). Anal. Calcd for $C_{19}H_{28}OSi_2$: C, 69.45; H, 8.59. Found: C, 69.15; H, 8.41.

3.3.11. α-Trimethylsilyl-α-trimethylsiloxy-2-ethylthiophene (5k). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.01 (9H, s), 0.12 (9H, s), 1.73 (1H, s), 6.67 (1H, dd, J=1.0, 3.6 Hz), 7.00 (1H, dd, J=3.6, 5.0 Hz), 7.12 (1H, dd, J=1.0, 5.0 Hz). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −4.40, 2.55, 25.18, 71.89, 120.32, 122.03, 126.49, 154.27. IR (neat) ν (cm^{-1}): 1250, 1040. MS *m/z* 272 (M^+). Anal. Calcd for $C_{12}H_{24}OSSi_2$: C, 52.88; H, 8.88. Found: C, 53.01; H, 8.93.

3.3.12. α-Ethoxy-α-trimethylsiloxy-α-trimethylsiloxytoluene (5l). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.04 (9H, s), 0.21 (9H, s), 1.28–1.32 (3H, m), 3.50–3.55 (2H, m), 7.16–7.54 (5H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −2.49, 2.21, 15.55, 58.96, 104.30, 124.77, 126.61, 127.33, 143.91. IR (neat) ν (cm^{-1}): 2950, 1250, 1100, 1040, 840 cm^{-1}. MS *m/z* 267 ($(M-OEt)^+$). Anal. Calcd for $C_{15}H_{28}O_2Si_2$: C, 60.75; H, 9.25. Found: C, 60.72; H, 9.20.

3.4. Procedure for synthesis of α-trimethylsilylstylene (8h)

A solution containing **5h** (10 mmol) and 6 N HCl aqueous (2 ml) in 20 ml of dry DMF was stirred for 8 h under a nitrogen atmosphere. Then the reaction mixture was poured into 200 ml of a saturated $NaHCO_3$ solution and was extracted by three 100 ml portions of ether. Usual work-up and subsequent evaporation of ether under reduced pressure gave the α-hydroxy-α-trimethylsilylethylbenzenein a 66% yield. Then anhydrous $KHSO_4$ and α-hydroxy-α-trimethylsilylethylbenzene was stirred at 150 °C in vacuo (10 mmHg). Distillation of reaction mixture gave the **8h** in a 55% yield.

3.4.1. α-Trimethylsilylstylene (8h). ^{1}H NMR (CCl_4, 270 MHz) δ (ppm): 0.20 (9H, s), 5.62 (1H, d, J=3.0 Hz), 5.81 (1H, d, J=3.0 Hz), 7.20–7.35 (5H, m). ^{13}C NMR (CCl_4, 67.5 MHz) δ (ppm): −0.88, 126.22, 126.69, 127.13, 144.76, 128.14, 153.51. IR (neat) ν (cm^{-1}): 2950, 1400, 1250, 840, 680 cm^{-1}. MS *m/z* 176 (M^+). Anal. Calcd for $C_{11}H_{16}Si$: C, 74.93; H, 9.15. Found: C, 74.88; H, 9.27.

3.5. Procedure for synthesis of 1-(4-methoxyphenyl)-2-phenyl-ethane-1,2-diol (9a)

A solution containing **5a** (1 mmol), *p*-methoxybenzaldehyde (3 mmol) and powder MS 4 Å (3 wt equiv) in 20 ml of dry THF was stirred for 2 h under nitrogen atmosphere. Then *n*-$Bu_4NSiPh_3F_2$ (2 mmol) was added to the solution at room temperature, and the mixture was stirred for another 2 h. After removal of THF, MeOH (20 ml) and acetic acid (0.3 ml) were added to the solution at room temperature, the resulting mixture was stirred for about 8 h. Subsequent removal of MS 4 Å by filtration and that of the solvent by distillation from the reaction mixture gave a crude oil. Purification of the crude oil by the column chromatography to gave **9a** in a 82% yield.

3.5.1. 1-(4-Methoxyphenyl)-2-phenyl-ethane-1,2-diol (9a).[15] One isomer was isolated by recrystallization (hexnane–AcOEt).

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.10 (1H, d, J= 2.8 Hz), 2.15 (1H, d, J=2.8 Hz), 3.77 (3H, s), 4.78 (1H, dd, J=2.8, 2.8 Hz), 4.81 (1H, dd, J=2.8, 2.8 Hz), 6.84–6.88 (2H, m), 7.18–7.22 (2H, m), 7.26–7.35 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 55.26, 77.81, 78.12, 113.69, 127.07, 128.08, 128.26, 128.32, 131.81, 139.93, 159.46. IR (neat) ν (cm^{-1}): 3350, 1460, 1040. MS *m/z* 244 (M). Mp: 129.2–131.0 °C (lit.: 135 °C).

3.6. General procedure for synthesis of cyclic siloxane (6,7)

To a 100 ml three-necked round flask equipped with a thermometer and a dropping funnel was placed aromatic carbonyl compound (**1**) (5 mmol) and magnesium turnings (30 mmol) in dry DMF (40 ml). After cooling the flask in a ice bath, 1,2-bis(chlorodimethylsilyl)ethane (**3**) or 1,5-dichloro-hexamethyltrisiloxane (**4**) (22.5 mmol) in DMF (20 ml) was added under magnetic stirring over 20 min. The resulting solution was stirred for 20 h at room temperature under nitrogen atmosphere. After stirring, the reaction solution was added in $NaHCO_3$ aqueous (300 ml) over 30 min and was extracted with ether. After evaporation of ether under reduced pressure, column chromatography of the crude products (eluent; hexane/EtOAc=20:1 or 10:1) gave the corresponding cyclic siloxane (**6**,**7**). All new products were identified by spectroscopic methods (^{1}H, ^{13}C NMR, IR, MASS) and elemental analysis.

3.6.1. 2,2,5,5,6-Pentamethyl-1-oxa-2,4-disilacyclohex-6-yl-benzene (6h). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.33 (3H, s), 0.09 (3H, s), 0.25 (3H, s), 0.26 (3H, s), 0.84–1.05 (4H, m), 1.70 (3H, s), 7.11–7.33 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.38, −4.22, 0.54, 1.53, 5.75, 9.36, 26.67, 73.09, 123.72, 124.64, 127.67, 148.70. IR (neat) ν (cm^{-1}): 3085, 3057, 3020, 2959, 2903, 1600, 1491, 1444, 1416, 1367, 1249, 1115, 1093, 1066, 1051. MS *m/z* 264 (M^+). Anal. Calcd for $C_{14}H_{24}OSi_2$: C, 63.57; H, 9.15. Found: C, 63.30; H, 9.04.

3.6.2. 3-(2,2,5,5,6-Pentamethyl-1-oxa-2,4-disilacyclohex-6-yl)-methoxybenzene (6m). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.31 (3H, s), 0.10 (3H, s), 0.25 (3H, s), 0.26 (3H, s), 0.79–1.04 (4H, m), 1.68 (3H, s), 3.82 (3H, s), 6.69 (1H, ddd, J=0.8, 2.8, 8.0 Hz), 6.82 (1H, ddd, J=0.8, 2.8, 8.0 Hz), 6.91 (1H, dd, J=1.6, 2.8 Hz), 7.21 (1H, t, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.36, −4.11, 0.54, 1.49, 5.78, 9.33, 26.75, 73.13, 109.65, 110.08, 116.28, 128.57, 150.72, 159.27. IR (neat) ν (cm^{-1}): 3078, 2956, 2903, 2832, 1600, 1579, 1482, 1464, 1431, 1367, 1313, 1284, 1250, 1195, 1162, 1050. MS *m/z* 294 (M^+). Anal. Calcd for $C_{15}H_{26}O_2Si_2$: C, 61.17; H, 8.90. Found: C, 60.94; H, 8.80.

3.6.3. 4-(2,2,5,5,6-Pentamethyl-1-oxa-2,4-disilacyclohex-6-yl)-toluene (6n). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.33 (3H, s), 0.08 (3H, s), 0.24 (3H, s), 0.25 (3H, s), 0.75–1.07 (4H, m), 1.67 (3H, s), 2.33 (3H, s), 7.09–7.17 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.32, −4.19, 0.57, 1.55, 5.78, 9.41, 20.95, 26.79, 72.96, 123.68, 128.37, 133.93, 145.73. IR (neat) ν (cm^{-1}): 3088, 3021, 2959, 2903, 1508, 1445, 1414, 1366, 1249, 1183, 1117, 1076, 1050. MS *m/z* 278 (M^+). Anal. Calcd for $C_{15}H_{26}OSi_2$: C, 64.68; H, 9.41. Found: C, 64.45; H, 9.19.

3.6.4. 3-(2,2,5,5,6-Pentamethyl-1-oxa-2,4-disilacyclohex-6-yl)-chlorobenzene (6o). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.31 (3H, s), 0.10 (3H, s), 0.25 (6H, s), 0.75–1.19 (4H, m), 1.67 (3H, s), 7.10–7.29 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.41, −4.19, 0.49, 1.48, 5.68, 9.23, 26.70, 72.92, 121.88, 124.01, 124.78, 128.88, 133.88, 151.19. IR (neat) ν (cm^{-1}): 3068, 2959, 2903, 1592, 1567, 1476, 1453, 1416, 1368, 1250, 1213, 1112, 1065, 1051. MS *m/z* 298 (M^+, ^{35}Cl), 300 (M^+, ^{37}Cl). Anal. Calcd for $C_{14}H_{23}ClOSi_2$: C, 56.25; H, 7.75. Found: C, 56.11; H, 7.67.

3.6.5. 4-(2,2,5,5,6-Pentamethyl-1-oxa-2,4-disilacyclohex-6-yl)-chlorobenzene (6p). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.33 (3H, s), 0.08 (3H, s), 0.24 (3H, s), 0.26 (3H, s), 0.92 (4H, m), 1.67 (3H, s), 7.19–7.28 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.43, −4.26, 0.51, 1.48, 5.64, 9.28, 26.62, 72.88, 125.19, 127.74, 130.32, 147.42. IR (neat) ν (cm^{-1}): 3084, 2959, 2903, 2801, 1899, 1486, 1445, 1397, 1367, 1250, 1216, 1172, 1115, 1092, 1074, 1049, 1011, 1074, 1049. MS *m/z* 298 (M^+, ^{35}Cl), 300 (M^+, ^{37}Cl). Anal. Calcd for $C_{14}H_{23}ClOSi_2$: C, 56.25; H, 7.75. Found: C, 56.28; H, 7.61.

3.6.6. 4-(6-Ethyl-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-yl)benzene (6i). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.38 (3H, s), 0.09 (3H, s), 0.26 (6H, s), 0.72 (3H, t, J=7.0 Hz), 0.78–1.07 (4H, m), 2.12 (2H, m), 7.10–7.32 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.41, −4.24, 0.60, 0.71, 5.85, 6.37, 9.42, 29.91, 76.23, 124.27, 124.28, 127.63, 146.26. IR (neat) ν (cm^{-1}): 3084, 3057, 3020, 2962, 2934, 2904, 1599, 1492, 1444, 1418, 1372, 1249, 1103, 1089, 1056, 1008. MS *m/z* 278 (M^+). Anal. Calcd for $C_{15}H_{26}OSi_2$: C, 64.68; H, 9.41. Found: C, 64.44; H, 9.21.

3.6.7. 6-Propyl-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-ylbenzene (6q). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.39 (3H, s), 0.07 (3H, s), 0.11 (3H, s), 0.25 (3H, s), 0.74–1.09 (8H, m), 1.37–1.49 (1H, m), 1.98–2.06 (2H, m), 7.09–7.14 (1H, m), 7.21–7.31 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.55, −4.24, −0.35, 0.57, 5.81, 9.41, 14.36, 15.04, 39.82, 76.15, 124.06, 124.25, 127.62, 146.69. IR (neat) ν (cm^{-1}): 3084, 3058, 3020, 2957, 2905, 2873, 2360, 1598, 1493, 1465, 1444, 1418, 1250, 1132, 1117, 1058, 1030. MS *m/z* 292 (M^+). Anal. Calcd for $C_{16}H_{28}OSi_2$: C, 65.69; H, 9.65. Found: C, 65.43; H, 9.40.

3.6.8. 6-Ethoxy-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-ylbenzene (6l). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.36 (3H, s), 0.12 (3H, s), 0.26 (3H, s), 0.29 (3H, s), 0.77–0.96 (3H, m), 1.15 (3H, t, J=7.0 Hz), 1.19–1.24 (1H, m), 3.18 (1H, dq, J=7.2, 9.2 Hz), 3.46 (1H, J= 7.2, 9.2 Hz), 7.20 (1H, m), 7.32 (3H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.04, −4.96, −0.07, −0.02, 5.25, 9.18, 15.21, 55.29, 102.58, 125.99, 126.07, 127.70, 143.11. IR (neat) ν (cm^{-1}): 3089, 3024, 2963, 2923, 2868, 1600,

1509, 1454, 1406, 1369, 1259, 1224, 1210, 1184, 1124, 1054. MS *m/z* 294 (M^+). Anal. Calcd for $C_{15}H_{26}O_2Si_2$: C, 61.17; H, 8.90. Found: C, 60.92; H, 8.99.

3.6.9. 3-(6-Ethoxy-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-yl)methoxybenzene (6r). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.33 (3H, s), 0.14 (3H, s), 0.26 (3H, s), 0.29 (3H, s), 0.77–0.96 (3H, m), 1.16 (3H, t, J=7.0 Hz), 1.19–1.24 (1H, m), 3.20 (1H, dq, J=7.2, 9.2 Hz), 3.46 (1H, dq, J=7.2, 9.2 Hz), 6.75–6.78 (1H, m), 6.90–6.93 (2H, m), 7.23–7.29 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.05, −4.86, −0.07, −0.02, 5.22, 9.12, 15.22, 55.09, 55.36, 102.47, 111.19, 111.85, 118.54, 128.65, 145.02, 159.28. IR (neat) ν (cm^{-1}): 3078, 2956, 2897, 2832, 1599, 1581, 1484, 1465, 1433, 1419, 1387, 1284, 1250. MS *m/z* 324 (M^+). Anal. Calcd for $C_{16}H_{28}O_3Si_2$: C, 59.21; H, 8.93. Found: C, 58.97; H, 8.93.

3.6.10. 4-(6-Ethoxy-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-yl)methylbenzene (6s). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.35 (3H, s), 0.11 (3H, s), 0.25 (3H, s), 0.29 (3H, s), 0.77–0.96 (3H, m), 1.14 (3H, t, J=7.0 Hz), 1.19–1.23 (1H, m), 3.17 (1H, dq, J=7.2, 9.2 Hz), 3.43 (1H, dq, J=7.2, 9.2 Hz), 7.09–7.20 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.00, −4.93, −0.07, −0.01, 5.26, 9.22, 15.21, 21.12, 55.12, 102.57, 125.94, 128.41, 135.49, 140.12. IR (neat) ν (cm^{-1}): 3022, 2971, 2896, 2801, 1605, 1586, 1482, 1443, 1408, 1386, 1248. MS *m/z* 308 (M^+). Anal. Calcd for $C_{16}H_{28}O_2Si_2$: C, 62.28; H, 9.15. Found: C, 62.39; H, 9.31.

3.6.11. 3-(6-Ethoxy-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-yl)chlorobenzene (6t). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.34 (3H, s), 0.12 (3H, s), 0.26 (3H, s), 0.29 (3H, s), 0.77–0.96 (3H, m), 1.15 (3H, t, J=7.0 Hz), 1.13–1.23 (1H, m), 3.12 (1H, dq, J=7.2, 9.2 Hz), 3.45 (1H, dq, J=7.2, 9.2 Hz), 7.16–7.31 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.05, −4.97, −0.11, −0.09, 5.14, 9.04, 15.17, 55.54, 102.07, 124.14, 126.13, 126.25, 128.99, 133.95, 145.56. IR (neat) ν (cm^{-1}): 3067, 2957, 2930, 2897, 1593, 1570, 1471, 1409, 1250. MS *m/z* 328 (M^+, ^{35}Cl), 330 (M^+, ^{37}Cl). Anal. Calcd for $C_{15}H_{25}ClO_2Si_2$: C, 54.76; H, 7.66. Found: C, 54.82; H, 7.43.

3.6.12. 6-Methoxy-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-ylbenzene (6u). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.33 (3H, s), 0.11 (3H, s), 0.27 (3H, s), 0.32 (3H, s), 0.80–0.98 (3H, m), 1.16–1.25 (1H, m), 3.06 (3H, s), 7.21–7.37 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −6.09, −5.03, −0.07, −0.02, 5.23, 9.19, 48.25, 102.81, 126.14, 126.26, 127.76, 142.34. IR (neat) ν (cm^{-1}): 3058, 3063, 3023, 2958, 2905, 2878, 2822, 1599, 1494, 1482, 1446, 1415, 1249. MS *m/z* 280 (M^+). Anal. Calcd for $C_{14}H_{24}O_2Si_2$: C, 59.94; H, 8.62. Found: C, 59.72; H, 8.91.

3.6.13. 6-Isoprpyl-2,2,5,5-tetramethyl-1-oxa-2,4-disilacyclohex-6-ylbenzene (6v). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.45 (3H, s), 0.21 (3H, s), 0.28 (3H, s), 0.33 (3H, s), 0.74–0.95 (3H, m), 0.98 (3H, d, J=6.0 Hz), 1.04–1.19 (1H, m), 1.11 (3H, d, J=6.0 Hz), 3.91 (1H, sept, J=6.0 Hz), 7.19–7.38 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −5.32, −4.14, 0.60, 1.46, 5.26, 8.51, 24.44, 25.29, 65.45, 102.86, 126.04, 126.16, 127.50, 144.36. IR (neat) ν (cm^{-1}): 3058, 3064, 3022, 2967, 2907, 2879, 1484, 1466, 1445, 1419, 1378, 1366, 1250. MS *m/z* 308 (M^+). Anal. Calcd for $C_{16}H_{28}O_2Si_2$: C, 62.28; H, 9.15. Found: C, 62.01; H, 9.33.

3.6.14. 2,2,5,5-Pentamethyl-1-oxa-2,4-disilacyclohex-6-yl-benzene (6a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.16 (3H, s), 0.01 (3H, s), 0.24 (3H, s), 0.25 (3H, s), 0.78–1.68 (4H, m), 4.78 (1H, s), 7.11–7.33 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −8.08, −4.17, −3.20, −0.72, 7.54, 9.33, 71.13, 124.27, 125.09, 127.87, 143.27. IR (neat) ν (cm^{-1}): 3083, 3061, 3023, 2957, 2900, 2822, 1601, 1439, 1449, 1415, 1249, 1204, 1157, 1076, 1048, 1024. MS *m/z* 250 (M^+). Anal. Calcd for $C_{13}H_{22}OSi_2$: C, 62.33; H, 8.85. Found: C, 62.51; H, 8.99.

3.6.15. 2,2,4,4,6,6,7-Heptamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-ylbenzene (7h). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.10 (3H, s), 0.17 (3H, s), 0.18 (3H, s), 0.21 (3H, s), 0.22 (3H, s), 0.25 (3H, s), 1.79 (3H, s), 7.17–7.36 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −3.67, −2.71, 0.69, 0.94, 1.24, 2.59, 24.79, 75.40, 124.56, 125.18, 127.69, 146.83. IR (neat) ν (cm^{-1}): 3086, 3057, 3022, 2963, 2925, 2903, 2868, 1599, 1492, 1444, 1409, 1370, 1261, 1220, 1072. MS *m/z* 326 (M^+). Anal. Calcd for $C_{14}H_{26}O_3Si_3$: C, 51.48; H, 8.02. Found: C, 51.23; H, 7.98.

3.6.16. 3-(2,2,4,4,6,6,7-Heptamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-yl)methoxybenzene (7m). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.07 (3H, s), 0.15 (3H, s), 0.18 (3H, s), 0.22 (3H, s), 0.24 (3H, s), 0.26 (3H, s), 1.79 (3H, s), 3.84 (3H, s), 6.73 (1H, ddd, J=0.8, 2.8, 8.0 Hz), 6.89 (1H, ddd, J=0.8, 2.8, 8.0 Hz), 6.99 (1H, dd, J=1.6, 2.8 Hz), 7.24 (1H, t, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −3.59, −2.57, 0.68, 0.71, 0.93, 2.58, 24.87, 55.07, 75.42, 109.96, 111.07, 117.03, 128.59, 148.80, 159.21. IR (neat) ν (cm^{-1}): 3081, 2963, 2833, 1599, 1580, 1486, 1464, 1432, 1370, 1314, 1286, 1260, 1196, 1165, 1120, 1058, 1012. MS *m/z* 356 (M^+). Anal. Calcd for $C_{15}H_{28}O_4Si_3$: C, 50.52; H, 7.91. Found: C, 50.47; H, 7.69.

3.6.17. 3-(2,2,4,4,6,6,7-Heptamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-yl)toluene (7n). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.09 (3H, s), 0.11 (3H, s), 0.16 (3H, s), 0.21 (3H, s), 0.22 (3H, s), 0.25 (3H, s), 1.78 (3H, s), 2.37 (3H, s), 6.98–7.20 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −3.62, −2.65, 0.69, 0.74, 0.95, 2.61, 21.80, 24.86, 75.37, 121.71, 125.28, 125.95, 127.59, 137.08, 146.81. IR (neat) ν (cm^{-1}): 3023, 2963, 2923, 2867, 1604, 1586, 1487, 1455, 1409, 1370, 1259, 1174, 1058. MS *m/z* 340 (M^+). Anal. Calcd for $C_{15}H_{28}O_3Si_3$: C, 52.89; H, 8.29. Found: C, 52.63; H, 8.19.

3.6.18. 4-(2,2,4,4,6,6,7-Heptamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-yl)toluene (7w). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.09 (3H, s), 0.11 (3H, s), 0.16 (3H, s), 0.20 (3H, s), 0.21 (3H, s), 0.24 (3H, s), 1.77 (3H, s), 2.34 (3H, s), 7.11–7.27 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −3.64, −2.71, 0.69, 0.73, 0.95, 2.58, 20.95, 24.86, 75.24, 124.54, 128.42, 134.62, 143.83. IR (neat) ν (cm^{-1}): 3089, 3024, 2963, 2923, 2868, 1600, 1509, 1454, 1406, 1369, 1259, 1224, 1210, 1184, 1124, 1054. MS *m/z* 340

(M^+). Anal. Calcd for $C_{15}H_{28}O_3Si_3$: C, 52.89; H, 8.29. Found: C, 52.82; H, 8.01.

3.6.19. 4-(2,2,4,4,6,6,7-Heptamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-yl)chlorobenzene (7p). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.09 (3H, s), 0.12 (3H, s), 0.18 (3H, s), 0.23 (3H, s), 0.24 (3H, s), 0.26 (3H, s), 1.78 (3H, s), 7.16–7.32 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −3.74, −2.77, 0.66, 0.71, 0.93, 2.57, 24.73, 75.18, 126.01, 127.78, 130.94, 145.54. IR (neat) ν (cm^{-1}): 3086, 3034, 2963, 2925, 2903, 2868, 1489, 1456, 1398, 1370, 1258. MS *m/z* 361 (M^+, ^{35}Cl), 363 (M^+, ^{37}Cl). Anal. Calcd for $C_{14}H_{25}ClO_3Si_3$: C, 46.57; H, 6.98. Found: C, 46.49; H, 6.72.

3.6.20. 7-Ethoxy-2,2,4,4,6,6,-hexamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-ylbenzene (7l). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.16 (3H, s), 0.16 (3H, s), 0.19 (3H, s), 0.27 (6H, s), 0.31 (3H, s), 1.21 (3H, t, J=7.0 Hz), 3.30–3.37 (1H, m), 3.41–3.48 (1H, m), 7.22–7.38 (5H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −2.71, −2.66, 0.68, 0.79, 0.99, 0.99, 15.34, 56.32, 126.63, 126.81, 127.70, 141.76. IR (neat) ν (cm^{-1}): 3064, 2965, 2899, 1259, 1206, 1126, 1090, 1037, 1014. MS *m/z* 356 (M^+). Anal. Calcd for $C_{14}H_{26}O_3Si_3$: C, 51.48; H, 8.02. Found: C, 51.23; H, 7.98.

3.6.21. 3-(7-Ethoxy-2,2,4,4,6,6,-hexamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-yl)methoxybenzene (7r). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.14 (3H, s), 0.15 (3H, s), 0.20 (3H, s), 0.26 (6H, s), 0.28 (3H, s), 1.20 (3H, t, J=7.0 Hz), 3.34 (1H, dq, J=7.2, 9.2 Hz), 3.45 (1H, dq, J=7.2, 9.2 Hz), 3.83 (3H, s), 6.77–6.79 (1H, m), 6.94–6.96 (2H, m), 7.23–7.28 (1H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −2.63, −2.52, 0.68, 0.79, 0.97, 1.00, 15.36, 55.13, 56.39, 103.74, 111.66, 112.80, 119.33, 128.65, 143.66, 159.24. IR (neat) ν (cm^{-1}):3079, 2963, 2901, 2833, 1599, 1582, 1487, 1465, 1433, 1314, 1285, 1258. MS *m/z* 386 (M^+). Anal. Calcd for $C_{16}H_{30}O_5Si_3$: C, 49.70; H, 7.82. Found: C, 49.89; H, 7.99.

3.6.22. 4-(7-Ethoxy-2,2,4,4,6,6,-hexamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-yl)toluene (7s). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.15 (3H, s), 0.15 (3H, s), 0.18 (3H, Si–CH_3, s), 0.26 (6H, s), 0.31 (3H, s), 1.20 (3H, t, J=7.0 Hz), 2.38 (3H, s), 3.34 (1H, dq, J=7.2, 9.2 Hz), 3.43 (1H, dq, J=7.2, 9.2 Hz), 7.04–7.06 (1H, m), 7.14–7.28 (3H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −2.68, −2.61, 0.69, 0.81, 1.01, 1.03, 15.37, 21.73, 56.26, 103.86, 123.96, 127.35, 127.42, 127.56, 137.17, 141.66. IR (neat) ν (cm^{-1}): 3024, 2964, 2900, 1605, 1587, 1484, 1444, 1410, 1387, 1258. MS *m/z* 370 (M^+). Anal. Calcd for $C_{16}H_{30}O_4Si_3$: C, 51.85; H, 8.16. Found: C, 51.69; H, δ 8.02.

3.6.23. 3-(7-Ethoxy-2,2,4,4,6,6,-hexamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-yl)chlorobenzene (7t). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): −0.15 (3H, s), 0.15 (3H, s), 0.19 (3H, s), 0.25 (3H, s), 0.26 (3H, s), 0.31 (3H, s), 1.20 (3H, t, J=7.0 Hz), 3.28 (1H, m), 3.44 (1H, m), 7.21–7.35 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −2.69, −2.67, 0.64, 0.76, 0.94, 1.02, 15.31, 56.55, 103.34, 124.94, 126.79, 126.90, 128.97, 133.94, 144.27. IR (neat) ν (cm^{-1}): 3069, 2964, 2900, 1593, 1571, 1472, 1444, 1410, 1388, 1259, 1198. MS *m/z* 390 (M^+, ^{35}Cl), 392 (M^+, ^{37}Cl). Anal. Calcd for $C_{15}H_{27}ClO_4Si_3$: C, 46.07; H, 6.96. Found: C, 45.98; H, 6.79.

3.6.24. 2,2,4,4,6,6,-Hexamethyl-1,3,5-trioxa-2,4,6-trisilacyclohept-7-ylbenzene (7a). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.02 (3H, s), 0.14 (3H, s), 0.19 (3H, s), 0.22 (6H, s), 0.27 (3H, s), 4.79 (1H, s), 7.13–7.22 (1H, m), 7.27–7.35 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): −4.69, −2.41, −1.96, −0.57, 0.70, 0.92, 71.03, 124.71, 125.49, 127.91, 142.06. IR (KBr) ν (cm^{-1}): 3082, 3063, 3024, 3002, 2962, 2900, 2843, 1600, 1494, 1452, 1411, 1259. MS *m/z* 312 (M^+). Anal. Calcd for $C_{13}H_{24}O_3Si_3$: C, 49.95; H, 7.74. Found: C, 49.99; H, 7.85.

Acknowledgements

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10. The present coupling of aromatic alkyl ketones (**1h**, **1i**, **1q**) with bis(chlorodimethylsilyl)ethane (**3**) gave the corresponding cyclic coupling products (**6h**, **6i**, **6q**) in similar yields, although that of **1i** with TMSCl gave the corresponding product (**5i**) in only 14% yield, accompanying unusual formation of 4-trimethylsilylpropiophenone (20%). This surprising phenomenon may be partially elucidated by much higher reactivity of TMSCl in comparison with bis(chlorodimethylsilyl)ethane (**3**), as shown in unusual attack of TMSCl to the *p*-position of reactive anion radical intermediate of **1i**.
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14. Ring strain of the cyclic products from the reaction of aromatic alkyl ketones (**1**) with bis(chlorodimethylsilyl) compounds (**3**, **4**) may be an additional effect for their lower yield.
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Synthesis of conjugated 2 and 2,5-(ethenyl) and (ethynyl)phenylethynyl thiophenes: fluorescence properties

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Abstract—Nano conjugated thienylethenyl and thienylethynyl compounds with controlled structure and dimensions have been efficiently prepared, by heterocoupling reaction between 1,4-(thienylethynyl)phenylacetylene (or thienylethenyl)phenylacetylene and 2- or 2,5-dihalothiophene. Conjugated 1,4-di(2-thienylethynylphenyl)- (or 2-thienylethenylphenyl)-1,3-butadiyne were obtained by the homocoupling of the terminal acetylenes in excellent yield. The end-capped (*N*,*N*-dimethylaminophenyl)- and [3,5-di(trimethylsilylethynyl)-1-ethynyl]-2,5-di(phenylethynyl)$_n$thiophene were obtained by the heterocoupling between the corresponding terminal acetylene and 2,5-di(iodo)thiophene, catalyzed by the bis(triphenylphosphine)palladium and cuprous iodide system in excellent yield.

1. Introduction

Nanometer-sized molecules of precise length showing π extended conjugation, exhibit in general high thermal stability and can present electroconductive, magnetic and optical properties.[1] Several potential applications such as artificial photosynthesis,[2] photocatalysis,[3] molecular photovoltaic cells,[4] molecular informatics,[5] and optoelectronic devices[6,7] are beginning to emerge from this new field of research.

Earlier studies on the heteroaromatic systems containing the thiophene ring shows three significant details: (i) an increasing of the first molecular hyperpolarizability (β)[8] (ii) the substitution of the thiophene ring by an aryl one, changes the donor versus the acceptor effect, [9] (iii) the electronic nature of the heteroaromatic ring affects the donor or acceptor strength through the inductive effects.[9]

Therefore, polythiophene has been obtained as a conjugated polymer with many interesting optical and electronic properties such as electrochromism and near-metallic conductivity.[10] Oligomers of thiophene are also technologically important materials and have been used in prototype organic thin-film transistors.[11] Interest in materials with these properties has directed substantial efforts towards the preparation of conjugated substituted oligo- and polythiophenes,[12] which exhibit an electronic conductivity that was dependent on the resonance along the polymeric chain.[10] Thiophene dendrimers with π-extended conjugated chains, shown that the π–π* conduction band decreases from the periphery to the heart, increasing the fluorescence quantum yield.[13] The conjugated thiophene chains show interesting solvatochromic properties.[14]

Recently, we have developed π-extended conjugated structures with important optical properties.[15] Now, we report the synthesis of conjugated end-capped (*N*,*N*-dimethylaminophenyl)- and [3,5-di(trimethylsilylethynyl)-1-ethynyl]-2,5-di(phenylethynyl) molecules containing the thiophene ring. Moreover, the conjugation effect through the double or triple bond linking the thiophene ring and the conjugated chains are also considered.

2. Results and discussion

The synthesis of (*E*,*E*)-1,4-di(2′-thienyl)-1,3-butadiene, (*E*,*E*)-**2**[16] and 1,4-di(2-thienyl)-1,3-butadiyne (**4**),[17] was carried out to compare the polarity-polarizability produced by the double or triple bond of the thiophene conjugated systems.

Thus, compound (*E*,*E*)-**2** was obtained by the homocoupling reaction of 2-(2′-chlorovinyl)thiophene (**1**), catalyzed by the zerovalent nickel(triphenylphosphine)$_n$ complexes. The mixture (*Z*/*E*)-2-chlorovinylthiophene (**1**),[18] (*Z*/*E*, 43:57), was obtained by the Wittig reaction between furfural and

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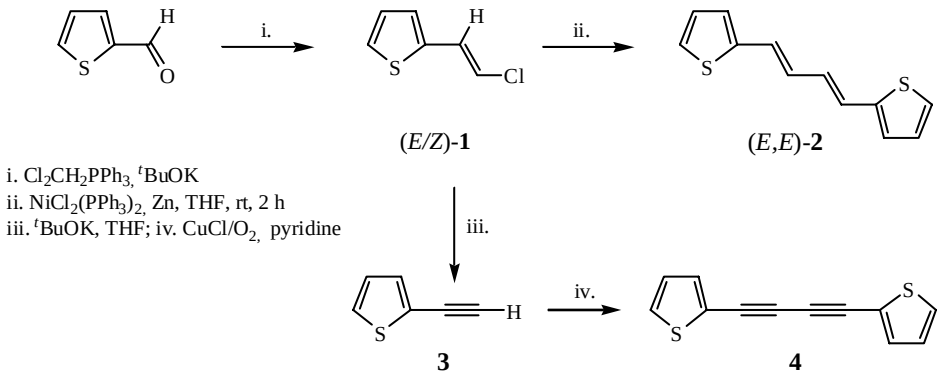


Scheme 1.

the (chloromethyl)(triphenyl)phosphonium ylide, in good yield. The homocoupling reaction of the (*Z*/*E*)-**1** mixture was catalyzed by the zerovalent nickel complexes, prepared in situ by reaction of dichloro bis[(triphenyl)phosphine]-nickel and powdered zinc in tetrahydrofuran giving (*E*,*E*)-1,4-di(2-thienyl)-1,3-butadiene **2** as the unique isomer in good yield (62%), Scheme 1.

Moreover, the (*Z*/*E*)-**1** mixture was treated with potassium *tert*-butoxide, at room temperature, giving 2-ethynylthiophene (**3**) in good yield (77%).[19] The oxidative dimerization of the terminal acetylene **3** was catalyzed by cuprous chloride in pyridine, under oxygen atmosphere, affording 1,4-di(thienyl)-1,3-butadiyne (**4**), in excellent yield (91%), Scheme 1.

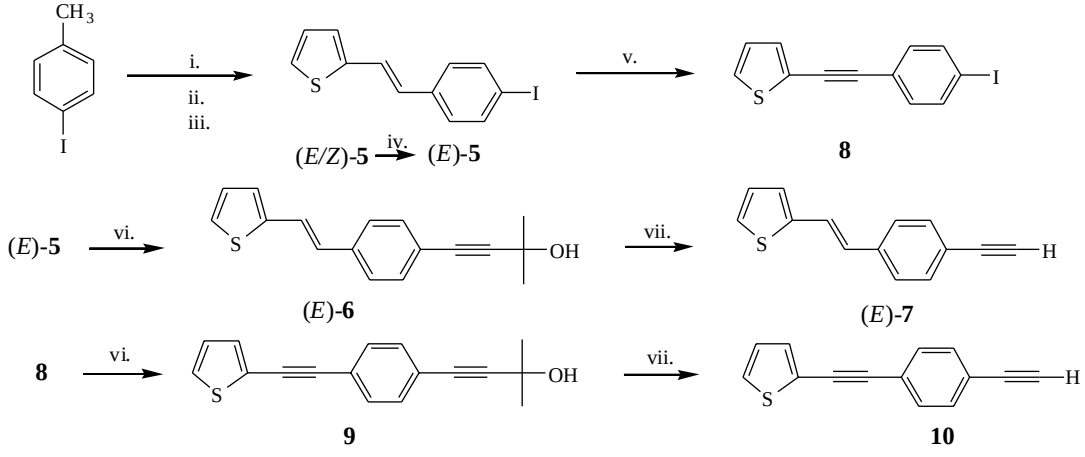
2.1. Synthesis of the terminal acetylenes

The previous synthesis of terminal acetylenes are necessary for the construction of the π extended conjugated thienyl-(*p*-ethynylphenyl) structures. Thus, the conjugated units of 2-(*E*)-phenylethenyl- and phenylethynyl- for the thiophene structures were prepared by heterocoupling between 2-[*p*-(iodophenyl)-2′-ethenyl]thiophene (*E*)-**5** and the ethynyl analogue **8**. Compound (*E*)-**5** was prepared by the Wittig reaction between furfural and *p*-(iodobenzyl)(triphenyl)-phosphonium ylide, giving the (*Z*/*E*)-**5** mixture (50:50).[20] The complete isomerization of (*Z*/*E*)-**5** to (*E*)-**5** was carried out by sunlight exposure in presence of iodine crystals, Scheme 2.

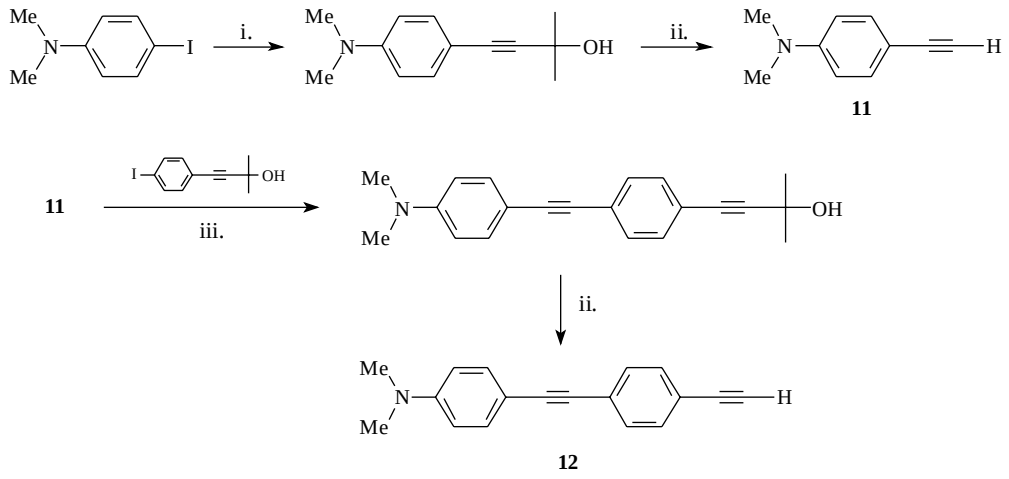
Now, the heterocoupling of (*E*)-**5** with 2-methyl-3-butyn-2-ol in presence of dichloro bis[(triphenyl)phosphine]palladium and cuprous iodide catalyst system, in diethylamine at room temperature, gives the propargyl compound (*E*)-**6**, which by treatment with powdered sodium hydroxide in dry toluene at reflux temperature gives the terminal acetylene (*E*)-**7** in good yield.

The 2-(*p*-iodophenylethynyl)thiophene (**8**) was prepared from (*E*)-**5** by bromine addition and successive elimination with potassium *tert*-butoxide in quantitave yield. The heterocoupling reaction between **8** and 2-methyl-3-butyn-2-ol, in presence of the palladium–copper catalyst, affords the propargyl intermediate **9** in good yield (85%), which was treated with powdered sodium hydroxide in dry toluene, giving the terminal acetylene **10**.

Thus, the heterocoupling between the acetylene **11** and 4-(hydroxyl-3-methyl-1-butyn)-1-iodobenzene gives an



Scheme 2.



i. 2-Methyl-3-butyn-2-ol, CuI, $PdCl_2(PPh_3)_2$, NEt_3; ii. NaOH, toluene at reflux; iii. CuI, $PdCl_2(PPh_3)_2$, NEt_3.

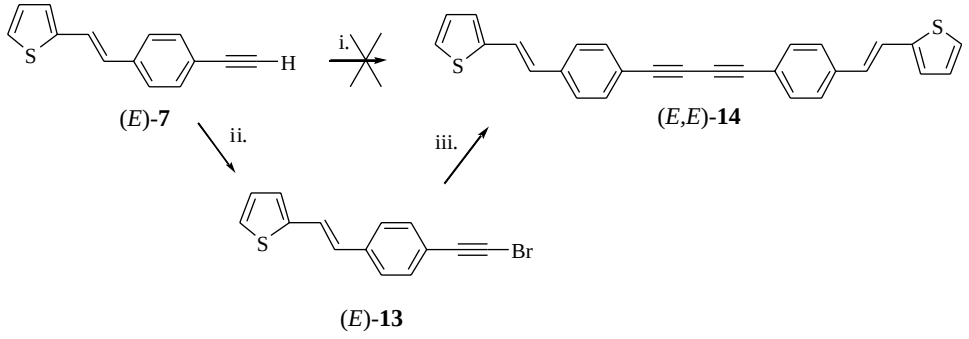
Scheme 3.

intermediate propargyl derivative, which by treatment with sodium hydroxide in dry toluene at the reflux temperature yields compound **12**, as a red solid, in excellent yield (90%), Scheme 3.

2.2. Oxidative dimerization of the terminal acetylenes

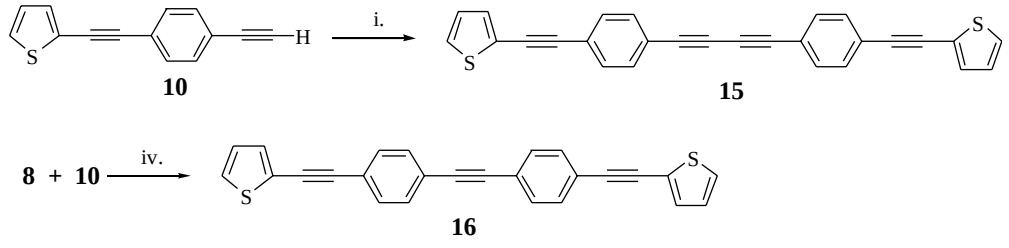
To extend the conjugation of the terminal acetylenes (*E*)-**7** and **10** were transformed by catalytic oxidative dimerization in (*E*,*E*)-**14** and **15**, respectively. Thus, the oxidative homocoupling of (*E*)-**7** was carried out in presence of cuprous chloride and under the Glaser (or Eglinton) conditions fails. The 1,3-butadiyne (*E*,*E*)-**14** was obtained by the Cadiot–Chodkiewicz reaction. Thus, through the oxidative bromination of compound (*E*)-**7**, which was carried out in situ with potassium hypobromide giving (*E*)-**13** in good yield, which in presence of cuprous chloride gives (*E*,*E*)-**14** in moderate yield, Scheme 4.

In contrast, the 1,3-butadiyne derivative **15** was obtained by oxidative homocoupling reaction of the terminal acetylene **10**, catalyzed by cuprous chloride in pyridine, at room temperature, under oxygen atmosphere, Scheme 5. The different reactive behavior of (*E*)-**7**, seems to be due to



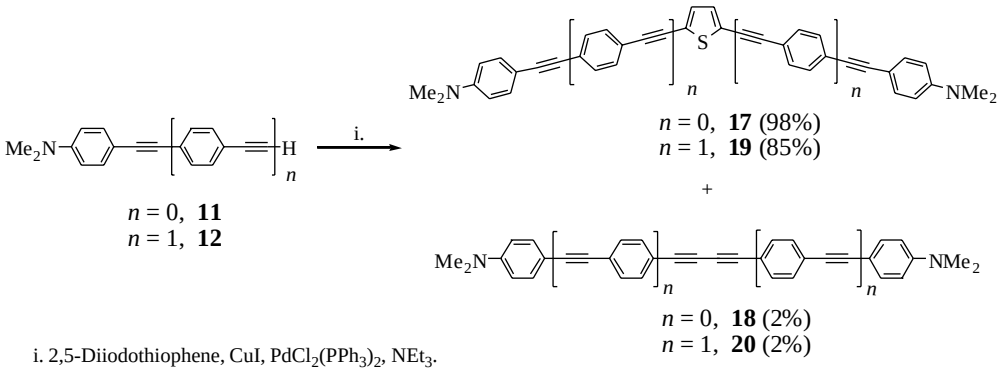
i. CuCl, O_2, pyridine; ii. KOBr, H_2O/THF; iii. (*E*)-**6**, Et_2NH, $NH_2OH{\cdot}HCl$, CuCl, MeOH.

Scheme 4.



i. CuCl, O_2, pyridine; ii. $PdCl_2(PPh_3)_2$, CuI, 2-methyl-3-butyn-2-ol.

Scheme 5.



i. 2,5-Diiodothiophene, CuI, $PdCl_2(PPh_3)_2$, NEt_3.

Scheme 6.

the double bond coordination to the cuprous salt catalyst, avoiding the intermediate cuprous acetylide formation.[21]

The 1,3-diyne **15** was analyzed by mass spectrometry (MALDI-TOF technique) using a laser radiation at 337 nm, with complete volatilization of the sample. During the laser irradiation the topo-oligomerization products were detected in the mass spectrum,[22] in the following ratio: dimer (21%); trimer (4%); tetramer (1%) and pentamer (in traces).

The conjugated structural homologue **16** was synthesized as a conjugated reference to compare their optical properties with the 1,3-diyne structure **15**. Compound **16** was obtained by the heterocoupling reaction between **8** and the terminal acetylene **10**, catalyzed by the palladium–copper system, in good yield (78%), Scheme 5.

2.3. Synthesis of the conjugated arylethynyl-2,5-thiophene structures

The heterocoupling reaction between 2,5-di(iodo)thiophene and the terminal acetylene **11**, in presence of the palladium–copper catalyst, provides 2,5-[di(*p*-*N*,*N*-dimethylamino)-phenylethynyl]thiophene (**17**) (98%) and the 1,3-butadiyne derivative **18** (2%). Compound **18** seems to be formed by the oxidative dimerization of the terminal acetylene, resulting from the Eglinton–Glaser behavior of the catalyst. At this point, it is remarkable the high reactivity of 2,5-di(iodo)thiophene compared with 2,5-dibromothiophene, that gives only the 1,3-butadiyne derivative (**18**).

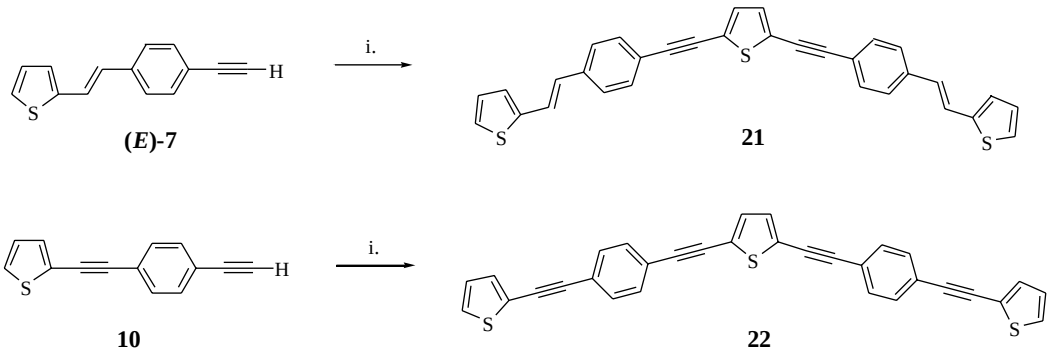
Similarly, 2,5-[di(*p*-*N*,*N*-dimethylamino)(phenylethynyl)(phenylethynyl)]thiophene (**19**) was obtained in good yield (85%) by the heterocoupling reaction between 2,5-di(iodo)thiophene and the terminal acetylene **12**, catalyzed with the palladium–copper system. In this reaction was also detected the oxidative dimerization product **20** in very low yield (2%), Scheme 6.

On the other hand, compounds **17** and **19** exhibit the conjugated chains on 2,5 positions of the thiophene ring forming a high-angle structure. High-angle structures containing the end-capped thiophene ring were also synthesized.

Thus, the heterocoupling reaction between 2,5-di(iodo)thiophene and the thienylethenyl terminal acetylene (*E*)-**7** (or the thienylethynyl terminal acetylene **10**) affords the conjugated high-angle structure **21** as a yellow solid in a 65% yield (or **22**, 85%), Scheme 7.

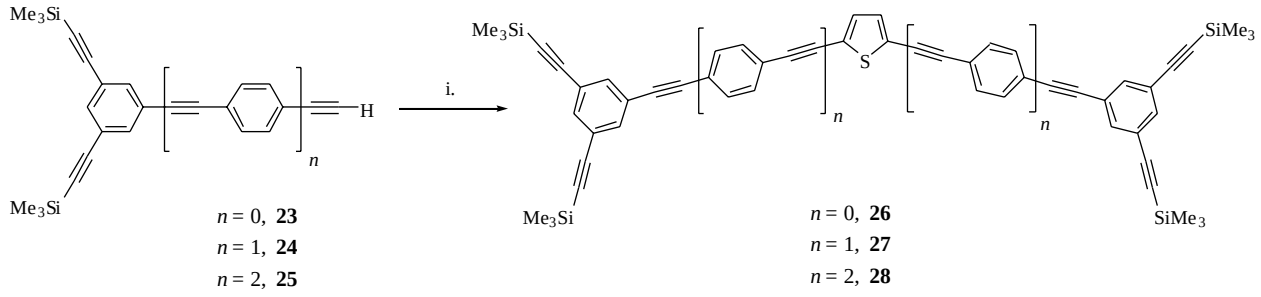
Finally the synthesis of high-angle 2,5-(ethynylphenyl)thiophenes, with trigonal-linear 3,5-di(trimethylsilylethynyl)-1-phenylethynyl structure, was carried out by the heterocoupling reaction between 2,5-di(iodo)thiophene and the terminal acetylenes **23** ($n=1$), **24** ($n=2$) or **25** ($n=3$), previously prepared,[14b] catalyzed by the palladium–copper system, giving the conjugated compounds **26** (97%), **27** (95%) and **28** (95%), respectively, Scheme 8.

The oxidation potential of compounds **26**–**28** was determined by cyclic voltammetry resulting of 1.04, 1.08 and



i. 2,5-Diiodothiophene, $PdCl_2(PPh_3)_2$, NEt_3, CuI.

Scheme 7.



n = 0, **23**
n = 1, **24**
n = 2, **25**

n = 0, **26**
n = 1, **27**
n = 2, **28**

i. 2,5-Diiodothiophene, $PdCl_2(PPh_3)_2$, CuI, NEt_3.

Scheme 8.

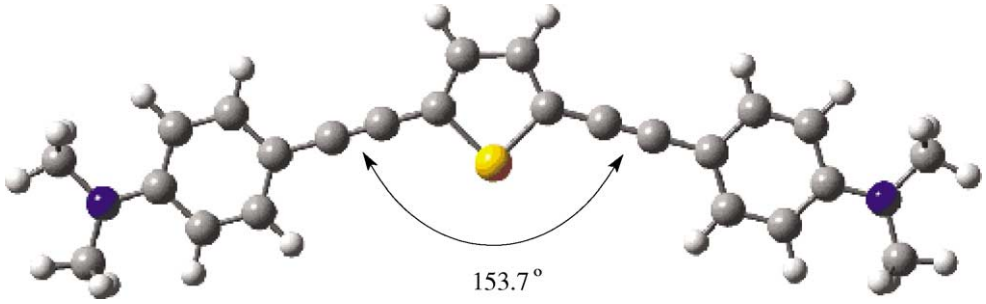


Figure 1. Computed analysis of compound **17**.

1.08 V, respectively, as irreversible oxidizable peaks. Hence, no dependence of the oxidative potential on the chain conjugation must be expected.

Compounds **17**, **19**, **21**, **22** and **26–28** exhibit the referred high-angle geometry for the linear chain on 2,5- positions of the thiophene ring. The internal angle for compound **17** reaches a value of 153.7°, calculated by theoretical computational methods[23] (Fig. 1), which agrees well with the data obtained by X-ray diffraction analysis.[24]

2.4. Fluorescent properties

The UV–vis absorption and fluorescent emission radiation of the terminal acetylenes, 1,3-butadiynes and conjugated arylethynyl-2,5-thiophene structures were analyzed.

All the 1,3-butadiynes and terminal acetylenes show fluorescence emission radiation in solution of dichloromethane. In a general analysis, it is noticeable that (*E*,*E*)-1,4-di(thienyl)-1,3-diene (*E*,*E*)-**2**, exhibits a fluorescent radiation with very low quantum yield, while 1,4-di(thienyl)-1,3-diyne (**4**) does not show appreciable fluorescence emission radiation in dichloromethane, Table 1.

The terminal *N*,*N*-dimethylamino compounds, such as the ethynyl conjugated 1,3-diyne **15** shows an unique fluorescence emission band at 421 nm while that their ethenyl conjugated 1,3-diyne analogue **14**, shows two emission bands at 427 and 454 nm (Table 1). Similarly, the terminal *N*,*N*-dimethylamino triyne conjugated **16** also exhibits two fluorescence emission bands at 390 and 410 nm with practically, the same quantum yield while their 1,3-diyne **15** shows only an emission band at 421 nm with higher quantum yield, Table 1.

The terminal *N*,*N*-dimethylamino 2,5-thiophene conjugated structures (compounds **17** and **19**) show fluorescent emission radiation with important quantum yields (Table 2). There is a significant increase of the radiation quantum yield with the conjugation by the number of

Table 1. UV–vis absorption and fluorescence emission radiation for compounds **2**, **4**, **7**, **10**, and **14–16** in CH_2Cl_2 at room temperature

Compound	UV–vis λ_{max} (nm)	ε (M^{-1} cm^{-1})	Fluorescence λ_{max} (nm)	Φ_f[a]
2	381	25,100	431	0.02
4	364	26,300	—	—
7	341	28,400	420, 450	0.13
10	337	30,000	392, 410	0.14
14	382	78,300	427, 454	0.29
15	359	81,250	421	0.36
16	352	57,100	390, 410	0.30

[a] Fluorescence quantum yield was determined relatively to 2-aminopyridine in 0.1 N H_2SO_4.

Table 2. UV–vis absorption and fluorescence emission radiation for the compounds **17**, **19**, and **21–22** in CH_2Cl_2 at room temperature

Compound	UV–vis λ_{max} (nm)	ε (M^{-1} cm^{-1})	Fluorescence λ_{max} (nm)	Φ_f
17	385	57,500	456	0.23[a]
19	393	104,320	512	0.30[b]
21	367	21,850	440, 462	0.10[a]
22	379	44,000	398, 423	0.34[a]

[a] Fluorescence quantum yield was determined relative to 2-aminopyridine in 0.1 N H_2SO_4.
[b] Fluorescence quantum yield was determined relative to quinine sulphate in 1 N H_2SO_4.

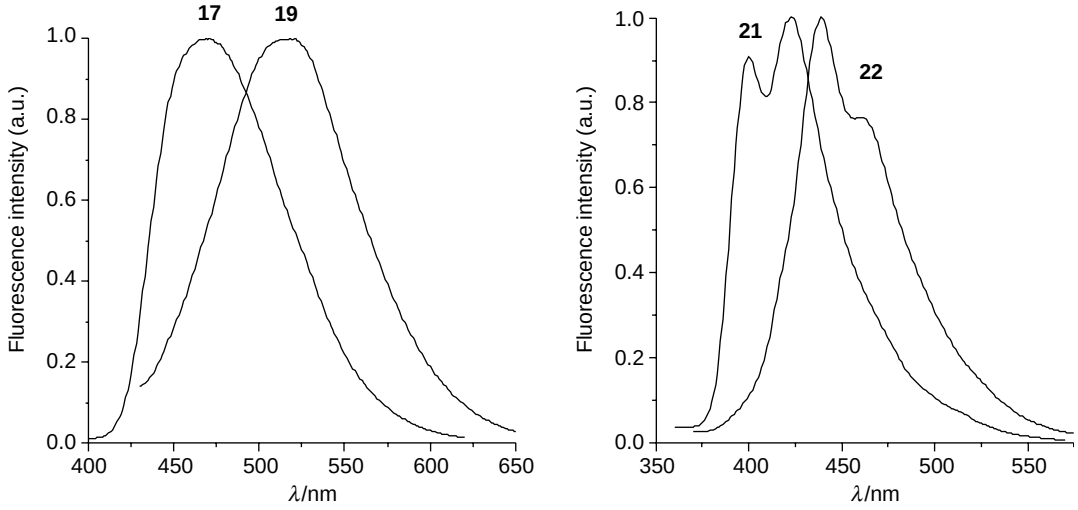


Figure 2. Normalized fluorescence emission spectra for compounds **17**, **19** and **21**–**22** in dichloromethane at room temperature.

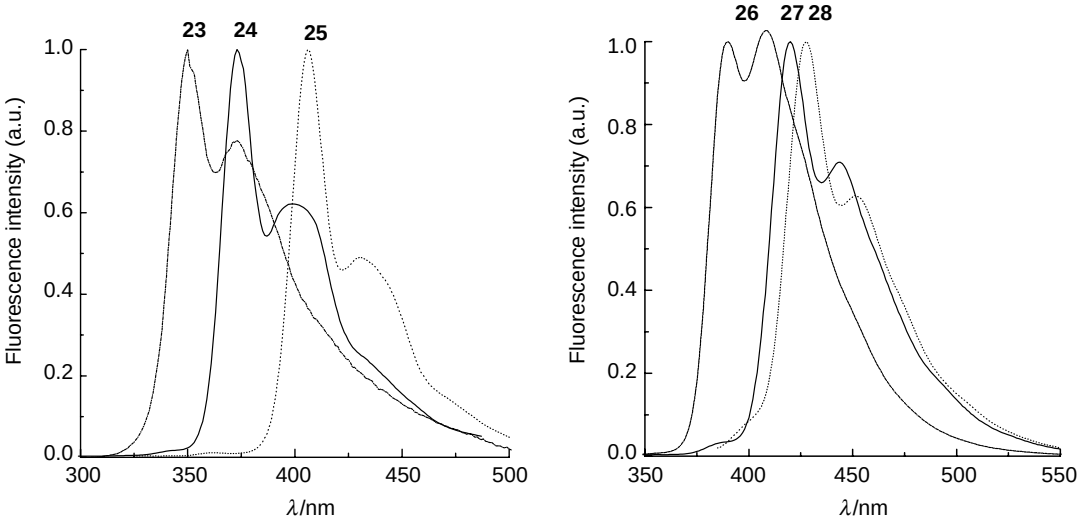


Figure 3. Normalized fluorescence emission spectra for compounds **23**–**25** and **26**–**28** in CH_2Cl_2 at room temperature.

the ethynylphenyl units in the chain, as it was observed in compounds **17** and **19**, Table 2.

However, an important increasing of the fluorescence emission quantum yield was observed in compound **22** triple bond linked to the thiophene ring versus compound **21** with the conjugated double bond connecting with the thiophene ring. Compounds **21** and **22** show two fluorescence wavelength emission bands, while the end-capped 1,4-(*N*,*N*-dimethylaminophenyl) chains show an unique emission band (compounds **17** and **19**), Figure 2.

Recently, we report the fluorescence emission of the terminal acetylenes **23**–**25** connected with different linear linkers such as benzene, 1,5-naphthalene and 1,3-diyne.[14d] In all the cases was observed a similar bathochromic shift close-up 20 nm by each ethynylphenyl unit increasing the conjugate chain. Nevertheless, the high-angle structure of the 2,5-tiophene in compounds **26**–**28** produces an irregular bathochromic shift for each ethynylphenyl unit in the conjugated chain, Figure 3. However, compounds **26**, **27** and **28** show a significant increasing in the fluorescence quantum yield with the number of the ethynylphenyl units in the conjugated chain, Table 3.

Table 3. UV–vis absorption and fluorescence emission radiation for compounds **23**–**28** in CH_2Cl_2 at room temperature

Compound	UV–vis λ_{max} (nm)	ε (M^{-1} cm^{-1})	Fluorescence λ_{max} (nm)	Φ_f[a]
23	344	55,100	350, 373	0.10
24	346	75,000	373, 395	0.28
25	345	99,100	406, 428	0.60
26	355	46,900	391, 410	0.20[a]
27	379	78,900	421, 447	0.42[a]
28	377	113,000	429, 454	0.54[a]

[a] Fluorescence quantum yield was determined relative to 2-aminopyridine in 0.1 N H_2SO_4.

3. Conclusions

New nano conjugated thienylethenyl and thienylethynyl derivatives can be synthesized through the Sonogashira

reaction between 2- or 2,5-dihalothiophene and 1,4-(thienylethynyl)phenylacetylene (or (thienylethenyl)phenylacetylene) in good yield. Conjugated 1,4-di(2-thienylethynylphenyl)- (or 2-thienylethenylphenyl)-1,3-butadiynes can be obtained by the homocoupling of the terminal acetylenes in excellent yield.

The conjugated 1,3-butadiyne derivatives can be efficiently prepared by the catalytic Eglinton–Glaser or Cadiot–Chodkiewicz reactions.

The end-capped (*N*,*N*-dimethylaminophenyl)- and [3,5-di(trimethylsilylethynyl)-1-ethynyl]-2,5-di(phenylethynyl)$_n$-thiophene were obtained in good yield by the heterocoupling between the appropriate terminal acetylene and 2,5-di(iodo)thiophene, catalyzed by the bis(triphenylphosphine)-palladium and cuprous iodide system in diethylamine.

All the new conjugated 2- or 2,5- thiophene derivatives show fluorescent radiation emission which, for the conjugation by triple bond linking ethynylphenyl module exhibit highest quantum yields than the double one (29–54%).

4. Experimental

4.1. General procedures

Melting points were determined in open capillaries and are uncorrected. FT-IR spectra were recorded using KBr pellets or NaCl plates and only partial data is reported. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center of the triplet at 77.00 ppm for deuteriochloroform. Mass spectra were obtained at an ionizing potential of 70 eV and reported as *m*/*e* (relative intensity). Accurate masses are reported for the molecular ion (M+1) or a suitable fragment ion. Flash chromatography was performed on silica gel 60 (200–400 mesh) using the indicated solvents. The UV–vis spectra frequencies are given in nm and ε in L mol^{-1} cm^{-1}.

4.1.1. (*E*,*E*)-1,4-Di(2′-thienyl)-1,3-butadiene[16] (2) To a solution of dichlorobistriphenylphosphine nickel (915 mg, 1.4 mmol) in dry tetrahydrofuran (10 ml), under argon atmosphere was added tetrabutylammonium iodide (518 mg, 1.4 mmol) and zinc powder (136 mg, 2 mmol) and the mixture was stirred until the solution takes a dark red color. After 30 min with stirring was added a solution of 1-chloro-2-(2′-thienyl)ethene (**1**) (200 mg, 1.4 mmol) in dry tetrahydrofuran (10 ml) and the mixture was stirred overnight at room temperature. Finally, was added dichloromethane and filtered to remove the catalyst. The organic layer was dried on anhydrous magnesium sulphate, filtered off and the solvent removed. The residual solid was purified by silica gel column chromatography using hexane as the eluent. The (*E*,*E*)-1,4-di(2′-thienyl)-1,3-butadiene (**2**), 187 mg (62%), was isolated as a yellow solid, mp 140–143 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 381, 362, 268. Fluorescence (CH_2Cl_2), λ_{max} (nm): 431 (ϕ=0.021). FT-IR (KBr, cm^{-1}): 1653, 1541, 1457, 978. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, 2H, J=4.4 Hz); 7.02 (d, 2H, J=6.9 Hz); 6.99 (dd, 2H, J=6.9, 4.4 Hz); 6.72 (d, 2H, J=17.0 Hz); 6.73 (dd, 2H, J=17.0, 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 128.6, 127.6, 125.9, 125.5, 124.4. MS (70 eV): 218 (M$^+$, 100), 184 (36), 173 (9), 134 (17), 121 (8), 109 (7), 97 (16).

4.1.2. (*E*)-1-(*p*-Iodophenyl)-2-(2′-thienyl)ethene (*E*)-5. To a solution of *p*-(iodobenzyl)(triphenyl)phosphonium bromide (560 mg, 1.0 mmol) in toluene (25 ml), under dryness and argon atmosphere and at 0 °C, was added potassium *tert*-butoxide (112 mg, 1.0 mmol). The mixture was stirred for 30 min and then, was slowly added a solution of 2-thiophenecarboxaldehyde (112 mg, 0.1 ml, 1.0 mmol) in anhydrous toluene (5 ml). The mixture was stirred at room temperature overnight. After evaporation of solvent, the residual solid was extracted with dichloromethane and a little amount of water. The organic layer was dried on anhydrous magnesium sulphate, filtered off and solvent removed, to give a (*Z*/*E*) isomers mixture (50:50).

A solution of the (*Z*/*E*) mixture in ethanol was completely transformed to the *E*-isomer by sunlight exposure for 72 h, giving (*E*)-1-(*p*-iodophenyl)-2-(2′-thienyl)ethene (*E*)-**5**, as a yellow solid, mp 155–157 °C, 129 mg (41%). UV–vis (CH_2Cl_2), λ_{max} (nm): 335, 284. FT-IR (KBr, cm^{-1}): 3075, 1525, 1487, 1429, 960, 815. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 1H, J=5.0 Hz); 7.60 (d, 2H, J=8.4 Hz); 7.23 (d, 1H, J=16.1 Hz); 7.19 (d, 2H, J=8.4 Hz); 7.06 (d, 1H, J=3.4 Hz); 7.00 (dd, 1H, J=5.0, 3.4 Hz); 6.83 (d, 1H, J=16.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 137.7, 136.5, 127.7, 127.3, 127.0, 126.5, 124.8, 122.5, 92.6. $C_{12}H_9IS$ (311.95): Anal. Calcd C 46.17, H 2.91; found: C 45.96, H 3.12.

4.1.3. 1-(Bromo-*p*-iodophenyl)-2-(bromo-2′-thienyl)-ethane. To a solution of (*E*)-1-(*p*-iodophenyl)-2-(2′-thienyl)ethene (*E*)-**5** (850 mg, 2.72 mmol) in tetrachloromethane (30 ml), at 0 °C was added slowly bromine (435.2 mg, 2.72 mmol) in tetrachloromethane (60 ml), and the mixture was vigorously stirred for 6 h. The solvent was removed to give 1-(bromo-*p*-iodophenyl)-2-(bromo-2′-thienyl)ethane, as a white solid, 1.29 g (100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H, J=8.1 Hz); 7.41 (d, 1H, J=4.8 Hz); 7.23 (d, 1H J=4.3 Hz); 7.22 (d, 2H, J=8.1 Hz); 7.00 (dd, 1H, J=4.8, 4.3 Hz); 5.75 (d, 1H, J=11.2 Hz); 5.30 (d, 1H, J=11.2 Hz).

4.1.4. 1-(*p*-Iodophenyl)-2-(2′-thienyl)ethylene (*E*)-8. To a solution of 1-(bromo-*p*-iodophenyl)-2-(bromo-2′-thienyl)ethane (1.29 g, 2.72 mmol) in anhydrous tetrahydrofuran (60 ml), and potassium *tert*-butoxide (919.4 mg, 8.20 mmol). The mixture was stirred at room temperature for 2 h and then, the solvent was removed to give 1-(*p*-iodophenyl)-2-(2′-thienyl)ethene (**8**) as a white solid, mp 89–91 °C, 828 mg (98%). UV–vis (CH_2Cl_2), λ_{max} (nm): 330, 310, 266. FT-IR (KBr, cm^{-1}): 3421, 1518, 1481, 819. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, 2H, J=8.4 Hz); 7.30 (d, 1H, J=5.2 Hz); 7.28 (d, 1H, J=3.4 Hz); 7.23 (d,

2H, J=8.4 Hz); 7.02 (dd, 1H, J=5.2, 3.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 132.8, 132.2, 127.6, 127.2, 122.9, 122.5, 94.3, 92.1, 84.1. $C_{12}H_7IS$ (309.93): Anal. Calcd C 46.47, H 2.27; found: C 46.31, H 2.55.

4.1.5. (*E*)-1-[4-(3-Hydroxy-3-methyl-1-butyn)phenyl]-2-(2′-thienyl)ethene, (*E*)-6. *General procedure to the heterocoupling reaction*. To a solution of (*E*)-1-(*p*-iodophenyl)-2-(2′-thienyl)ethene (*E*)-**5**, 5 g (16.02 mmol) in freshly distilled and saturated in argon diethylamine (25 ml), and 2-methylbut-3-yn-2-ol (2.05 g, 24.3 mmol), was added in this order, dichlorobis[(triphenyl)phosphine]-palladium (113 mg, 0.16 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature and after 20 h, was concentrated at reduced pressure and then was added an aqueous solution of saturated ammonium chloride and potassium cyanide. The mixture was extracted with dichloromethane and the organic layer was dried on anhydrous magnesium sulphate. After filtration, solvent was removed to give (*E*)-1-(4-(3-hydroxy-3-methyl-1-butyn)-phenyl)-2-(2′-thienyl)ethene, 4.03 g (94%) as a brown solid, mp 144–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (br s, 4H); 7.25 (d, 1H, J= 5.0 Hz); 7.24 (d, 1H, J=16.1 Hz); 7.08 (d, 1H, J=3.4 Hz); 7.00 (dd, 1H, J=5.0, 3.4 Hz); 6.88 (d, 1H, J=16.1 Hz); 1.62 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 136.8, 131.9, 127.4, 127.7, 126.5, 126.0, 124.7, 122.5, 121.6, 94.6, 84.0, 65.6, 31.0.

4.1.6. (*E*)-1-(2′-Thienyl)-2-(*p*-ethynylphenyl)ethene, (*E*)-7. To a solution of the propargylic derivate (*E*)-**6** (5.04 g, 18.8 mmol) in dry toluene (50 ml), under argon atmosphere, was added a little amount of powered sodium hydroxide. The mixture was warmed at reflux temperature during 12 h. After, the solution was filtered and the solvent was eliminated at reduced pressure. The residual oil was purified by silica gel column chromatography using hexane/dichloromethane 2:1 as the eluent to give (*E*)-**7**, 2.8 g (72%) as a yellow solid, mp 117–119 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 341, 240. Fluorescence (CH_2Cl_2), λ_{max} (nm): 450 and 420 (ϕ=0.129). FT-IR (KBr, cm^{-1}): 3271, 1590, 1514, 1411, 949, 829. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (d, 2H, J=8.6 Hz), 7.39 (d, 2H, J=8.6 Hz); 7.24 (d, 1H, J= 16.1 Hz); 7.22 (d, 1H, J=5.0 Hz); 7.08 (d, 1H, J=3.4 Hz); 7.00 (dd, 1H, J=5.0, 3.4 Hz); 6.88 (d, 1H, J=16.1 Hz); 3.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 137.5, 132.5, 127.7, 127.4, 126.6, 126.1, 124.8, 122.9, 118.9, 83.7, 77.9. $C_{14}H_{10}S$ (210.05): Anal. Calcd C 79.96, H 4.79; found: C 79.71, H 4.60.

4.1.7. 1-[4-(3-Hydroxy-3-methyl-1-butyn)phenyl]-2-(2′-thienyl)ethyne (9). Following the general method used for the synthesis of **6**, a mixture of 1-(*p*-iodophenyl)-2-(2′-thienyl)ethyne (550 mg, 1.77 mmol) (**8**), 2-methyl-but-3-yn-2-ol (149 mg, 1.77 mmol) in diethylamine (10 ml), dichlorobis[(triphenyl)phosphine]palladium (13.3 mg, 0.018 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 8 h. After purification gives 1-(4-(3-hydroxy-3-methyl-1-butyn)phenyl)-2-(2′-thienyl)ethylene (**9**), 400 mg (85%) as a white solid, mp 102–105 °C. FT-IR (KBr, cm^{-1}): 3240, 1523, 1428, 832. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, 2H, J= 8.6 Hz); 7.37 (d, 2H, J=8.6 Hz); 7.29 (d, 1H, J=5.2 Hz); 7.27 (d, 1H, J=3.4 Hz); 7.01 (dd, 1H, J=5.2, 3.4 Hz); 1.61 (s, 6H).

4.1.8. 1-(2′-Thienyl)-2-(*p*-ethynylphenyl)ethyne[25] (10) Following the general method used for the synthesis of **7**, propargylic derivate (**9**) (400 mg, 1.50 mmol) in dry toluene (15 ml) was warmed at the reflux temperature during 12 h to give 1-(2′-thienyl)-2-(4-ethynylphenyl)ethyne (**10**), 295 mg (94%) as a yellow solid, mp 90–92 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 337, 316, 281, 269. Fluorescence (CH_2Cl_2), λ_{max} (nm): 410 and 392 (ϕ=0.142). FT-IR (KBr, cm^{-1}): 3273, 2195, 1523, 1489, 1421, 832. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 4H); 7.32 (d, 1H, J=4.8 Hz); 7.30 (d, 1H, J= 3.2 Hz); 7.03 (dd, 1H, J=4.8, 3.2 Hz); 3.19 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.2, 132.1, 131.2, 127.7, 127.2, 123.4, 122.9, 122.0, 92.5, 83.2, 79.0, 77.4. $C_{14}H_8S$ (208.03): Anal. Calcd C 80.73, H 3.87; found: C 80.61, H 4.02.

4.1.9. 1-[*p*-(3-Hydroxy-3-methyl-1-butyn)phenyl]-2-(*p*-*N*,*N*-dimethylaminophenyl)ethyne. Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **11** (221 mg, 0.64 mmol), 2-methyl-but-3-yn-2-ol (53 mg, 0.64 mmol) in diethylamine (3 ml), dichlorobis [(triphenyl)phosphine]palladium (6 mg, 0.0064 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 8 h. After purification gives 1-[*p*-(3-hydroxy-3-mehyl-1-butyn)phenyl]-2-(*p*-*N*,*N*-dimethylaminophenyl)ethyne 158 mg (82%) as a brown solid, mp 90–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, 2H, J= 8.6 Hz); 7.40 (d, 2H, J=9.0 Hz); 7.35 (d, 2H, J=8.6 Hz); 6.66 (d, 2H, J=9.0 Hz); 3.00 (s, 6H); 1.62 (s, 6H).

4.1.10. 1-(*p*-*N*,*N*-Dimethylaminophenyl)-2-(*p*-ethynylphenyl)ethyne (12). Following the general method used for the synthesis of **7**, propargylic derivate (158 mg, 0.52 mmol) in dry toluene (5 ml) was warmed at the reflux temperature during 12 h to give 1-(*p*-*N*,*N*-dimethylaminophenyl)-2-(*p*-ethynylphenyl)ethyne (**12**), 115.4 mg (90%) as a red solid, mp 138–140 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 354, 280, 269. Fluorescence (CH_2Cl_2), λ máx (nm): 443 (ϕ=0.238). FT-IR (KBr): 3240 (C≡CH); 2208 (C≡C); 1606 and 1523 (C=C); 1351 (C–N); 818 (*p*-disust. ArH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (s, 4H,); 7.40 (d, 2H, J=8.6 Hz); 6.66 (d, 2H, J=8.6 Hz); 3.15 (s, 1H); 3.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.2, 132.7, 131.9, 131.0, 124.7, 120.8, 111.7, 109.5, 92.9, 87.0, 83.5, 78.4, 40.1. $C_{18}H_{15}N$ (245.12): Anal. Calcd C 88.13, H 6.16, N 5.71; found: C 87.92, H 6.14, N 5.58.

4.1.11. (*E*)-1-(2′-Thienyl)-2-(4-bromoethynylphenyl)-ethene (*E*)-13. Bromine (152 mg) was added to a solution of potassium hydroxide (142 mg, 2.54 mmol) in water (5 ml) and vigorously stirred at −5 °C for 15 min. A pale yellow solution of KOBr was formed and then, was slowly added (*E*)-1-(2′-thienyl)-2-(*p*-ethenylphenyl)ethene (*E*)-**7** (200 mg, 0.95 mmol) in 15 ml of tetrahydrofuran, maintained the solution between 10–20 °C. The mixture was stirred at room temperature overnight and then the solvent removed. The residual solid was extracted with dichloromethane and the organic layer was dried on anhydrous magnesium sulphate, filtered and solvent evaporated to give a brown solid that was purified by silica gel column

chromatography using hexane–dichloromethane (1/1) as the eluent, to give (*E*)-1-(2-thienyl)-2-(4-bromoethenylphenyl)-ethene (*E*)-**13**, 200 mg (70%) as a red-orange solid. This compound should be used without delay.

4.1.12. (*E*,*E*)-1,4-Di(4-(2-(2-thienyl)ethenyl)phenyl)-1,3-butadiyne, (*E*,*E*)-14. To a solution of hydroxylamine·HCl (200 mg) in water (10 ml), an aqueous solution of ethylamine (70%, 10 ml) methanol (50 ml) and a little amount of copper(I) chloride, under argon atmosphere, was added (*E*)-1-(2-thienyl)-2-(4-ethenylphenyl)ethene (*E*)-**7** (147 mg, 0.70 mmol) and (*E*)-1-(2′-thienyl)-2-(4-bromoethenylphenyl)ethene (*E*)-**13** (200 mg, 0.70 mmol) between 30–35 °C. After 1 h the mixture was hydrolyzed with a saturated aqueous ammonium chloride solution with vigorous stirring and extracted with dichloromethane. The organic layer was dried on anhydrous magnesium sulphate, filtered and the solvent evaporated to give (*E*,*E*)-1,4-di-(4-(2-(2-thienyl)ethenyl)phenyl)butadiyne (*E*,*E*)-**14**, 65 mg (45%), as a yellow solid, mp >300 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 347, 248. Fluorescence (CH_2Cl_2), λ_{max} (nm): 454 and 427 (ϕ=0.289). FT-IR (KBr, cm^{-1}): 2143, 1621, 1514, 1410, 831. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 2H, J=8.6 Hz); 7.40 (d, 2H, J=8.6 Hz); 7.24 (d, 1H, J=16.1 Hz); 7.21 (d, 1H, J=5.0 Hz); 7.09 (d,1H, J=3.4 Hz); 7.01 (dd, 1H, J=5.0, 3.4 Hz); 6.88 (d, 1H, J=16.1 Hz). MS (70 eV): 418 (M^+, 100), 209 (M^{2+}, 6). $C_{28}H_{18}S_2$ (418.08): Anal. Calcd C 80.34, H 4.33; found: C 80.17, H 4.49.

4.1.13. (1,4-Di(4-(2′-thienyl)ethynyl)phenyl)-1,3-butadiyne (15). To a solution of cuprous chloride (35.4 mg, 0.18 mmol) in dry pyridine (5 ml), under an oxygen atmosphere, at 40 °C was added a solution of 1-(2′-thienyl)-2-(*p*-ethynylphenyl)ethyne (**8**) (150 mg, 0.72 mmol) in dry pyridine (5 ml) and the mixture was stirred for 30 min. The solvent was removed and the residual solid was washed with ammonium hydroxide and extracted with dichloromethane. The organic layer was dried on anhydrous magnesium sulphate, filtered and solvent evaporated to give (1,4-di(4-(2′-thienyl)ethynyl)-phenyl)-1,3-butadiyne (**15**), 69 mg (61%) as a yellow solid, mp 239–240 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 359, 260, 244. Fluorescence (CH_2Cl_2), λ_{max} (nm): 421 (ϕ=0.364). FT-IR (KBr, cm^{-1}): 2198, 1594, 1521, 1487, 829. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 8H); 7.33 (d, 2H, J=5.4 Hz); 7.30 (d, 2H, J=3.8 Hz); 7.03 (dd, 2H, J=5.4, 3.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.1, 132.8, 131.6, 129.3, 127.8, 123.8, 121.9, 120.9, 92.4, 85.8, 82.6, 75.6. MS (MALDI-TOF): 414.0. $C_{28}H_{14}S_2$ (414.05): Anal. Calcd C 81.13, H 3.40; found: C 80.98, H 3.63.

4.1.14. (Di-(*p*-(2′-thienyl)ethynyl)phenyl)ethyne (16). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **8** (100 mg, 0.32 mmol), 1-(2′-thienyl)-2-(*p*-ethynylphenyl)ethylene (**10**) (66 mg, 0.32 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (23 mg, 0.032 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 30 min. After purification gives (di(*p*-(2′-thienyl)ethynyl)phenyl)ethyne (**16**), 99 mg (38%), as a brown-red solid, p.f.> 230 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 352, 243. Fluorescence (CH_2Cl_2), λ_{max} (nm): 410 and 390 (ϕ=0.296). FT-IR (KBr, cm^{-1}): 2197, 1595, 1524, 1424, 831. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 8H), 7.33 (d, 2H, J=5.2 Hz); 7.30 (d, 2H, J=3.7 Hz); 7.03 (dd, 2H, J=5.2, 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.4, 131.5, 131.3, 127.8, 127.2, 123.9, 123.0, 121.5, 92.5, 85.4, 82.1. MS (MALDI-TOF): 390.0. $C_{26}H_{14}S_2$ (390.05): Anal. Calcd C 79.96, H 3.61; found: C 79.75, H 3.97.

4.1.15. 2,5-[Di(*p*-*N*,*N*-dimethylamino)phenylethynyl]-thiophene (17). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **11** (100 mg, 0.68 mmol), 2,5-di(iodo)thiophene (231 mg, 0.68 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (48 mg, 0.068 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 3 h. After purification gives 2,5-[di(*p*-*N*,*N*-dimethylamino)phenylethynyl]thiophene (**17**) 246 mg (98%), as a yellow solid, p.f. 181–183 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 385. Fluorescence (CH_2Cl_2), λ_{max} (nm): 456 (ϕ=0.23). FT-IR (KBr, cm^{-1}): 2157, 1578, 1466, 1372. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, 4H, J=8.0 Hz); 7.05 (s, 2H); 6.64 (d, 4H, J=8.0 Hz); 2.99 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 133.4, 131.5, 122.3, 113.8, 112.3, 92.7, 86.4, 41.0. MS (FAB+) *m*/*z* 370.1 (M^+, 100), 170.1 (31). $C_{24}H_{22}N_2S$ (370.15): Anal. Calcd C 77.80, H 5.98, N 7.56; found: C 78.63, H 5.78, N 7.43

4.1.16. 2,5-[Di(*p*-*N*,*N*-dimethylamino)(phenylethynyl)(phenylethynyl)]thiophene (19). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **12** (115.4 mg, 0.47 mmol), 2,5-di(iodo)thiophene (157 mg, 0.47 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (33 mg, 0.047 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 5 h. After purification gives 2,5-[di(*p*-*N*,*N*-dimethylamino)(phenylethynyl)(phenylethynyl)]-thiophene (**19**) 227 mg (85%), as a yellow solid, p.f. 227–230 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 393. Fluorescence (CH_2Cl_2), λ_{max} (nm): 512 (ϕ=0.30). FT-IR (KBr, cm^{-1}): 2153, 1552, 1428, 1381. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (m, 8H); 7.43 (d, 4H, J=8.0 Hz); 7.16 (s, 2H); 6.66 (d, 4H, J=8.0 Hz); 3.00 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 133.2, 131.9, 131.5, 122.6, 122.3, 113.9, 112.2, 92.9, 92.8, 92.7, 86.5, 40.4. MS (FAB+): 570.2 (M^+, 100), 370.1 (43). $C_{24}H_{22}N_2S$ (570.20): Anal. Calcd C 84.18, H 5.30, N 4.91; found: C 84.93, H 5.29, N 4.73.

4.1.17. 2,5-Di-[2-(4-((*E*)-2-(thiophen-2-yl)vinyl)phenylethynyl)]thiophene (21). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **7** (60 mg, 0.29 mmol), 2,5-di(iodo)thiophene (50 mg, 0.15 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (21 mg, 0.03 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 7 h. After purification gives 2,5-di-[2-(4-((*E*)-2-(thiophen-2-yl)vinyl)phenylethynyl)]thiophene (**21**) 46 mg (65%), as a yellow solid, p.f. 261–262 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 367. Fluorescence (CH_2Cl_2), λ_{max} (nm): 462 and 440 (ϕ=0.10). FT-IR (KBr, cm^{-1}): 3295, 1579, 1505, 1437, 825. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 8H); 7.35 (d, 1H, J=4.8 Hz), 7.27 (d, 2H, J=15.9 Hz); 7.15 (d, 2H, J=3.8 Hz); 7.10 (s, 2H); 7.02 (dd, 2H, J=4.8, 3.8 Hz); 6.90 (d, 2H, J=15.9 Hz). MS (MALDI-TOF):

500.0. $C_{32}H_{20}S_3$ (500.07): Anal. Calcd C 76.76, H 4.03; found: C 76.61, H 4.32.

4.1.18. 2,5-Di-[2-(thienylethynyl)(phenylethynyl)]thiophene (22). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **10** (47 mg, 0.23 mmol), 2,5-di(iodo)thiophene (41 mg, 0.12 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (16 mg, 0.023 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 7 h. After purification gives 2,5-di-[2-(thienylethynyl)(phenylethynyl)]thiophene (**22**) 48 mg (85%), as a yellow solid, p.f. 234–235 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 379. Fluorescence (CH_2Cl_2), λ_{max} (nm): 423 and 398 ($\phi=0.34$). FT-IR (KBr, cm^{-1}): 3311, 1592, 1519, 1448, 830. ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 8H); 7.32 (d, 2H, $J=4.8$ Hz); 7.31 (d, 2H, $J=4.3$ Hz); 7.18 (s, 2H); 7.03 (dd, 2H, $J=4.8$, 4.3 Hz). MS (MALDI-TOF): 495.9. $C_{32}H_{16}S_3$ (496.04): Anal. Calcd C 77.38, H 3.25; found: C 77.72, H 3.06.

4.1.19. 2,5-Di-[(3,5-bis-trimethylsilylethynylphenyl)-ethynyl]thiophene (26). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **23** (175 mg, 0.60 mmol), 2,5-di(iodo)thiophene (100 mg, 0.30 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (42 mg, 0.06 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 12 h. After purification gives 2,5-di-[(3,5-bis-trimethylsilylethynylphenyl)ethynyl]thiophene (**26**) 191 mg (97%), as a green solid, p.f. 139–140 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 355. Fluorescence (CH_2Cl_2), λ_{max} (nm): 410 and 391 ($\phi=0.20$). FT-IR (KBr, cm^{-1}): 2156, 1579, 1410, 1250, 758. ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, 4H, $J=1.6$ Hz); 7.53 (t, 2H, $J=1.6$ Hz); 7.14 (s, 2H); 0.24 (s, 36H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.1, 134.3, 132.2, 124.5, 123.8, 123.0, 103.0, 95.9, 92.6, 83.1, −0.2. MS (70 eV): 668 (M^+, 100), 320 (23), 73 (90). $C_{40}H_{44}SSi_4$ (669.19): Anal. Calcd C 71.79, H 6.63; found: C 71.83, H 6.60.

4.1.20. 2,5-Di-{[(3,5-bis-trimethylsilylethynylphenyl)-ethynylphenyl]ethynyl}thiophene (27). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **24** (233 mg, 0.60 mmol), 2,5-di (iodo)thiophene (100 mg, 0.30 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (42 mg, 0.06 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 12 h. After purification gives 2,5-di-{[(3,5-bis-trimethylsilylethynylphenyl)ethynylphenyl]ethynyl}thiophene (**27**) 249 mg (97%), as a green solid, p.f. 218–220 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 379. Fluorescence (CH_2Cl_2), λ_{max} (nm): 447 and 421 ($\phi=0.42$). FT-IR (KBr, cm^{-1}): 2159, 1577, 1409, 1249, 759. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, 4H, $J=1.6$ Hz), 7.53 (t, 2H, $J=1.6$ Hz), 7.51 (d, 4H, $J=8.7$ Hz), 7.46 (d, 4H, $J=8.7$ Hz), 7.18 (s, 2H), 0.24 (s, 36H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.0, 134.5, 132.1, 131.6, 131.4, 124.7, 123.8, 123.4, 123.0, 122.7, 103.1, 95.8, 93.9, 89.9, 89.8, 84.9, −0.2. MS (70 eV): 868.3 (M^+, 100); 419.3 (30). $C_{56}H_{52}SSi_4$ (869.42): Anal. Calcd C 77.36, H 6.03; found: C 77.43, H 5.98.

4.1.21. 2,5-Di-{{{[3,5-bis(trimethylsilylethynyl)phenyl]-ethynylphenyl}ethynylphenyl}ethynyl}thiophene (28). Following the general method used for the synthesis of **6**, a mixture of terminal acetylene **25** (100 mg, 0.20 mmol), 2,5-di(iodo)thiophene (34 mg, 0.10 mmol) in diethylamine (10 ml), dichlorobis[triphenylphosphine]palladium (10 mg, 0.02 mmol) and a little amount of copper(I) iodide. The mixture was stirred at room temperature for 12 h. After purification gives 2,5-di-{{{[3,5-bis(trimethylsilylethynyl)-phenyl]ethynylphenyl}ethynylphenyl}ethynyl}thiophene (**28**) 88 mg (80%), as a green solid, p.f. 291–293 °C. UV–vis (CH_2Cl_2), λ_{max} (nm): 377. Fluorescence (CH_2Cl_2), λ_{max} (nm): 454 and 429 ($\phi=0.54$). FT-IR (KBr, cm^{-1}): 2159, 1577, 1409, 1249, 759. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, 4H, $J=1.6$ Hz), 7.53 (t, 2H, $J=1.6$ Hz), 7.52 (br s, 8H), 7.51 (d, 4H, $J=8.9$ Hz), 7.47 (d, 4H, $J=8.9$ Hz), 7.18 (s, 2H), 0.24 (s, 36H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.0, 134.5, 132.2, 131.6, 131.4, 124.7, 123.8, 123.5, 123.2, 123.1, 122.9, 103.1, 95.8, 94.0, 91.2, 91.1, 90.1, 89.7, 84.27, −0.2. MS (70 eV): 1068 (M^+, 100), 520 (40). $C_{72}H_{66}SSi_4$ (1069.65): Anal. Calcd C 80.85, H 5.65; found: C 80.91, H 5.59.

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Synthesis of *N*,*N*′-bis and *N*,*N*,*N*′,*N*′-tetra-[(3,5-di-substituted-1-pyrazolyl)methyl]-*para*-phenylenediamines: new candidate ligands for metal complex wires

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Abstract—A series of tridentate ligands *N*,*N*-bis-[(di-substituted-1-pyrazolyl)methyl]arylamines **2**–**3a**,**b** and benzylamine **4a**,**b**, tetradentate *N*,*N*′-bis-[(di-substituted-1-pyrazolyl)methyl]*para*-phenylenediamines **7a**,**b** and hexadentate *N*,*N*,*N*′,*N*′-tetra-[(di-substituted-1-pyrazolyl)-methyl]*para*-phenylenediamines **8a**,**b** has been prepared in good yield by condensation of arylamines, benzylamine or *para*-phenylenediamine with *N*-hydroxymethyl disubstituted pyrazoles **1a**,**b**. The synthesis and characterisation of these various polydentate ligands are described.

1. Introduction

Polymetallic complexes with suitable polydentate bridging ligands can be useful models of molecular wires.[1] By reference to macroscopic electrical devices, the concept of a wire is fundamentally based on intramolecular electron transfer that occurs in its simplest form in mixed-valence complexes. Bimetallic metal complexes with suitable bridging ligands can be useful models to study electronic interaction or electron transfer rates with distance including in biological electron transfer.[1] Another interesting use of long distance coordinating ligands is the electronic communication between remote metallic atoms and the development of molecular switches, that is, molecules able to promote or block intramolecular electron transfer.[1] This development clearly requires the mastering of long distance electron transfer (over 15–20 Å).

In search of new terminal coordinating groups to study intramolecular electron transfers, we have considered the case of polydendate pyrazole ligands. Such compounds are particularly interesting as ligands for the building of polynuclear complexes as models for bioinorganic systems[2] as well as for the discovery of new catalyst precursors.[3]

The flexibility of the pyrazolic *N*-coordinating groups of the tridentate ligands could allow them to act as meridional[4,5] or as facial ligands[6,7] when coordinating to transition metal complexes (Scheme 1).

In the case of polydentate ligands, they could coordinate in facial and meridional fashion as proposed in Scheme 1, such as by combination of bis-tridentate ligands with Ru^{2+} metal sites. In contrast, with bis-bidentate ligand, the four nitrogen atoms cannot coordinate to the same metal atom and are expected to lead to polymeric metal complex.[8–11]

To gain insight into the coordination behaviour of larger ligand systems containing at the same time pyrazolyl nitrogen groups and electron releasing amine *N*-donor

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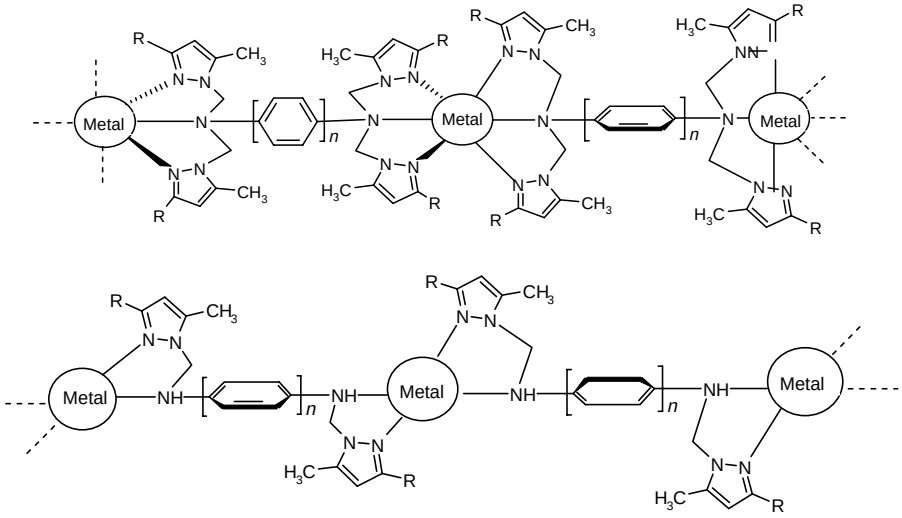


Scheme 1. Examples of possible polymetallic wires.

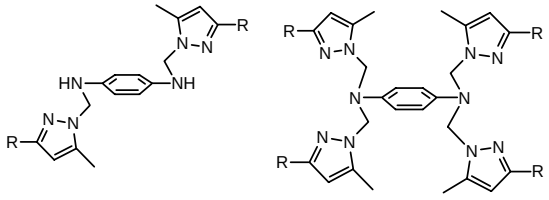
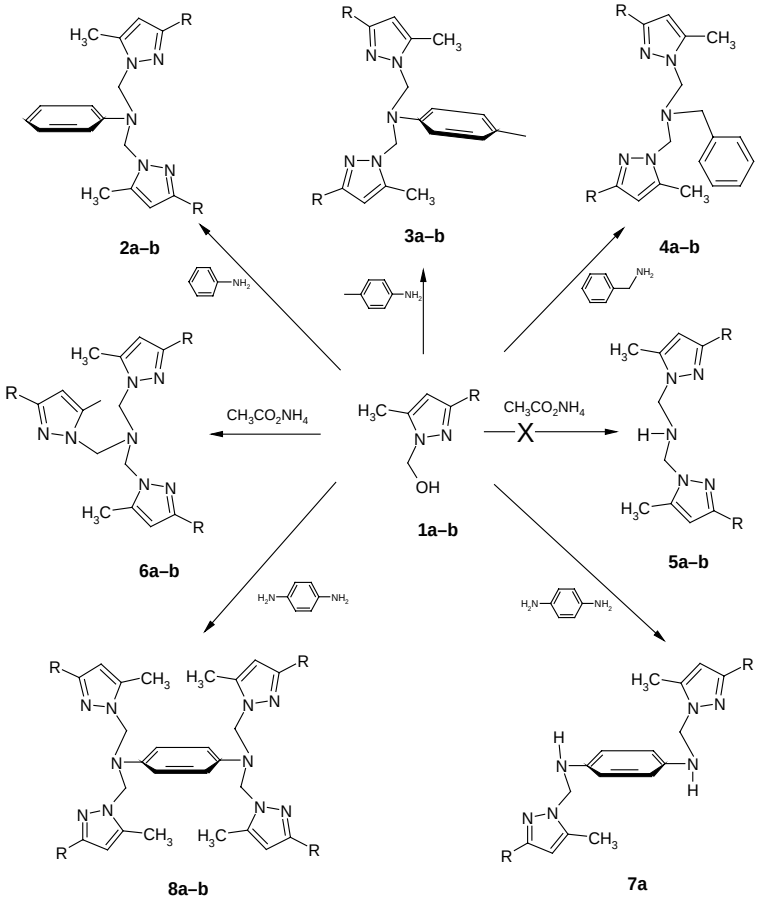


Figure 1.

atoms we have developed initial work on tridentate *N*,*N*-bis-[(3,5-dimethyl-1-pyrazolyl)methyl] alkylamines.[12]

In the present paper, we report the synthesis of a family of tridentate, tetradentate, bis-bidentate and bis-tridentate ligands containing pyrazol groups bridged by aminomethyl groups, with the general topology shown in Figure 1, on reaction of (pyrazol-1-yl)methanol and primary amines.



Scheme 2. Synthesis of tridentate (**2**–**4**), tetradentate (**6a**–**b**), bis-bidentate (**7a**) and bis-tridentate (**8a**–**b**) *N*-ligands with [R = –CH_3 (**a**), –CO_2CH_3 (**b**)].

2. Results and discussion

On the basis of our initial work for the synthesis of compounds **2a**[12] the new tridentate ligands **2b**, **3a**,**b**, **4a**,**b** were prepared on reaction of (3,5-dimethyl-1*H*-pyrazol-1-yl)methanol **1a** and methyl 1-(hydroxymethyl)-5-methyl-1*H*-pyrazole-3-carboxylate **1b**, respectively, with aniline, *p*-methylaniline or benzylamine. The tridentate compounds **2**–**4** were easily prepared from the condensation of 2 equiv of 1-(hydroxymethyl)-3,5-dimethyl-pyrazole **1a** or 1-(hydroxymethyl)-3-methoxycarbonyl-5-methyl-pyrazole **1b** with 1 equiv of arylamine under mild conditions (room temperature), using anhydrous acetonitrile as solvent. The reaction is very slow but selective at room temperature. Thus after 4–5 days of stirring at room temperature the derivatives **2b** (94%), **3a** (74%), **3b** (64%), **4a** (77%) and **4c** (53%) were isolated (Scheme 2).

Tetradentate molecules **6a**,**b** have been prepared using ammonium acetate as the source of ammonia as outlined in Scheme 2. In this way, the reaction of **1a**–**b** with ammonium acetate in acetonitrile could not be stopped to afford the expected tridentate ligands **5a**,**b** with central N–H group, and the tetradentate compounds **6a**,**b** were directly obtained.

The reaction of precursors **1a**,**b** with the *p*-phenylenediamine in CH_3CN at room temperature produces bis-bidentate ligand **7a** and bis-tridentate ligands **8a**,**b**. This reaction selectivity is simply controlled by the use of 2 and 4 equiv of **1a**–**b**, respectively, with respect to *p*-phenylenediamine, and **7a** (61%), **8a** (67%) and **8b** (73%) were isolated after 5 days of stirring at room temperature (Scheme 2). The crystal structure of hexadentate compound **8a** was recently reported and confirmed the molecular structure.[13]

By comparison with various bis-bidentate and bis-tridentate ligands for the synthesis of known bimetallic or polymetallic complexes in the literature,[14,15] we describe here bis-bidentate and bis-tridentate compounds, for which the synthesis is relatively easy. Their synthesis from *p*-phenylenediamine could certainly be generalised to a large variety of other aromatic diamines.

3. Experimental

3.1. General methods

Infrared spectra were recorded on a PYE Unicam SP3-300 spectrometer as KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on Varian EM 360 (operating at 60 MHz for ^1H) or/and Bruker spectrometer (250 and 400 MHz) using TMS as internal standard. Chemical shifts are reported downfield from the standard in ppm. The FAB mass spectra were obtained on a NERMANG R10-LOC instrument. For the chemical ionisation ($DCI/NH_3/CH_3$), the compounds were dissolved in DMSO or MeOH and dispersed in a matrix solution, currently the 3-nitrobenzyl (MNBA) or Glycerol (GLY). Elemental analyses were performed by the Service Central d'Analyse du CNRS LCC (Toulouse).

3.2. Synthesis of compounds 2–8.

General procedure for the synthesis of **2**–**4** *and* **6**. The products were prepared by the addition of arylamine (p-R-$C_6H_4NH_2$), and ($C_6H_5CH_2NH_2$) or ammonium acetate to **1a** or **1b**. To a solution of the substituted hydroxymethylpyrazole **1a** (1.26 g, 10 mmol) or **1b** (1.70 g, 10 mmol) in acetonitrile (25 ml) was added the desired amine (5 mmol) and the mixture was continued at room temperature for 4–5 days. The formed compound was precipitated by addition of cold water to acetonitrile solution, washed with hexane and dried under vacuum. Compounds **2**–**4** and **6** were obtained as white solids (60–94% yield).

General procedure for the synthesis of **7**–**8**. The products **7**–**8** were prepared by the addition of *p*-phenylenediamine (NH_2–C_6H_4–NH_2) to **1a** or **1b**. To a solution of the substituted hydroxymethylpyrazole **1a** (1.26 g, 10 mmol) or **1b** (1.70 g, 10 mmol) in acetonitrile (25 ml) was added *p*-phenylenediamine (2.5 mmol) for **8** or (5 mmol) for **7** and the mixture and the stirring was continued at room temperature for 4–5 days. The product was precipitated by simple addition of cold water, washed with hexane and dried under vacuum. The compounds **7**–**8** were obtained as white solids (60–67%).

3.2.1. *N*,*N*-Bis[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl] aniline (2a). Yield 65%. Mp 85 °C (mp lit.[16] = 83 °C). IR (KBr, υ cm^{-1}): 3260 (=C–H Ar), 3080 (C–H Me), 1600 (C=C), 1500, 1470 (C=N); 1500, 1350, 1290, 1230, 1170, 1110, 1050. ^1H NMR (60 MHz, $CDCl_3$) δ ppm: 7.00 (m, 5H, Ph), 5.75 (s, 2H, pyrazol–$H^{4,4'}$), 5.40 (s, 4H, NCH_2N), 2.30 (s, 6H, CH_3), 2.10 (s, 6H, CH_3). MS (DCI/NH_3, CH_2Cl_2): Calcd for $[M]^+$ $C_{18}H_{23}N_5$: 310. Found $[M+H]^+$ (m/z) = 311 (45%).

3.2.2. Methyl-1-[({[3-(methoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl]methyl}anilino)methyl]-5-methyl-1*H* pyrazole-3-carboxylate (2b). Yield 94%. Mp 124–126 °C. IR (KBr, υ cm^{-1}): 3200 (CH, Ar), 2920 (CH), 1730 (C=O), 1600 (C=C), 1490 (C=N), 1460, 1420, 1230. ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 6.70–7.45 (m, 5H, C_6H_5), 6.5 (s, 2H, pyrazol–$H^{4,4'}$), 5.65 (s, 4H, NCH_2N), 3.90 (s, 6H, OCH_3), 2.05 (s, 6H, pyrazol–CH_3). MS (MeOH/GLY): Calcd for $[M]^+$ $C_{20}H_{23}N_5O_4$: 397. Found $[M+H]^+$ (m/z) = 398 (19%). Elemental analysis for $C_{20}H_{23}N_5O_4$ Calcd (Found): C 60.45 (60.48), H 5.79 (5.81), N 17.63 (17.56).

3.2.3. (3,5-Dimethyl-1*H*-pyrazol-1-yl)-*N*-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]methanamine (3a). Yield 74%. Mp 108–109 °C. IR (KBr, υ cm^{-1}): 3025 (=C–H Ar), 2950 (CH), 1720/1600 1500/1472 (C=N). ^1H NMR (60 MHz, $CDCl_3$) δ ppm: 6.8, 7.3 (m, 4H, Ph), 5.90 (s, 2H, pyrazol–$H^{4,4'}$), 5.60 (s, 4H, $2NCH_2N$), 2.25 (s, 15H, CH_3-Ph + CH_3-pz). MS (DCI/NH_3, CH_2Cl_2): Calcd for $[M]^+$ $C_{19}H_{25}N_5$: 323. Found $[M+H]^+$ (m/z) = 324 (23%).

3.2.4. (3-(Methoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl)methyl]methanamine (3b). Yield 64%. ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.10 (d, 2H, C_6H_5), 6.90 (d, 2H, C_6H_5), 6.50 (s, 2H, pyrazol–$H^{4,4'}$), 5.70 (s, 4H,

2NCH$_2$N), 3.95 (s, 6H, 2OCH$_3$), 2.30 (s, 3H, CH$_3$-ph), 2.10 (s, 6H, pyrazol–CH$_3$). MS (CI/CH$_3$): Calcd for [M]$^{\cdot+}$ $C_{21}H_{25}N_5O_4$: 411. Found [M+H]$^{\cdot+}$ (m/z)=412 (4.92%).

3.2.5. (3,5-Dimethyl-1*H*-pyrazol-1-yl)-*N*-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]benzylamine (4a). Yield 65%. Mp 73 °C. IR (KBr, υ cm^{-1}): 3085 (=C–H aromat), 2930 (CH), 1550 (C=C), 1450 (C=N), 1380, 1310, 1100, 1000, 960, 800, 750. ^{1}H (60 MHz, CDCl$_3$) δ ppm: 7.4 (s, 5H, C$_6$H$_5$), 5.9 (s, 2H, pz, C$^{4,4'}$), 5 (s, 2N–CH$_2$–N), 3.9 (s, 2H, ph-CH$_2$–N), 2.3 (s, 6H, 2CH$_3$, C$^{3,3'}$), 2.1 (s, 6H, 2CH$_3$, C $^{5,5'}$). MS (DCI/NH$_3$): Calcd for [M]$^{\cdot+}$ $C_{19}H_{25}N_5$: 323. Found [M+H]$^{\cdot+}$ (m/z)=324 (92.5%), 228 (100%), 137 (21.7%), 120 (37.5%), 114 (42.5%).

3.2.6. (-3-(Methoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl)methyl]]benzylamine (4b). Yield 65%. Mp 85 °C. IR (KBr, υ cm^{-1}): 3025 (=CH aromat), 2950 (CH), 1750 (C=O), 1600, 1450 (C=C), 1310, 1220 (C–O), 940, 820, 780. ^{1}H (400 MHz, CDCl$_3$) δ ppm: 7.4. (s, 5H, C$_6$H$_5$), 5.2 (s, 4H, 2NCH$_2$N), 3.9 (s, 6H, 2O–CH$_3$), 3.8 (s, 2H, ph-*CH*$_2$–N), 2.1 (s, 6H, 2CH$_3$, C$^{5,5'}$). C^{13} (400 MHz, CDCl$_3$) δ ppm: 163.04 (CO$_2$Me), 142.62–140.69 (ph), 130.1 (C$^{3,3'}$), 122.85 (C$^{5,5'}$), 108.83 (C$^{4,4'}$), 66.73 (N–*CH*$_2$–N), 52.04 (O–CH$_3$), 20.84 (ph-*CH*$_2$–N), 11.08 (CH$_3$–CH3$^{5,5'}$). Elemental analysis for $C_{21}H_{25}N_5O_4$ Calcd (Found): C 61.31 (61.48), H 6.08 (6.20), N 17.03 (17.40). MS (CI/CH$_3$): Calcd for [M]$^{\cdot+}$ $C_{21}H_{25}N_5O_6$: 411. Found [M+C_2H_5]$^{\cdot+}$ (m/z)=440 (5%).

3.2.7. (3,5-Dimethyl-1*H*-pyrazol-1-yl)-*N*-[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl] amine (6a). Yield 77%. Mp 94–96 °C. IR (KBr, υ cm^{-1}): 3000 (=C–H aromat), 290 (CH), 1560, 1440 (C=N), 1400, 1350, 1290, 1230, 1160, 1050, 830, 690. ^{1}H (60 MHz, CDCl$_3$) δ ppm: 5.70 (s, 3H, pz, H^4), 5.00 (s, NCH$_2$N), 2.10 (s, 9H, 3CH$_3$), 1.90 (s, 9H, 3CH$_3$). MS (DCI/NH$_3$): Calcd for [M]$^{\cdot+}$ $C_{18}H_{27}N_7$: 341. Found [M+H]$^{\cdot+}$ (m/z)=342 (100%).

3.2.8. (-3-(Methoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl)methyl]] amine (6b). Yield 53%. IR (KBr, υ cm^{-1}): 3080 (=C–H aromat), 2940 (CH), 1730 (C=O), 1450 (C=N), 1380, 1330, 1240, 1180, 1120, 1040, 830, 800. ^{1}H (400 MHz, CDCl$_3$) δ ppm: 6.50 (s, 3H, pz, H^4), 5.20 (s, 6H, 3NCH$_2$N), 3.90 (s, 9H, 3O–CH$_3$), 1.90 (s, 9H, 3CH$_3$). C^{13} (400 MHz, CDCl$_3$) δ ppm: 162.67 (CO$_2$Me), 142.85 (C$^{3,3',3''}$), 141.13 (C$^{5,5',5''}$), 109.15 (C$^{4,4',4''}$), 63.55 (N–CH$_2$–N), 52.04 (O–CH$_3$); 10.09 (CH$_3$–C$^{5,5',5''}$). MS (CI/CH$_3$): Calcd for [M]$^{\cdot+}$ $C_{21}H_{27}N_7O_6$: 473. Found [MH]$^{\cdot+}$ (m/z)=474 (3%).

3.2.9. *N*,*N*′ Bis[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-1,4-benzenediamine (7a). Yield 61.5%. Mp 158–160 °C. IR (KBr, υ cm^{-1}): 3300 (–NH), 2920 (=CH), 1520 (C=C), 1450 (C=N), 1380, 1180. NMR ^{1}H (60 MHz, CDCl$_3$) δ ppm: 6.65 (s, 4H, Ph), 5.7 (s, 2H, pyrazol–C^4), 5.4 (s, 4H, N*CH*$_2$N), 4.4 (s, 2H, Ph-N–H), 2.2 (s, 6H, CH$_3$, C$^{3,3'}$), 2.1 (s, 6H, CH$_3$, C$^{5,5'}$). MS (DCI/NH$_3$, CH$_2$Cl$_2$): Calcd for [M]$^+$ $C_{18}H_{24}N_6$: 324.219. Found [M+H]$^{\cdot+}$ (m/z)=325 (2.52%).

3.2.10. *N*,*N*,*N*′,*N*′-Tetrakis[(3,5-dimethyl-1*H*-pyrazol-1-yl)methyl]-1,4-benzenediamine (8a). Yield 67%. Mp 174–176 °C. IR (KBr, υ cm^{-1}): 2980 (C–H), 1590 (C=C), 1220, 1170, 1490. ^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7 (s, 4H, Ph), 5.8 (s, 4H, pyrazol), 5.5 (s, 8H, NCH$_2$N), 2.3 (s, 12H, CH$_3$), 2.0 (s, 12H, CH$_3$). MS Calcd for [M]$^+$ $C_{34}H_{40}N_{10}O_8$: 716; [M+Na$^+$]$^{\cdot}$ (m/z)= 739, 613, 585, 460. MS (FAB<0, MeOH/GLY): Calcd for [M]$^{\cdot+}$ $C_{30}H_{40}N_{10}$: 540. Found [M+H]$^{\cdot+}$ (m/z)=541 (11.5%). Elemental analysis for $C_{30}H_{40}N_{10}$ Calcd (Found): C 65.66 (65.82), H 7.40 (6.98), N 25.90 (25.24).

3.2.11. Methyl-1-[(4-(bis{[3-(methoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl]methyl}amino){[3-(methoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl]methyl}anilino)methyl]-5-methyl-1*H*-pyrazole-3-carboxylate (8b). Yield 73.5%. Mp 196–198 °C. IR (KBr, υ cm^{-1}): 3140 (=CH), 2990 (CH), 1730 (C=O), 1540 (C=C), 1480 (C=N), 1450, 1410. ^{1}H NMR (250 MHz, CDCl$_3$) δ ppm: 7.3 (s, 4H, Ph), 6.6 (s, 4H, pyrazol), 5.6 (s, 8H, 4N–CH$_2$–N), 4.0 (s, 12H, 4O–CH$_3$), 2.2 (s, 12H, 4CH$_3$). MS (FAB<0, DMSO/MNBA): Calcd for [M]$^+$ $C_{34}H_{40}N_{10}O_8$: 716; [M+Na]$^{\cdot+}$ (m/z)=739 (100%). Elemental analysis for $C_{30}H_{40}N_{10}O_8$ Calcd (Found): C 56.97 (56.62), H 5.63 (5.51), N 19.54 (19.47).

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Regioselective synthesis of polysubstituted benzenes from Baylis–Hillman adducts via [4+2] annulation protocol

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Abstract—A new and regioselective [4+2] benzannulation protocol toward polysubstituted benzenes was developed. A nitroalkane derivative, which was prepared from Baylis–Hillman adduct, served as the four-carbon unit and a Michael acceptor as a two-carbon unit. Vinyltriphenylphosphonium salt could also be used as a Michael acceptor efficiently.

1. Introduction

Polysubstituted aromatic compounds are highly useful entities, which are widely used in industry as well as in the laboratory. The synthesis of polysubstituted aromatic compounds in high yields in a regioselective manner is one of the challenging problems in organic synthesis.[1] Classical methods for the synthesis of polysubstituted aromatics are based on aromatic substitution, which introduces a substituent to the given arene. A variety of synthetic methodologies based on this route have been developed including the electrophilic or nucleophilic substitutions, catalyzed coupling reactions, and metalation–functionalization reactions. However, these methods suffer from a long multi-step reaction sequence, low yields of products, and production of regiochemical ambiguities originating from the activating or deactivating and orienting effects of the substituents.

Numerous approaches for the synthesis of aromatic compounds from acyclic precursors have received growing interest due to their short synthetic steps and the avoidance of regioisomeric problems. These general features are common in the most useful benzannulation reactions such as [3+2+1] Dötz reaction of Fisher carbene complexes,[2] Danheiser alkyne-cyclobutenone [4+2] cyclization,[3] [4+2] cycloaddition of metalacyclopentadienes and alkynes,[4] transition-metal-catalyzed [2+2+2] and [4+2] cycloadditions,[5] [4+2] Yamamoto benzannulation of *o*-alkynyl benzaldehyde and alkyne,[6] [3+3] cyclocondensation between bielectrophiles and binucleophiles,[7] and 1,6-electrocyclization reaction.[8] Recently, an efficient approach was developed for the synthesis of highly substituted phenols using a [5+1] benzannulation strategy by the reaction of α-alkenoyl ketene-(*S*,*S*)-acetals and nitroalkane.[9] Ballini and co-workers also reported an interesting synthetic approach for acetophenones and methyl benzoates via an anionic domino process from the reaction of primary 1,3-dinitroalkanes with 2-ene-1,4-dione or 2-ene-4-oxo ester derivatives.[10]

2. Results and discussion

The Baylis–Hillman reaction and chemical transformations of the Baylis–Hillman adducts have been investigated deeply by us and other groups.[11,12] Recently, we have reported an efficient regioselective construction method of polysubstituted pyridine ring starting from Baylis–Hillman adducts via sequential introduction of tosylamide, Michael reaction, aldol condensation, and elimination of TsH (Scheme 1).[12a] As an extension, we envisioned that we could prepare highly substituted benzene ring in a regiocontrolled manner if we used nitroalkane derivative **2** (Scheme 2) instead of the tosylamide derivative in Scheme 1. Appropriate Michael acceptor can serve as the remaining two-carbon unit for the purpose as depicted in Scheme 2.[13]

The synthesis of starting material **2** (four-carbon unit) was carried out by the addition–elimination protocol from the acetate of the Baylis–Hillman adduct of methyl (or ethyl) vinyl ketone **1** and primary nitroalkane in the presence of K_2CO_3.[14–16] The benzylidene moiety, which will be

Keywords: Polysubstituted benzenes; Baylis–Hillman adducts; Michael acceptor; Schweizer reagent.
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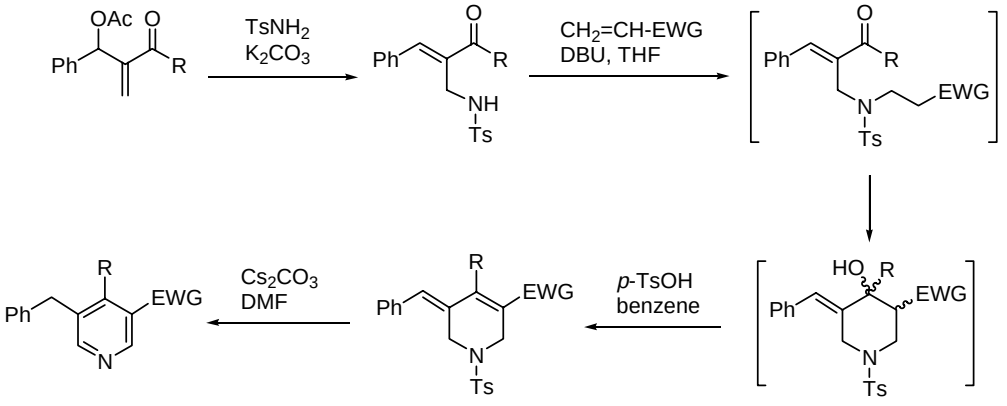
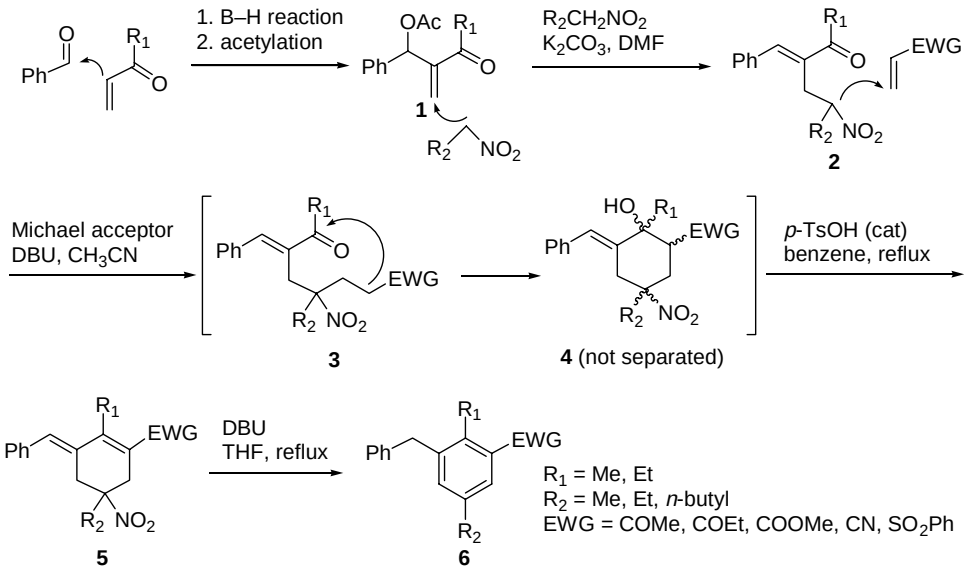


Scheme 1.



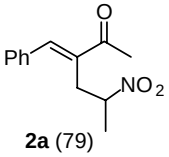
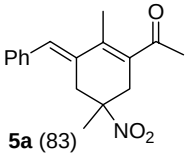
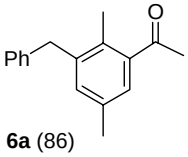
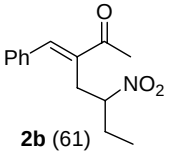
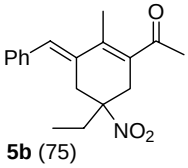
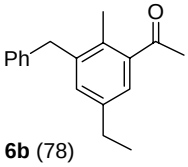
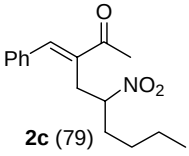
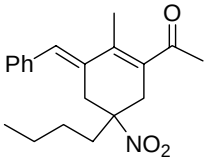
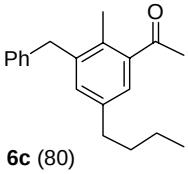
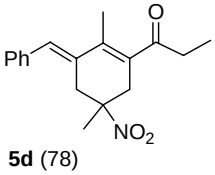
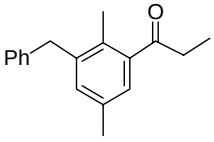
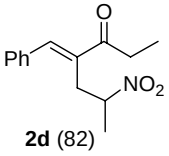
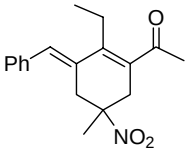
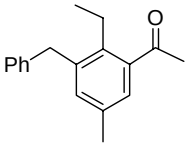
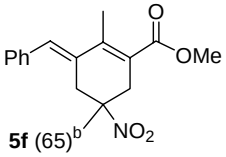
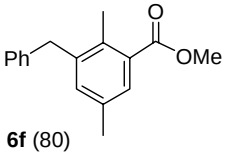
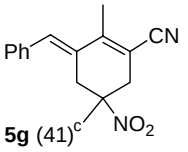
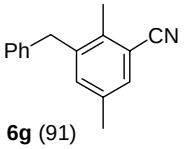
Scheme 2.

isomerized at the final stage to benzyl group, is essential for the construction of benzene ring at the final aromatization stage (vide infra). The next step was the construction of six-membered ring intermediate **4** via the consecutive Michael addition of **2** to the Michael acceptor and aldol-type cyclization, which occurred with the aid of DBU in CH_3CN in good yield. The intermediate **4** was not separated due to the complex nature of **4** by the formation of diasteroisomeric mixtures. Thus, we subjected the crude mixtures, after usual workup, in the dehydration conditions (*p*-TsOH, benzene, reflux) and obtained the dehydration product **5** in good overall yield. The final step was the elimination of HNO_2 and isomerization of the *exo*-double bond to the desired benzene ring. We expected that elimination of HNO_2 can occur with DBU and the isomerization will also occur simultaneously due to the favorable aromatization effect. As expected, the final step occurred in good yield with DBU in THF under refluxing conditions to our delight.

As shown in Table 1, variation of the substituents of the Baylis–Hillman adducts or of nitroalkanes did not alter the reactivity (entries 1–3 and 5). However, the reactivity was affected by the nature of the Michael acceptor. The reaction rates of the Michael addition of **2** to methyl vinyl ketone, ethyl vinyl ketone, phenyl vinyl sulfone, methyl acrylate, and acrylonitrile were similar (TLC monitoring). But, the reactivities of the next aldol cyclization reaction were found to be different depending on the nature of the electron-withdrawing group of the Michael acceptors presumably due to the different acidities of the α-protons nearby the EWG groups of the Michael acceptors. Fortunately, the following dehydration, elimination, and aromatization reactions from **4** to the final product **6** were all straightforward in these cases also (entries 4, 6, and 7). The use of acrylonitrile (entry 7) as the Michael acceptor required a long reaction time for the cyclization and gave low yield of **5g** (41%). Actually, we could isolate the Michael addition product **3g** in 41% after the whole reaction. This type of Michael addition product was also found in the cases of methyl acrylate (entry 6) and phenyl vinyl sulfone (Scheme 3). Especially, when we used phenyl vinyl sulfone as the Michael acceptor we found the formation of *exo*-methylene compound **5h′**, which showed the same reactivity to give **6h**.

For the next trial, we examined the reaction of **2** and vinyltriphenylphosphonium bromide, which was known as Schweizer reagent,[17] as the other effective Michael acceptor (two-carbon unit). Our synthetic rationale is shown in

Table 1. Synthesis of regioselectively substituted benzenes

Entry	Substrate (%)	Conditions	Cyclohexene (%)	Product (%)[a]
1	 **2a** (79)	(1) DBU (1.0 equiv), MVK (1.5 equiv), CH_3CN, rt, 30 min; (2) aq workup; (3) *p*-TsOH (0.1 equiv), PhH, reflux, 1 h	 **5a** (83)	 **6a** (86)
2	 **2b** (61)	(1) DBU (1.0 equiv), MVK (1.5 equiv), CH_3CN, rt, 30 min; (2) aq workup; (3) *p*-TsOH (0.1 equiv), PhH, reflux, 1 h	 **5b** (75)	 **6b** (78)
3	 **2c** (79)	(1) DBU (1.0 equiv), MVK (1.8 equiv), CH_3CN, rt, 5 h; (2) aq workup; (3) *p*-TsOH (0.1 equiv), PhH, reflux, 1 h	 **5c** (71)	 **6c** (80)
4	**2a**	(1) DBU (1.0 equiv), EVK (1.5 equiv), CH_3CN, rt, 1 h; (2) aq workup; (3) *p*-TsOH (0.1 equiv), PhH, reflux, 3 h	 **5d** (78)	 **6d** (85)
5	 **2d** (82)	(1) DBU (1.0 equiv), MVK (1.5 equiv), CH_3CN, rt, 12 h; (2) aq workup; (3) *p*-TsOH (0.1 equiv), PhH, reflux, 3 h	 **5e** (73)	 **6e** (89)
6	**2a**	(1) DBU (2.0 equiv), methyl acrylate (1.8 equiv), CH_3CN, rt, 40 h; (2) aq workup; (3) *p*-TsOH (0.1 equiv), PhH, reflux, 4 h	 **5f** (65)[b]	 **6f** (80)
7	**2a**	(1) DBU (2.0 equiv), acrylonitrile (2.0 equiv), CH_3CN, rt, 4 days; (2) aq workup; (3) *p*-TsOH (0.1 equiv), PhH, reflux, 15 h	 **5g** (41)[c]	 **6g** (91)

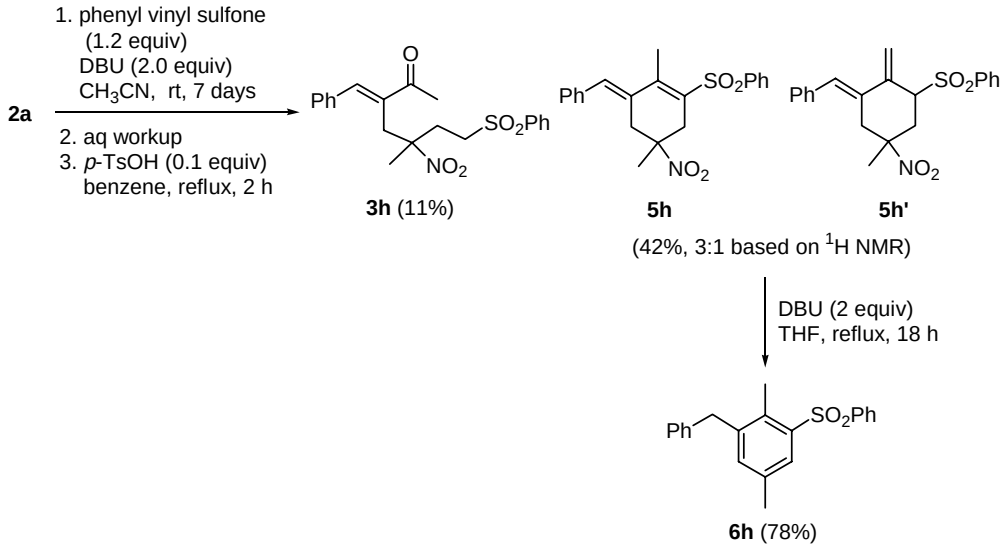
[a] DBU (2 equiv), THF, reflux, 5–96 h.
[b] Michael addition product **3f** was isolated in 7%.
[c] Michael addition product **3g** was isolated in 41% yield.

Scheme 4. The reaction of **2** and vinyltriphenylphosphonium bromide could provide benzylidene cyclohexene intermediate **7** via the successive Michael addition and Wittig reaction in the presence of appropriate base. The compound **7** could be converted into the aromatized product **8** under basic conditions via elimination of nitrous acid followed by isomerization of double bond.

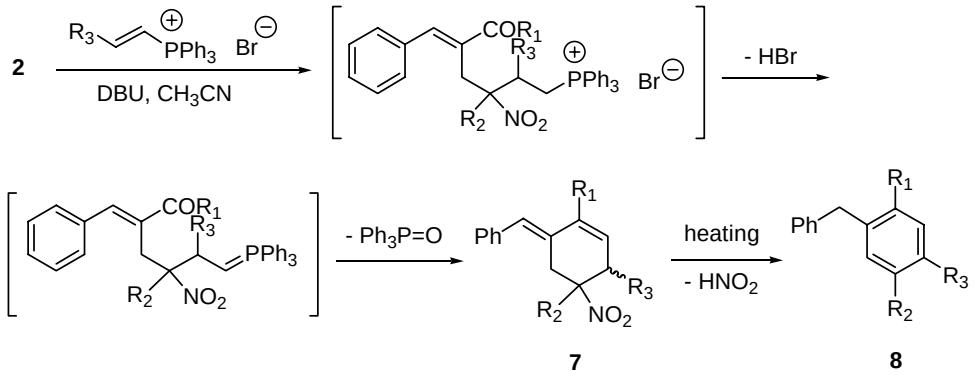
As expected, the reaction of **2a** and vinyltriphenylphosphonium bromide in the presence of DBU (3 equiv) in CH_3CN at refluxing temperature for 18 h gave desired **8a** in 86% yield. We were encouraged by the first successful results and extended the trial to the synthesis of a variety of polysubstituted benzene derivatives **8b–f** as summarized in Table 2. The synthesis of **8** was carried out without isolation of the corresponding intermediates **7** (see, Section 3). However, we could confirm the structure of corresponding intermediate **7a**, which was obtained in 48% yield when we carried out the reaction at around 40–50 °C for 3 h.

As shown in Table 2, changes of the structure of starting materials **2** did not affect the reaction progress (entries 1–3). When we used **2e** and **2f**, which were made from ethyl nitroacetate, the reaction was completed in a short time at lower temperature (entries 4 and 6). However, when we used propenyltriphenylphosphonium bromide[17c] (entry 5) the yield of product **8e** was low.

We examined the reaction of nitroalkane derivative **2g**, which was made from the acetate of the Baylis–Hillman



Scheme 3.



Scheme 4.

adduct of *n*-hexanal and nitroethane.[15d] However, unfortunately, intractable complex mixtures were observed on TLC under the same reaction conditions of Scheme 2 with methyl vinyl ketone, as shown in Scheme 5. The reaction of **2a** and 2-cyclohexen-1-one also showed a complex nature and we could not obtain the desired product.

In summary, we disclosed a new route for the synthesis of polysubstituted benzene derivatives starting from Baylis–Hillman adducts via a regioselective [4+2] benzannulation protocol. Nitroalkane derivative, which was prepared from Baylis–Hillman adduct, served as the four-carbon unit and Michael acceptor including Schweizer reagent as a two-carbon unit.

3. Experimental

3.1. General procedure

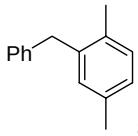
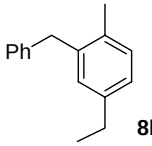
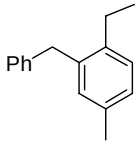
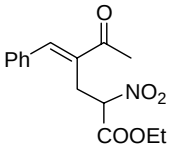
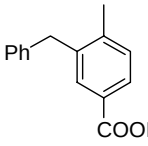
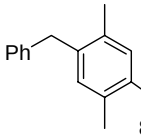
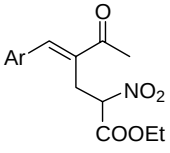
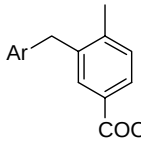
^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejon, Korea. All reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

3.2. Synthesis of starting material 2

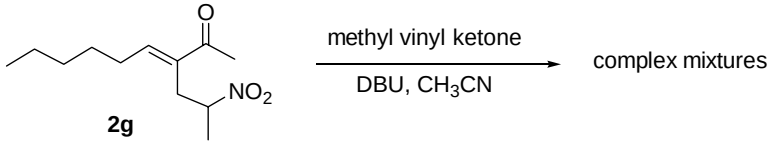
The starting materials **2a–d** and **2g** were prepared according to the previous paper.[14–16] Compounds **2e** and **2f** were synthesized analogously by using ethyl nitroacetate and the spectroscopic data are as follows.

3.2.1. Compound 2e. 73%; clear oil; IR (film) 1751, 1666, 1558, 1373, 1254, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J=7.2 Hz, 3H), 2.47 (s, 3H), 3.35 (dd, J=14.4, 6.6 Hz, 1H), 3.49 (dd, J=14.4, 9.3 Hz, 1H), 4.12–4.23 (m, 2H), 5.52 (dd, J=9.3, 6.6 Hz, 1H), 7.30–7.46 (m, 5H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.73, 25.76, 27.37, 62.89, 85.65, 128.72, 128.82, 129.27, 134.15, 135.04, 145.03, 164.01, 199.47; ESIMS *m/z* 292.1 (M^++H). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.97; H, 5.75; N, 4.96.

Table 2. Synthesis of regioselectively substituted benzenes

Entry	Substrate (%)	Conditions	Product (%)
1	**2a**	CH_2=$CHPPh_3Br$ (1.2 equiv), DBU (3.0 equiv), CH_3CN reflux, 18 h	 **8a** (86)
2	**2b**	CH_2=$CHPPh_3Br$ (1.2 equiv), DBU (3.0 equiv), CH_3CN reflux, 40 h	 **8b** (81)
3	**2d**	CH_2=$CHPPh_3Br$ (1.2 equiv), DBU (3.0 equiv), CH_3CN reflux, 28 h	 **8c** (74)
4	 **2e** (73)	CH_2=$CHPPh_3Br$ (1.2 equiv), DBU (3.0 equiv), CH_3CN 40–50 °C, 5 h	 **8d** (88)
5	**2a**	CH_2=$CHCH_2PPh_3Br$ (1.2 equiv), DBU (3.0 equiv), CH_3CN reflux, 40 h	 **8e** (40)
6[a]	 **2f** (79)	CH_2=$CHPPh_3Br$ (1.2 equiv), DBU (3.0 equiv), CH_3CN 40–50 °C, 3 h	 **8f** (86)

[a] Ar is 4-chlorophenyl.



Scheme 5.

3.2.2. Compound 2f. 79%; clear oil; IR (film) 2985, 1751, 1670, 1562, 1377, 1250, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (t, J=7.2 Hz, 3H), 2.46 (s, 3H), 3.30 (dd, J=14.4, 6.3 Hz, 1H), 3.44 (dd, J=14.4, 9.3 Hz, 1H), 4.16–4.26 (m, 2H), 5.53 (dd, J=9.3, 6.3 Hz, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.74, 25.75, 27.42, 62.99, 85.61, 129.10, 130.06, 132.55, 135.33, 135.55, 143.65, 163.90, 199.21. Anal. Calcd for $C_{15}H_{16}ClNO_5$: C, 55.31; H, 4.95; N, 10.88. Found: C, 55.26; H, 4.92; N, 10.67.

3.3. Synthesis of the intermediate 5

Typical procedure for the synthesis of cyclohexene intermediate **5a**: to a stirred solution of **2a** (233 mg, 1.0 mmol) and methyl vinyl ketone (105 mg, 1.5 mmol) in CH_3CN (5 mL) was added DBU (153 mg, 1.0 mmol) and stirred at rt for 30 min. TLC observation showed complete disappearance of starting material **2a** and the formation of diastereomeric mixtures of **4a**. After aq workup the crude diastereomeric mixtures were dissolved in benzene (5 mL), added *p*-TsOH (20 mg, 0.1 mmol), and heated to reflux for 1 h. After the usual workup and column chromatographic purification process (hexanes/ether, 5:1) we obtained desired **5a** as a white solid, 237 mg (83%). The other compounds **5b–h** were synthesized analogously and the spectroscopic data of prepared compounds are as follows.

3.3.1. Compound 5a.[13] 83%; white solid, mp 81–83 °C; IR (KBr) 1685, 1539, 1350, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H), 2.03 (t, J=1.8 Hz, 3H), 2.37 (s, 3H), 2.66 (dd, J=17.7, 1.8 Hz, 1H), 2.82 (dd, J=15.3, 1.8 Hz, 1H), 3.28 (d, J=17.7 Hz, 1H), 3.43 (d, J=15.3 Hz, 1H), 6.92 (s, 1H), 7.25–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$,

75 MHz) δ 15.78, 25.74, 29.82, 36.34, 36.62, 86.01, 127.36, 128.34, 128.98, 131.18, 133.09, 133.66, 133.83, 136.60, 204.25. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.76; H, 6.83; N, 4.87.

3.3.2. Compound 5b. 75%; clear oil; IR (film) 2974, 1685, 1539, 1442, 1354, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, J=7.5 Hz, 3H), 1.81–1.99 (m, 2H), 2.01 (t, J=1.8 Hz, 3H), 2.38 (s, 3H), 2.65 (d, J=17.4 Hz, 1H), 2.78 (dd, J=15.6, 1.8 Hz, 1H), 3.25 (d, J=17.4 Hz, 1H), 3.46 (d, J=15.6 Hz, 1H), 6.89 (s, 1H), 7.24–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.76, 15.83, 29.87, 32.17, 34.46, 34.61, 89.68, 127.33, 128.36, 128.95, 130.97, 132.98, 133.69, 133.96, 136.67, 204.60. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.16; H, 7.19; N, 4.65.

3.3.3. Compound 5c. 71%; clear oil; IR (film) 2958, 1685, 1539, 1442, 1354, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, J=6.9 Hz, 3H), 1.04–1.29 (m, 4H), 1.77–1.90 (m, 2H), 2.02 (t, J=1.5 Hz, 3H), 2.38 (s, 3H), 2.65 (dd, J=18.0, 1.8 Hz, 1H), 2.78 (dd, J=15.6, 1.8 Hz, 1H), 3.25 (d, J=18.0 Hz, 1H), 3.46 (d, J=15.6 Hz, 1H), 6.89 (s, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.63, 15.84, 22.31, 25.31, 29.87, 34.86, 35.00, 38.88, 89.37, 127.32, 128.36, 128.94, 130.96, 133.04, 133.70, 133.98, 136.70, 204.59. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.51; H, 7.69; N, 4.31.

3.3.4. Compound 5d. 78%; clear oil; IR (film) 2931, 1689, 1539, 1450, 1346, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, J=7.2 Hz, 3H), 1.58 (s, 3H), 1.97 (t, J=1.8 Hz, 3H), 2.60–2.70 (m, 3H), 2.82 (dd, J=15.3, 1.8 Hz, 1H), 3.25 (d, J=17.7 Hz, 1H), 3.43 (d, J=15.3 Hz, 1H), 6.87 (s, 1H), 7.25–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.83, 15.84, 25.80, 35.23, 36.39, 36.73, 86.09, 127.34, 128.39, 129.02, 130.55, 132.20, 132.98, 134.21, 136.70, 208.10. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.18; H, 7.19; N, 4.51.

3.3.5. Compound 5e. 73%; white solid, mp 79–81 °C; IR (KBr) 2974, 1689, 1539, 1350, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, J=7.5 Hz, 3H), 1.58 (s, 3H), 2.36 (s, 3H), 2.40–2.50 (m, 2H), 2.64 (d, J=17.4 Hz, 1H), 2.81 (dd, J=15.3, 1.8 Hz, 1H), 3.27 (d, J=17.4 Hz, 1H), 3.41 (d, J=15.3 Hz, 1H), 6.95 (s, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.68, 22.12, 25.60, 29.59, 36.47, 36.58, 85.96, 127.34, 128.34, 128.99, 130.93 (2C), 133.09, 136.66, 139.41, 203.95. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.43; H, 7.12; N, 4.69.

3.3.6. Compound 5f. 65%; white solid, mp 74–76 °C; IR (KBr) 2951, 1716, 1539, 1435, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 3H), 2.26 (t, J=1.8 Hz, 3H), 2.76 (dd, J=18.3, 1.8 Hz, 1H), 2.85 (dd, J=14.7, 1.5 Hz, 1H), 3.36 (d, J=14.7 Hz, 1H), 3.37 (d, J=18.3 Hz, 1H), 3.80 (s, 3H), 7.02 (s, 1H), 7.02–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.00, 25.49, 36.22, 37.23, 51.78, 85.84, 124.20, 127.49, 128.36, 129.03, 132.41, 133.64, 136.56, 140.52, 168.45. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.94; H, 6.44; N, 4.58.

3.3.7. Compound 5g. 41%; white solid, mp 83–85 °C; IR (KBr) 2206, 1543, 1450, 1346, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 3H), 2.29 (t, J=1.5 Hz, 3H), 2.70 (dd, J=17.7, 1.8 Hz, 1H), 2.80 (dd, J=15.6, 1.8 Hz, 1H), 3.31 (d, J=17.7 Hz, 1H), 3.49 (d, J=15.6 Hz, 1H), 7.01 (s, 1H), 7.27–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.28, 25.81, 35.91, 36.92, 85.07, 105.45, 118.50, 128.15, 128.52, 129.10, 130.89, 134.25, 135.43, 148.07. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.77; H, 6.25; N, 10.26.

3.3.8. Compound 5h. 42%; clear oil; IR (film) 2927, 1539, 1300, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.59 (s, 3H), 2.32 (s, 3H), 2.67 (d, J=15.3 Hz, 1H), 2.97 (d, J=18.9 Hz, 1H), 3.51 (d, J=15.3 Hz, 1H), 3.66 (d, J=18.9 Hz, 1H), 7.07 (s, 1H), 7.21–7.96 (m, 10H). In the ^1H NMR spectrum of **5h** small amounts (25%) of **5h′** was mixed: 1.66 (s, 3H), 2.38–2.50 (m, 1H), 2.81–2.88 (m, 1H), 3.06–3.16 (m, 1H), 3.44–3.70 (m, 1H), 4.16–4.22 (m, 1H), 4.66 (s, 1H), 5.41 (s, 1H), 6.60 (s, 1H), 7.21–7.96 (m, 10H). We did not take ^{13}C NMR due to the lack of pure **5h**.

3.4. Synthesis of benzene derivatives 6a–h

Typical procedure for the synthesis of cyclohexene intermediate **6a**: to a stirred solution of **5a** (143 mg, 0.5 mmol) in THF (3 mL) was added DBU (152 mg, 1.0 mmol) and heated to reflux for 6 h. After the usual workup and column chromatographic purification process (hexanes/ether, 10:1) we obtained desired **6a** as a white solid, 103 mg (86%). The other compounds **6b–h** were synthesized analogously and the spectroscopic data of prepared compounds are as follows (reaction time was noted in the parenthesis).

3.4.1. Compound 6a.[13] 86% (6 h); white solid, mp 40–41 °C; IR (KBr) 2924, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.32 (s, 3H), 2.54 (s, 3H), 3.99 (s, 2H), 7.05–7.29 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.97, 20.86, 30.45, 39.57, 126.01, 126.80, 128.41, 128.55, 132.06, 133.65, 134.84, 139.96, 140.34, 140.53, 204.00; ESIMS m/z 239.1 (M^++H). Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.71; H, 7.75.

3.4.2. Compound 6b. 78% (48 h); clear oil; IR (film) 2966, 1685, 1454, 1354, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J=7.5 Hz, 3H), 2.26 (s, 3H), 2.55 (s, 3H), 2.61 (q, J=7.5 Hz, 2H), 4.01 (s, 2H), 7.07–7.29 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.52, 15.03, 27.27, 29.48, 38.70, 124.59, 125.01, 127.41, 127.54, 131.35, 131.55, 138.98, 139.36, 139.67, 140.28, 203.09; ESIMS m/z 253.1 (M^++H). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.59; H, 7.81.

3.4.3. Compound 6c. 80% (72 h); clear oil; IR (film) 2927, 1685, 1454, 1354, 1284 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J=7.2 Hz, 3H), 1.23–1.43 (m, 2H), 1.52–1.76 (m, 2H), 2.26 (s, 3H), 2.54 (s, 3H), 2.58 (t, J=7.8 Hz, 2H), 4.01 (s, 2H), 7.06–7.28 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.88, 16.02, 22.29, 30.47, 33.54, 35.04, 39.69, 125.99, 126.17, 128.40, 128.52, 132.34, 133.11, 139.94, 140.00, 140.25, 140.56, 204.08; ESIMS m/z 281.2 (M^++H).

Anal. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63. Found: C, 85.91; H, 8.61.

3.4.4. Compound 6d. 85% (5 h); clear oil; IR (film) 2931, 1693, 1454, 1342, 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, $J=7.5$ Hz, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.83 (q, $J=7.5$ Hz, 2H), 3.98 (s, 2H), 7.02 (s, 1H), 7.07–7.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.29, 15.86, 20.86, 35.99, 39.54, 125.78, 125.99, 128.39, 128.57, 131.34, 133.05, 134.85, 139.97, 140.16, 141.14, 207.62; ESIMS *m/z* 253.2 ($M^+ + H$). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.73; H, 7.89.

3.4.5. Compound 6e. 89% (12 h); clear oil; IR (film) 2966, 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, $J=7.5$ Hz, 3H), 2.30 (s, 3H), 2.55 (s, 3H), 2.74 (q, $J=7.5$ Hz, 2H), 4.03 (s, 2H), 7.02 (s, 1H), 7.08–7.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.64, 20.86, 22.30, 30.61, 38.45, 126.00, 127.07, 128.38, 128.61, 134.06, 134.91, 138.28, 139.69, 140.06, 140.61, 203.79; ESIMS *m/z* 253.1 ($M^+ + H$). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.47; H, 8.08.

3.4.6. Compound 6f. 80% (96 h); clear oil; IR (film) 2924, 1724, 1454, 1308, 1207 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 2.36 (s, 3H), 3.87 (s, 3H), 4.01 (s, 2H), 7.06–7.09 (m, 3H), 7.15–7.29 (m, 3H), 7.48 (d, $J=1.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.15, 20.75, 39.70, 51.88, 126.00, 128.41, 128.52, 128.74, 131.50, 134.45 (2C), 134.87, 140.00, 140.05, 169.21; ESIMS *m/z* 255.1 ($M^+ + H$). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.19; H, 7.27.

3.4.7. Compound 6g. 91% (9 h); clear oil; IR (film) 2924, 2225, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 3H), 2.39 (s, 3H), 3.98 (s, 2H), 7.04–7.08 (m, 2H), 7.14 (s, 1H), 7.16–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.32, 20.61, 39.40, 113.51, 118.74, 126.36, 128.52, 128.59, 131.15, 135.36, 136.18, 137.45, 139.05, 140.12; ESIMS *m/z* 222.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.87; H, 6.95; N, 6.18.

3.4.8. Compound 6h. 78% (18 h); white solid, mp 113–114 °C; IR (KBr) 2924, 1450, 1304, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.38 (s, 3H), 3.94 (s, 2H), 6.98–7.86 (m, 11H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.39, 20.92, 39.35, 126.24, 127.34, 128.39, 128.47, 128.52, 128.94, 132.80, 133.43, 135.86, 136.40, 139.18, 139.25, 141.52, 141.79; ESIMS *m/z* 337.1 ($M^+ + H$). Anal. Calcd for $C_{21}H_{20}O_2S$: C, 74.97; H, 5.99. Found: C, 75.07; H, 5.93.

3.5. Analytical data of Michael addition products 3f–h

3.5.1. Compound 3f. 7%; clear oil; IR (film) 1739, 1674, 1539 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3H), 1.83–1.95 (m, 1H), 2.02–2.34 (m, 3H), 2.48 (s, 3H), 3.24 (d, $J=14.1$ Hz, 1H), 3.36 (d, $J=14.1$ Hz, 1H), 3.63 (s, 3H), 7.26–7.45 (m, 5H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.82, 25.77, 28.72, 33.95, 34.00, 51.80, 90.07, 128.44, 128.83, 128.85, 134.95, 137.43, 143.67, 172.51, 199.54; ESIMS *m/z* 320.1 ($M^+ + H$). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 64.02; H, 6.61; N, 4.45.

3.5.2. Compound 3g. 41%; white solid, mp 93–95 °C; IR (KBr) 2249, 1670, 1543 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.85–1.95 (m, 1H), 2.15–2.35 (m, 3H), 2.49 (s, 3H), 3.25 (d, $J=13.8$ Hz, 1H), 3.34 (d, $J=13.8$ Hz, 1H), 7.14–7.48 (m, 5H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.50, 22.10, 25.70, 33.51, 34.23, 89.53, 118.31, 128.32, 129.02, 129.13, 134.69, 136.68, 144.56, 199.36; ESIMS *m/z* 287.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.35; H, 6.19; N, 9.73.

3.5.3. Compound 3h. 11%; clear oil; IR (film) 2927, 1670, 1539, 1308, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (s, 3H), 1.90–2.01 (m, 1H), 2.22–2.38 (m, 1H), 2.44 (s, 3H), 2.85–3.01 (m, 2H), 3.22 (d, $J=14.1$ Hz, 1H), 3.31 (d, $J=14.1$ Hz, 1H), 7.25–7.71 (m, 8H), 7.75 (s, 1H), 7.80–7.84 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.27, 25.65, 31.62, 33.80, 51.30, 89.28, 128.02, 128.41, 128.97, 129.04, 129.37, 133.98, 134.70, 136.71, 138.44, 144.26, 199.31; ESIMS *m/z* 402.1 ($M^+ + H$). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.49. Found: C, 62.98; H, 5.65; N, 3.47.

3.6. Synthesis of 7a and 8a–f

Typical procedure for the synthesis of intermediate **7a** and benzene derivative **8a**: to a stirred solution of **2a** (233 mg, 1.0 mmol) and vinyltriphenylphosphonium bromide (443 mg, 1.2 mmol) in CH_3CN (5 mL) was added DUB (456 mg, 3 mmol) and heated to reflux for 18 h. After usual workup and column chromatographic purification process (hexanes/ether, 40:1) we obtained the desired benzene derivative **8a** (169 mg, 86%). We could obtain the corresponding intermediate **7a** in 48% yield when we carried out the reaction at around 40–50 °C for 3 h. We synthesized other benzene derivatives **8b–f** analogously without isolation of the corresponding intermediates. The spectroscopic data of prepared compounds are as follows.

3.6.1. Compound 7a. 48%; clear oil; IR (film) 1539, 1450, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 3H), 1.93 (s, 3H), 2.49 (d, $J=18.0$ Hz, 1H), 2.89 (d, $J=15.3$ Hz, 1H), 3.07 (d, $J=18.0$ Hz, 1H), 3.33 (d, $J=15.3$ Hz, 1H), 5.63–5.67 (m, 1H), 6.62 (s, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.60, 25.43, 36.16, 36.56, 86.91, 123.30, 126.81, 126.97, 128.25, 129.05, 133.27, 133.37, 137.03. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.03; H, 7.21; N, 5.71.

3.6.2. Compound 8a.[18a] 86%; clear oil; IR (film) 2920, 1496, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3H), 2.78 (s, 3H), 3.94 (s, 2H), 6.92–7.28 (m, 8H); ESIMS *m/z* 197.1 ($M^+ + H$).

3.6.3. Compound 8b.[18b] 81%; clear oil; IR (film) 2962, 2927, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, $J=7.5$ Hz, 3H), 2.18 (s, 3H), 2.57 (q, $J=7.5$ Hz,

2H), 3.95 (s, 2H), 6.94–7.27 (m, 8H); ESIMS *m/z* 211.1 ($M^+ + H$).

3.6.4. Compound 8c. 74%; clear oil; IR (film) 2962, 2924, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, $J=7.5$ Hz, 3H), 2.27 (s, 3H), 2.56 (q, $J=7.5$ Hz, 2H), 3.98 (s, 2H), 6.92 (s, 1H), 6.98–7.28 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.98, 20.94, 25.33, 38.72, 125.81, 127.32, 128.31, 128.39, 128.67, 131.09, 135.22, 137.91, 139.38, 141.05; ESIMS *m/z* 211.1 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.29; H, 8.71.

3.6.5. Compound 8d. 86%; clear oil; IR (film) 1720, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, $J=7.2$ Hz, 3H), 2.52 (s, 3H), 4.02 (s, 2H), 4.34 (q, $J=7.2$ Hz, 2H), 7.06–7.28 (m, 6H), 7.81–7.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.28, 19.83, 39.39, 60.69, 126.04, 127.73, 128.31, 128.40, 128.48, 130.37, 131.13, 138.95, 139.67, 142.28, 166.72; ESIMS *m/z* 255.1 ($M^+ + H$). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.34; H, 7.29.

3.6.6. Compound 8e.[18c] 40%; clear oil; IR (film) 2920, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 2.19 (s, 3H), 2.21 (s, 3H), 3.91 (s, 2H), 6.88 (s, 1H), 6.93 (s, 1H), 7.09–7.27 (m, 5H); ESIMS *m/z* 211.1 ($M^+ + H$).

3.6.7. Compound 8f. 86%; clear oil; IR (film) 1716, 1269 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, $J=7.2$ Hz, 3H), 2.24 (s, 3H), 3.98 (s, 2H), 4.35 (q, $J=7.2$ Hz, 2H), 7.02 (d, $J=8.1$ Hz, 2H), 7.22 (d, $J=8.1$ Hz, 2H+1H), 7.82 (s, 1H), 7.84 (d, $J=8.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.31, 19.81, 38.77, 60.78, 127.95, 128.45, 128.54, 129.82, 130.51, 131.05, 131.88, 138.19, 138.44, 142.18, 166.64; ESIMS *m/z* 255.1 ($M^+ + H$). Anal. Calcd for $C_{17}H_{17}ClO_2$: C, 70.71; H, 5.93. Found: C, 70.58; H, 5.89.

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Synthesis and properties of *N*,*N*′-dialkylimidazolium bis(nonafluorobutane-1-sulfonyl)imides: a new subfamily of ionic liquids

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Abstract—A series of *N*,*N*′-dialkylimidazolium bis(nonafluorobutane-1-sulfonyl)imides was synthesized in high yields by quaternization of imidazole derivatives with various readily available alkylating reagents, followed by anion exchange with highly stable and non-hygroscopic potassium bis(nonafluorobutane-1-sulfonyl)imide. The latter was obtained by an improved method starting from ammonium chloride and nonafluorobutane-1-sulfonyl fluoride. The quaternary imidazolium salts thus obtained constitute a new subfamily of thermally stable and remarkably hydrophobic ionic liquids with melting points in the range 0–40 °C and solubilities in water and organic solvents (aromatic hydrocarbons, dialkyl ethers) in the range of 0.5–1.5 wt%. The ionic liquids can be easily purified from ionic byproducts (e.g., halogenide salts) by aqueous extraction followed by thorough drying in a high vacuum without loss of yield. Due to the above features, these new ionic fluids may be considered as promising recyclable media in repeated catalytic processes.

1. Introduction

Low-melting salts containing lipophilic quaternary organic cations, ionic liquids, have attracted much interest in the area of electrochemistry as well as novel solvents and reaction media.[1] These fluids consisting of only ions were found to have no detectible equilibrium vapor pressure. In recognition of this remarkable property they were termed as environmentally benign or 'green' solvents.[1g] Many classical organic reactions were successfully modeled and often optimized in these media.

The first generation of ionic liquids comprised mainly the derivatives of inorganic halogen-ligated *ate*-complexes such as $BF_4^{\ominus}$, $PF_6^{\ominus}$ and $AlCl_4^{\ominus}$ as the anionic moieties. These anions, especially the latter two, are prone to releasing harmful and corrosive HF and HCl upon interaction with traces of moisture, which in turn imposes significant restrictions on applications of the corresponding ionic liquids. Moreover, uncontrolled halogenide content often affects and/or deteriorates transition metal catalysis.[1h] To circumvent these difficulties, other types of anions were introduced including *n*-alkyl sulfates, trifluoromethanesulfonates, bis(trifluoromethanesulfonyl)imides and tetraalkylborates. Alternative alkylating reagents, alkyl sulfates and sulfonates were employed in place of 'traditional' alkyl halogenides for synthesis of the *N*,*N*′-dialkylimidazolium moieties in order to completely eliminate the possibility of generating heavy halogenides ($Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$). Special attention has been paid to ionic liquids containing *N*,*N*′-dialkylimidazolium cations combined with fluoroanions. As recently reviewed,[2] much diversity and availability of fluorine-containing anions ensure a broad range of properties and applications of the respective ionic liquids. Recently, *N*,*N*′-dialkylimidazolium bis(trifluoromethanesulfonyl)imides have received interest as remarkably thermo- and chemically stable ionic liquids.[2,3] In this respect, the anions combining high stability of bis(trifluoromethanesulfonyl)imide with much higher hydrophobicity due to higher fluorine content are of interest for design of novel ionic liquids as special solvent components for bi- and triphasic solvent systems. Herein, we report the synthesis and properties of *N*,*N*′-dialkylimidazolium bis(nonafluorobutane-1-sulfonyl)imides (**1** and **3**) and *N*,*N*′-dialkylimidazolium nonafluorobutane-1-sulfonates (**2**) as new series of ionic liquids (Fig. 1).

Keywords: Nonafluorobutane-1-sulfonyl fluoride; Dialkyl imidazolium; Bis(nonafluorobutane-1-sulfonyl)imide; Hydrophobicity; Ionic liquids.
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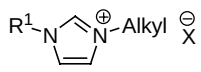


1–3

1: $R^1 = CH_3$, X = NNf_2
2: $R^1 = CH_3$, X = ONf
3: $R^1 = CH_3(CH_2)_2$, X = NNf_2
Nf:$CF_3(CF_2)_3SO_2$

Figure 1.

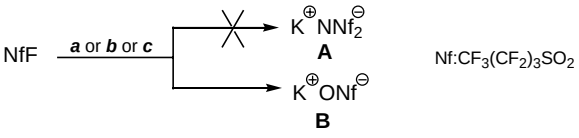
2. Results and discussion

Our approach towards the synthesis of compounds **1–3** is based on a two-step protocol, which comprises the quaternization of imidazole derivatives with various readily available alkylating reagents (alkyl bromides, chlorides, sulfates) followed by anion exchange with highly stable and non-hygroscopic potassium bis(nonafluorobutane-1-sulfonyl)imide (**A**) or potassium nonafluorobutane-1-sulfonate (**B**). We anticipated that the resulting salts **1–3** should be low-melting solids or even rt ionic liquids. They would be hydrophobic enough to make possible reduction of the residual halogenide content below detection limit by repeated extraction with deionized water without significant loss of yield at the purification step.

An inspection of available literature data showed that the potassium salt **A** could be synthesized directly from trifluoroacetamide or acetamide using the convenient and relatively inexpensive sulfonylating reagent, nonafluorobutane-1-sulfonyl fluoride (NfF),[4] in the presence of potassium carbonate.[5] As acetamide is widely available and cheap, it became a reactant of choice for the present study.

However, in our hands, no anticipated potassium imide **A** ($KNNf_2$) was obtained as a main reaction product (Scheme 1). Instead, potassium nonafluorobutane-1-sulfonate (KONf) (**B**) was isolated in reasonably good yield resulting from the reproduction of the literature procedure[5] (conditions **a**). The same results were obtained at rt employing either K_2CO_3 or more basic K_3PO_4 as an auxiliary base[6] in DMF as a solvent (modified conditions **b**).

A control experiment carried out with K_2CO_3 in the absence of acetamide (conditions **c**) revealed the same reaction



Scheme 1. a: $CH_3C(O)NH_2$, K_2CO_3 in THF 6 h at 65 °C, (62% yield);[7] **b**: $CH_3C(O)NH_2$, K_2CO_3 (73% yield) or K_3PO_4 (75% yield)[7] in DMF at rt; **c**: as in **b** employing K_2CO_3 but without $CH_3C(O)NH_2$, salt **B** (74% yield).

features (appearance, progress) resulting in a similar yield of KONf **B** as under conditions **b**. The identity of the main reaction product, KONf **B**[7] in all four protocols described above (see Scheme 1) was confirmed by FAB-MS analysis as well as by ^{19}F NMR measurements of the mixed samples indicating complete overlap of all the relevant signals (see Section 3).[8]

In the experiments with K_2CO_3, we noticed evolution of CO_2 gas during the reaction course and therefore inferred the following mechanism for the salt **B** formation (Scheme 2).

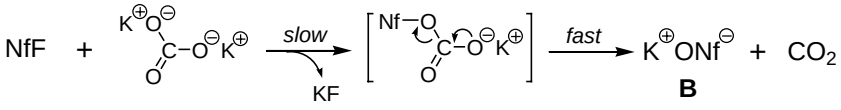
Presumably, acetamide remains mainly unreacted during the entire reaction course, and NfF interacts directly with K_2CO_3 owing to its affinity to anionic hard nucleophilic centers.[9] The lack of acetamide reactivity is attributed to the insufficient basicity of K_2CO_3 or K_3PO_4 failing to produce a sufficient equilibrial concentration of the reactive $CH_3C(O)NH^{\ominus}$ species for the desired *N*-sulfonylation to take place in favour of the direct interaction between NfF and K_2CO_3 (see Scheme 2).

To circumvent the difficulties caused by using K_2CO_3 we decided to develop a new protocol employing NH_4Cl instead of $CH_3C(O)NH_2$ and Et_3N,[10] which is fully compatible with NfF in MeCN as a reaction solvent.[11] This synthetic protocol proved to be successful and enabled us to obtain the intermediate triethylammonium salt $Et_3NH^{\oplus}NNf_2^{\ominus}$ (Scheme 3).

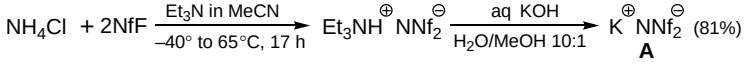
Subsequent treatment of the intermediate salt $Et_3NH^{\oplus}NNf_2^{\ominus}$ with aqueous KOH furnishes the desired pure potassium salt **A** as a white crystalline solid, which readily precipitates out of the aqueous solution[12] in good overall yield (see Section 3).

Both KONf and $KNNf_2$ were found to be thermally stable and non-hygroscopic salts.[13] They are poorly soluble in water, KONf somewhat better than $KNNf_2$. Remarkably, both salts show good solubilities in a number of organic solvents such as THF, MeCN, Me_2CO, AcOEt, DMSO, DMF, dioxane, 1,2-dimethoxyethane and alcohols although they are virtually insoluble in chlorohydrocarbon- and hydrocarbon solvents.

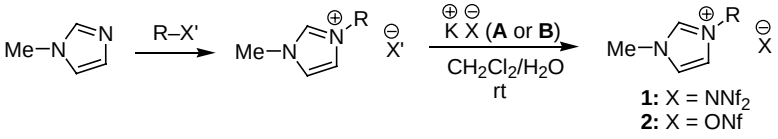
Having the requisite potassium salts **A** and **B** in hand, we established the synthesis of the target *N*-methyl-*N*′-alkyl imidazoliums **1** and **2** (Scheme 4). In a first step, an alkylation of *N*-methyl imidazole with a slight excess of RX′ was carried out upon heating without solvent



Scheme 2.



Scheme 3.



Scheme 4.

Table 1. Synthesis and properties of *N*-methyl-*N′*-alkyl imidazolium bis(nonafluorobutane-1-sulfonyl)imides **1** and nonaflates **2**

Entry	Reaction conditions			Product		Properties	
	RX' (equiv)	T (°C)	Time (h)	X	Salt 1 or 2 (yield, %)	Mp (°C)	Decomposition (°C)
1	$MeCH_2OSO_2Et$	rt[a]	17	NNf_2^-	**1a** (98)	<25[b] (31 °C)[15]	290
2	$Me(CH_2)_2Br$	70	4	NNf_2^-	**1b** (98)	<4[c]	300
3	$Me(CH_2)_3Cl$[17]	90	24	NNf_2^-	**1c** (>99)	<25[b]	320
4	$Me(CH_2)_4Br$	70	3	NNf_2^-	**1d** (97)	<25[b]	295
5	$Me_2CH(CH_2)_2Br$	70	5	NNf_2^-	**1e** (>99)	39–40	280
6	Me_2CHCH_2Br	70	17	NNf_2^-	**1f** (>99)	<4[c]	295
7	Me_2CHBr	70	24	NNf_2^-	**1g** (99)	28–29 °C	310
8	$MeCH_2CH(Me)Br$	70	24	NNf_2^-	**1h** (>99)	<4[c]	280
9	$Me(CH_2)_2Br$	70	4	ONf^-	**2a** (82)	33–34	285
10	$Me(CH_2)_3Cl$[17]	90	24	ONf^-	**2b** (82)	<25[b] (20 °C)[3]	295
11	Me_2CHBr	70	24	ONf^-	**2c** (81)	<25[b]	310
12	$MeCH_2CH(Me)Br$	70	24	ONf^-	**2d** (79)	42–43	280

[a] An appreciable exothermic effect was observed during the alkylation.
[b] Crystallizes in a fridge (+4 °C) and melts at rt again.
[c] Crystallizes in a deep freezer (−18 °C) and melts in a fridge (+4 °C) again.

(see Table 1) followed by removal of volatiles (if any) in high vacuum to give a nearly quantitative yield of the corresponding *N*-methyl-*N′*-alkyl imidazolium salts.[14]

The desired ionic fluids **1**, **2** were then produced by anion exchange with KX (**A** or **B**) in biphasic CH_2Cl_2/H_2O mixture followed by thorough washing of the organic phase with deionized water until a negative halogenide test with aqueous $AgNO_3$ was achieved. Removal of CH_2Cl_2 followed by thorough drying in high vacuum enabled us to obtain the ionic liquids **1**[15] and **2**[16] in high yields and purities. The alkylation reaction conditions, yields and properties of the *N*-methyl-*N′*-alkyl imidazolium salts **1** and **2** obtained are summarized in the Table 1.

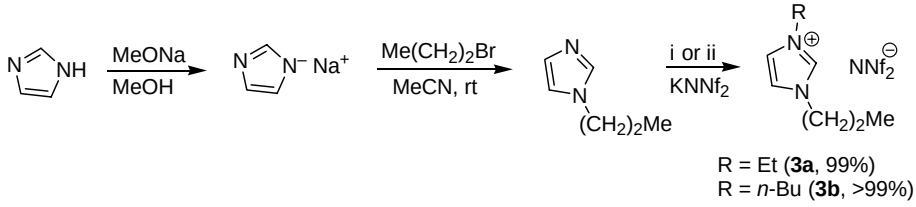
Unfortunately, among the few commercially available *N*-alkyl imidazoles, only *N*-methyl imidazole is offered at an affordable price. Hence, the ionic liquids obtained as described above are limited invariably to imidazolium derivatives comprising a *N*-methyl substituent.

To circumvent this limitation, we developed a one pot sequential alkylation protocol starting from parent imidazole. The protocol is exemplified by the synthesis of the products **3a**,**b** (Scheme 5).

Treatment of imidazole with MeONa in MeOH followed by removal of the solvent gave sodium imidazolide quantitatively. The first alkylation with *n*-propyl bromide was carried out in MeCN and enabled the introduction of only one propyl group with >95% selectivity. The second alkylation conducted after removal of MeCN in vacuum furnished the desirable unsymmetrical *N*,*N′*-dialkyl imidazolium moiety. This protocol culminated with anion exchange with $KNNf_2$ as described above resulting in the isolation of the anticipated products **3a**,**b** in high yields and at least 95% purity according to ^1H NMR spectroscopic data.

The imidazolium salts **1**–**3** are thermally stable (up to 300—320 °C), colourless or yellowish non-hygroscopic fluids or low-melting crystalline solids (Table 1). They neither change appearance nor gain weight upon exposure to atmospheric moisture for at least 1 week. The NNf_2-derivatives tend to melt at lower temperatures than their ONf-counterpart. Not surprisingly, symmetrical *N*,*N′*-dimethyl imidazolium bis(nonafluorobutane-1-sulfonyl)imide has a higher melting point (69 °C)[15] compared to the unsymmetrically substituted salts **1** and **3**.

In general, all NNf_2-derived ionic liquids presented in this work have interesting specific properties. We believe that the high content of perfluorobutyl groups in NNf_2-derived ionic liquids is accountable for their unique characteristics. Unlike conventional ionic liquids, which are often miscible with chlorohydrocarbon solvents, the salts **1** tend to form



Scheme 5. (i) $(EtO)_2SO_2$, 0 °C to rt, 17 h; (ii) $Me(CH_2)_3Br$, 70 °C, 3 h.

two-phase mixtures with chloroform. Thus, the salt **1h** forms a two-phase system upon mixing with $CDCl_3$, with the concentrations of **1h** in the upper and lower phases 3.5 and 45.5 wt%, respectively. The mixture turns homogeneous upon heating and separates to two-phases upon cooling down to rt.

The nature of the ionic liquids **1** is especially pronounced in their remarkably low solubilities in typical organic solvents (toluene, dialkyl ethers) and water. For example, the ionic liquid **1c** shows solubilities of 0.7 wt% in water, 0.3 wt% in toluene and 1.2 wt% in diisopropyl ether, that is, it is virtually immiscible with the above solvents. Specific solvation effects in the salts **1** make them truly orthogonal reaction media and should allow an easy recycling of these ionic liquids by extractive removal of organic products and inorganic salts with organic solvents and water, respectively. This feature may turn out to be useful in the design of new recoverable catalytic systems.[18]

3. Experimental

3.1. General

NMR spectra were recorded on Bruker 400 UltraShield instrument in $CDCl_3$ as a solvent unless stated otherwise. ^1H and ^{13}C chemical shifts are expressed as ppm downfield from $SiMe_4$ ($\delta=0$) used as an internal standard. ^{19}F chemical shifts are given in ppm upfield from $PhCF_3$ ($\delta=-63.7$ ppm)[19] used as an internal standard. ^{13}C signals of the $CF_3(CF_2)_3$ groups were not given due to very complicated and overlapping heteronuclear $^{13}C,^{19}F$ coupling patterns. ^{15}N NMR signals of the 1-isopropyl-3-methylimidazolium cation in the salt **1g** are obtained using insensitive nuclei enhanced by polarization (INEPT) technique with the chemical shifts expressed as ppm upfield from $MeNO_2$ ($\delta=0$) used as an external standard. Mass spectra were registered with Finnigan MAT 95XP (FAB-HRMS) and with Macromass Quattro micro™ API (ESI-MS) spectrometers. Decomposition temperatures of the salts **B**, **1** and **2** were determined with SDT 2960 Simultaneous DSC-TGA instrument. Microanalyses were performed with Euro Elemental Analyser. Melting points were determined using Büchi Melting Point B-540 apparatus and are uncorrected.

The syntheses of the potassium salts **A** and **B** were carried out under an atmosphere of argon in heat-gun dried reaction flasks. Solvents for syntheses were dried following standard procedures and freshly distilled prior to use: DMF (vacuum distillation from CaH_2), MeCN (distillation from CaH_2), THF (distillation from Na–K alloy/Ph_2CO). Solvents for extraction were distilled before use. Nonafluorobutane-1-sulfonyl fluoride was obtained from Bayer AG; it can also be purchased from commercial suppliers. *N*-Methyl imidazole (Fluka) was distilled and stored over BaO.

The alkylating reagents (see Table 1), purchased from Lancaster, Aldrich and Fluka were distilled before use.

K_2CO_3 (Fluka), $K_3PO_4\cdot H_2O$ (Riedel-de-Haen), NH_4Cl (Merck), $CH_3C(O)NH_2$ (Acros Organics) and imidazole (Lancaster) were dried in high vacuum before use. Et_3N (Riedel-de-Haen) was stored over KOH pellets.

3.1.1. Potassium bis(nonafluorobutane-1-sulfonyl)imide (A). NH_4Cl (13.9 g, 250 mmol) was placed into 1 L reaction flask equipped with efficient magnetic stirring bar and dried under high vacuum (hereafter HV) to remove traces of moisture before MeCN (125 mL) and NfF (166.9 g, 550 mmol) were added. The resulting two-phase suspension was cooled down to −40 °C, and Et_3N (127.6 g, 1250 mmol) pre-cooled with liquid nitrogen was quickly added to the reaction mixture upon vigorous stirring. After gradual warming up to ambient temperature, the resulting mixture was heated up to 65 °C and stirred at this temperature overnight. After cooling down to ambient temperature the bulk of MeCN was removed in vacuum. The residue was partitioned between CH_2Cl_2 (400 mL) and deionized water (200 mL). The organic layer was then thoroughly washed with deionized water (3×200 mL) until it showed a negative chloride test with aqueous $AgNO_3$. Volatiles were removed in vacuum to give the intermediate $Et_3NH^{\oplus}NNf_2^{\ominus}$ (165.85 g, 97% yield) as a tawny crystalline solid, mp 42–43 °C, ^1H NMR (400.23 MHz): δ 1.33 (9H, t, $^3J=7.3$ Hz, $3CH_2\mathit{CH}_3$), 3.18 (6H, br q, $^3J=7.3$ Hz, $3\mathit{CH}_2CH_3$), 7.19 (1H, br s, NH^+). ^{13}C NMR (100.65 MHz): δ 8.5 ($CH_2\mathit{CH}_3$), 47.2 (CH_2CH_3). ^{19}F NMR (376.59 MHz): δ −127.1 (4F, t*, $J=14.3$ Hz, $2CF_2$-3), −122.1 (4F, m_c, $2CF_2$-2), −113.9 (4F, t*, $J=14.3$ Hz, $2CF_2$-1), −81.9 (6F, tt, $J_1=10.0$ Hz, $J_2=2.3$ Hz, $2CF_3$); *further splitting due to the multiple $^{19}F,^{19}F$ couplings.

Without further purification, $Et_3NH^{\oplus}NNf_2^{\ominus}$ (165.9 g, 243 mmol) was dissolved in MeOH (30 mL) and added dropwise to the solution of KOH (27.0 g, 590 mmol) in water (300 mL) upon vigorous stirring. Instantaneous precipitation of the desired $KNNf_2$ **A** was observed. The reaction mixture was stirred overnight before filtering the precipitate. The crystalline residue was washed thoroughly with cold deionized water until neutral pH followed by drying on the sinter funnel and washing additionally with $CHCl_3$ (3×150 mL) to give the salt **A** (148.83 g, 81% yield) as a white crystalline solid, mp 340–341 °C (decomp.). **A**, ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.2 (4F, t*, $J=13.9$ Hz, $2CF_2$-3), −123.5 (4F, m_c, $2CF_2$-2), −115.8 (4F, t*, $J=13.5$ Hz, $2CF_2$-1), −82.8 (6F, tt, $J_1=9.8$ Hz, $J_2=2.3$ Hz, $2CF_3$); *further splitting due to the multiple $^{19}F,^{19}F$ couplings. HRMS (FAB negative, Cs, 20 keV, direct, glycerin, *m/z*), found: 579.9083. Calcd ($C_8F_{18}NO_4S_2^-$): 579.8976. Anal. Calcd for $C_8F_{18}KNO_4S_2$: C, 15.52; F, 55.22; N, 2.26; S, 10.36. Found: C, 15.50; H, 0; N, 2.32; S, 10.60.

3.1.2. Attempts to prepare the potassium salt (A) by interaction of acetamide with NfF in the presence of K_2CO_3 or K_3PO_4: potassium nonafluorobutanesulfonate (B) (see Scheme 1).

a: according to the literature procedure:[5] The synthesis was attempted using $CH_3C(O)NH_2$ (0.827 g, 14.0 mmol), K_2CO_3 (5.00 g, 36.0 mmol), THF (15 mL) and NfF (2× 4.23 g, 2×14 mmol). After heating for the designated time (2×3 h) and removal of volatiles in vacuum, the mixed

solid residue was treated with Me_2CO (25 mL) and filtered; the insoluble precipitate on the sinter funnel was washed with Me_2CO, the combined filtrate was evaporated in vacuum, MeOH (10 mL) was added to the residue, and the resulting mixture was refluxed for a few minutes until the crystalline residue was completely dissolved. The resulting homogenous solution was diluted with $CHCl_3$. The crystalline precipitate was filtered off and dried to give 5.40 g of white crystalline solid, which was identified as potassium nonaflate **B** (62% yield).

b: room temperature modification employing DMF as a solvent: K_2CO_3 (81.8 g, 592 mmol) was dried at 200 °C in a HV for 3 h and transferred into 500 mL reaction flask equipped with efficient magnetic stirring bar. After flushing with dry argon and cooling, DMF (160 mL), dry CH_3-$C(O)NH_2$ (9.54 g, 161.5 mmol) and followed by NfF (103.4 g, 342 mmol) were consecutively added at rt. The reaction mixture was stirred for 40 h. During first 24 h, evolution of CO_2 was clearly observed. The isolation carried out as described above furnished 84.42 g of white crystalline solid, which was identified as potassium nonaflate **B** (73% yield). Likewise, the analogous reaction carried out with K_3PO_4 in place of K_2CO_3 afforded the salt **B** in 75% yield.

c: a reference experiment in DMF conducted in the absence of $CH_3C(O)NH_2$: The experiment was carried out with K_2CO_3 (3.24 g, 23.4 mmol), DMF (15 mL) and NfF (4.75 g, 15.7 mmol) as described above, the progress and appearance being identical. The workup and the isolation as described above resulted in the salt **B** (3.72 g, 74% yield) as a white crystalline solid, decomp. ca. 450 °C. **B**, ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.1 (4F, t*, J=13.5 Hz, $2CF_2$-3), −123.8 (4F, m$_c$, $2CF_2$-2), −117.2 (4F, t*, J=13.5 Hz, $2CF_2$-1), −83.0 (6F, tt, J_1=9.8 Hz, J_2=2.9 Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. HRMS (FAB negative, Cs, 20 keV, direct, glycerin, *m/z*), found: 298.9449. Calcd ($C_4F_9O_3S^-$): 298.9419. Anal. Calcd for $C_4F_9KO_3S$: C, 14.21; F, 50.56; S, 9.48. Found: C, 14.48; H, 0; S, 9.75.

3.2. Synthesis of *N*-methyl-*N′*-alkyl imidazolium bis(nonafluorobutane-1-sulfonyl)imides (1) and nonaflates (2) (see Scheme 4): general procedure (GP1)

A mixture of *N*-methylimidazole (1.05 equiv) and the alkylating reagent R′X (1.1 equiv) was stirred under the conditions (temperature and time) specified in the Table 1. The volatiles were then removed in HV, the residue was dissolved in CH_2Cl_2 (typically 0.15–0.20 mmol/mL) and transferred into the separating funnel containing a suspension of the salt **A** or **B** (0.85–1 equiv) in water (typically 0.25–0.30 mmol/mL). The content of the funnel was vigorously shaken for 3–5 min so that no further precipitate was present in the resulting two-phase mixture. The organic layer was washed with dilute HCl (pH 1) and 3–4 times with deionized water so that the last aqueous layer after extraction should indicate pH 6–7 and give a negative halogenide test with aqueous $AgNO_3$. CH_2Cl_2 was removed in vacuum, and the residue was vigorously stirred for 15–17 h at 40–50 °C under HV to give the desired molten salt **1** or **2** in the designated yield (see Table 1).

3.2.1. 1-Ethyl-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1a). The title compound was prepared from *N*-methylimidazole (1.314 g, 16.0 mmol), $(EtO)_2SO_2$ (2.35 g, 15.2 mmol) and the salt **A** (9.00 g, 14.5 mmol) as described in GP1; yield 9.82 g (98%) as a clear viscous slightly yellowish liquid. **1a**, ^{1}H NMR (400.23 MHz, DMSO-d_6): δ 1.42 (3H, t, ^3J=7.3 Hz, CH_2CH_3), 3.85 (3H, s, NCH_3), 4.19 (2H, q, ^3J=7.3 Hz, NCH_2), 7.69 (1H, t, J=1.8 Hz) and 7.78 (1H, t, J=1.8 Hz) (both *CH*=*CH*), 9.11 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz, DMSO-d_6): δ 15.1 (CH_2CH_3), 35.7 (NCH_3), 44.1 (NCH_2), 122.0 and 123.6 (both *CH*=*CH*), 136.3 (N–*CH*=N). ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.1 (4F, t*, J=14 Hz, $2CF_2$-3), −123.4 (4F, m$_c$, $2CF_2$-2), −115.7 (4F, br t, J=14 Hz, $2CF_2$-1), −82.8 (6F, tt, J_1=9.7 Hz, J_2=2.5 Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 111.03 [$C_6H_{11}N_2^+$] (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 579.86 [$(C_4F_9SO_2)_2N^-$] (100), 296.95 [$C_4F_9SO_2N^-$] (24.3) and lighter fragments.

3.2.2. 1-Propyl-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1b). The title compound was prepared from *N*-methylimidazole (1.223 g, 14.9 mmol), $Me(CH_2)_2Br$ (1.93 g, 15.7 mmol) and the salt **A** (8.79 g, 14.2 mmol) as described in GP1; yield 9.85 g (98%) as a clear yellowish viscous liquid. **1b**, ^{1}H NMR (400.23 MHz, DMSO-d_6): δ 0.87 (3H, t, ^3J=7.4 Hz, CH_2CH_3), 1.81 (2H, sextet, ^3J=7.3 Hz, CH_2CH_3), 3.86 (3H, s, NCH_3), 4.13 (2H, t, ^3J=7.1 Hz, NCH_2), 7.70 (1H, t, J=1.8 Hz) and 7.76 (1H, t, J=1.8 Hz) (both *CH*=*CH*), 9.10 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz, DMSO-d_6): δ 10.3 (CH_2CH_3), 22.9 (CH_2CH_3), 35.7 (NCH_3), 50.3 (NCH_2), 122.3 and 123.7 (both *CH*=*CH*), 136.6 (N–*CH*=N). ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.1 (4F, t*, J=14 Hz, $2CF_2$-3), −123.3 (4F, m$_c$, $2CF_2$-2), −115.6 (4F, br t, J=14 Hz, $2CF_2$-1), −82.8 (6F, tt, J_1=9.7 Hz, J_2=2.5 Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 125 [$C_7H_{13}N_2^+$] (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 580 [$(C_4F_9SO_2)_2N^-$] (100) and lighter fragments.

3.2.3. 1-Butyl-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1c). The title compound was prepared from *N*-methylimidazole (1.20 g, 14.6 mmol), $Me(CH_2)_3Cl$ (1.42 g, 15.3 mmol) and the salt **A** (8.61 g, 13.9 mmol) as described in GP1; yield 9.96 g (>99%) as a clear yellowish viscous liquid. **1c**, ^{1}H NMR (400.23 MHz): δ 0.94 (3H, t, ^3J=7.4 Hz, CH_2CH_3), 1.36 (2H, sextet, ^3J=7.4 Hz, CH_2CH_3), 1.85 (2H, m$_c$, NCH_2CH_2), 3.93 (3H, s, NCH_3), 4.18 (2H, t, ^3J=7.6 Hz, NCH_2), 7.38 (1H, t, J=1.7 Hz) and 7.40 (1H, t, J=1.7 Hz) (both *CH*=*CH*), 8.71 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 12.6 (CH_2CH_3), 19.0 (CH_2CH_3), 31.8 (NCH_2CH_2), 35.8 (NCH_3), 49.7 (NCH_2), 122.3 and 123.6 (both *CH*=*CH*), 135.7 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.0 (4F, t*, J=14 Hz, $2CF_2$-3), −122.0 (4F, m$_c$, $2CF_2$-2), −113.8 (4F, br t, J=14 Hz, $2CF_2$-1), −82.0 (6F, tt, J_1=9.9 Hz, J_2=2.3 Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 139.1

$[C_8H_{15}N_2^+]$ (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 580.0 $[(C_4F_9SO_2)_2N^-]$ (100) and lighter fragments.

3.2.4. 1-Pentyl-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1d). The title compound was prepared from *N*-methylimidazole (1.172 g, 14.3 mmol), $Me(CH_2)_4Br$ (2.27 g, 15.0 mmol) and the salt **A** (8.42 g, 13.6 mmol) as described in GP1; yield 9.66 g (97%) as a clear yellowish viscous liquid. **1d**, ^{1}H NMR (400.23 MHz): δ 0.87 (3H, t, $^3J=7$ Hz, CH_2CH_3), 1.23–1.38 (4H, *m*, $CH_2CH_2CH_3$), 1.84 (2H, quintet, $^3J=7.5$ Hz, NCH_2CH_2), 3.91 (3H, s, NCH_3), 4.14 (2H, t, $^3J=7.6$ Hz, NCH_2), 7.32 (1H, t, $J=1.8$ Hz) and 7.33 (1H, t, $J=1.8$ Hz) (both *CH*=*CH*), 8.73 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 13.4 (CH_2CH_3), 21.8 (CH_2CH_3), 28.0 and 29.7 (both CH_2) 36.0 (NCH_3), 50.0 (NCH_2), 122.2 and 123.7 (both *CH*=*CH*), 135.9 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.1 (4F, t*, $J=14$ Hz, $2CF_2$-3), −122.2 (4F, m_c, $2CF_2$-2), −114.0 (4F, br t, $J=14$ Hz, $2CF_2$-1), −82.0 (6F, tt, $J_1=9.9$ Hz, $J_2=2$ Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 153.172 $[C_9H_{17}N_2^+]$ (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 579.951 $[(C_4F_9SO_2)_2N^-]$ (100) and lighter fragments.

3.2.5. 1-(3-Methyl-butyl)-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1e). The title compound was prepared from *N*-methylimidazole (1.223 g, 14.9 mmol), $Me_2CH(CH_2)_2Br$ (1.93 g, 15.7 mmol) and the salt **A** (8.42 g, 13.6 mmol) as described in GP1; yield 9.97 g (>99%) as a yellowish crystalline solid, mp 39–40 °C. **1e**, ^{1}H NMR (400.23 MHz, DMSO-d_6): δ 0.92 (6H, d, $^3J=6.7$ Hz, Me_2CH), 1.52 (1H, nonet, $^3J=6.7$ Hz, Me_2CH), 1.70 (2H, dt, $^3J_1=7.8$ Hz, $^3J_2=6.7$ Hz, NCH_2CH_2), 3.85 (3H, s, NCH_3), 4.18 (2H, t, $^3J=7.6$ Hz, NCH_2), 7.69 (1H, t, $J=1.8$ Hz) and 7.78 (1H, t, $J=1.8$ Hz) (both *CH*=*CH*), 9.12 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz, DMSO-d_6): δ 21.9 (Me_2CH), 24.8 (Me_2CH), 35.7 (NCH_3), 38.2 (NCH_2CH_2), 47.2 (NCH_2), 122.3 and 123.6 (both *CH*=*CH*), 136.5 (N–*CH*=N). ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.1 (4F, t*, $J=14$ Hz, $2CF_2$-3), −123.4 (4F, m_c, $2CF_2$-2), −115.7 (4F, br t, $J=14$ Hz, $2CF_2$-1), −82.8 (6F, tt, $J_1=9.8$ Hz, $J_2=2.6$ Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 153.2 $[C_9H_{17}N_2^+]$ (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 580.0 $[(C_4F_9SO_2)_2N^-]$ (100) and lighter fragments.

3.2.6. 1-Isobutyl-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1f). The title compound was prepared from *N*-methylimidazole (1.20 g, 14.6 mmol), Me_2CHCH_2Br (1.42 g, 15.3 mmol) and the salt **A** (8.61 g, 13.9 mmol) as described in GP1; yield 9.99 g (>99%) as a clear yellowish viscous liquid. **1f**, ^{1}H NMR (400.23 MHz): δ 0.94 (6H, d, $^3J=6.7$ Hz, Me_2CH), 2.15 (1H, nonet, $^3J=6.8$ Hz, Me_2CH), 3.95 (3H, s, NCH_3), 4.00 (2H, t, $^3J=7.4$ Hz, NCH_2), 7.39 (1H, t, $J=1.8$ Hz) and 7.41 (1H, t, $J=1.8$ Hz) (both *CH*=*CH*), 8.72 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 18.6 (Me_2CH), 29.1 (Me_2CH), 35.8 (NCH_3), 56.7 (NCH_2), 122.7 and 123.6 (both *CH*=*CH*), 135.9 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.0 (4F, t*, $J=14$ Hz, $2CF_2$-3), −122.0 (4F, m_c, $2CF_2$-2), −113.8 (4F, br t, $J=14$ Hz, $2CF_2$-1), −82.0 (6F, tt, $J_1=9.9$ Hz, $J_2=2.3$ Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 139.1 $[C_8H_{15}N_2^+]$ (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 580.0 $[(C_4F_9SO_2)_2N^-]$ (100) and lighter fragments.

3.2.7. 1-Isopropyl-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1g). The title compound was prepared from *N*-methylimidazole (1.22 g, 14.9 mmol), Me_2CHBr (1.93 g, 15.7 mmol) and the salt **A** (8.79 g, 14.2 mmol) as described in GP1; yield 9.87 g (99%) as a slightly yellowish deliquescent crystalline solid, mp 28–29 °C. **1g**, ^{1}H NMR (400.23 MHz, DMSO-d_6): δ 1.48 (6H, d, $^3J=6.7$ Hz, Me_2CH), 3.85 (3H, s, NCH_3), 4.63 (1H, heptet, $^3J=6.7$ Hz, $NCHMe_2$), 7.71 (1H, t, $J=1.8$ Hz) and 7.87 (1H, t, $J=1.8$ Hz) (both *CH*=*CH*), 9.17 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz, DMSO-d_6): δ 22.3 (Me_2CH), 35.7 (NCH_3), 52.2 ($NCHMe_2$), 120.5 and 123.7 (both *CH*=*CH*), 135.4 (N–*CH*=N). ^{15}N NMR (40.57 MHz, DMSO-d_6): δ −183.6 and −210.4 (both endocyclic N). ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.1 (4F, t*, $J=14$ Hz, $2CF_2$-3), −123.3 (4F, m_c, $2CF_2$-2), −115.6 (4F, br t, $J=14$ Hz, $2CF_2$-1), −82.8 (6F, tt, $J_1=9.8$ Hz, $J_2=2.6$ Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 125.114 $[C_7H_{13}N_2^+]$ (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 579.950 $[(C_4F_9SO_2)_2N^-]$ (100) and lighter fragments.

3.2.8. 1-*sec*-Butyl-3-methylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (1h). The title compound was prepared from *N*-methylimidazole (1.20 g, 14.6 mmol), $MeCH_2CH(Me)Br$ (2.10 g, 15.3 mmol) and the salt **A** (7.25 g, 11.7 mmol) as described in GP1; yield 8.38 g (>99%) as a clear viscous tawny liquid. **1h**, ^{1}H NMR (400.23 MHz, DMSO-d_6): δ 0.78 (3H, t, $^3J=7.4$ Hz, CH_3CH_2), 1.47 (3H, d, $^3J=6.9$ Hz, CH_3CH), 1.80 (2H, m_c, CH_3CH_2), 3.86 (3H, s, NCH_3), 4.41 (1H, sextet, $^3J=6.9$ Hz, NCH), 7.73 (1H, t, $J=1.7$ Hz) and 7.86 (1H, t, $J=1.7$ Hz) (both *CH*=*CH*), 9.17 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz, DMSO-d_6): δ 9.9 (CH_2CH_3), 20.2 (CH_3CHN), 29.1 (CH_2CH_3), 35.8 (NCH_3), 57.8 (NCH), 120.4 and 123.9 (both *CH*=*CH*), 135.7 (N–*CH*=N). ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.1 (4F, t*, $J=14$ Hz, $2CF_2$-3), −123.4 (4F, m_c, $2CF_2$-2), −115.7 (4F, br t, $J=14$ Hz, $2CF_2$-1), −82.8 (6F, tt, $J_1=9.8$ Hz, $J_2=2.6$ Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 139.1 $[C_8H_{15}N_2^+]$ (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 580.0 $[(C_4F_9SO_2)_2N^-]$ (100) and lighter fragments.

3.2.9. 1-Propyl-3-methylimidazolium nonafluorobutanesulfonate (2a). The title compound was prepared from *N*-methylimidazole (2.044 g, 24.9 mmol), $Me(CH_2)_2Br$ (3.21 g, 26.1 mmol) and the salt **B** (8.00 g, 23.7 mmol) as described in GP1; yield 8.25 g (82%) as a slightly yellowish crystalline solid, mp 33–34 °C. **2a**, ^{1}H NMR (400.23 MHz): δ 0.94 (3H, t, $^3J=7.4$ Hz, CH_2CH_3), 1.90 (2H, sextet, $^3J=7.4$ Hz, CH_2CH_3), 3.96 (3H, s, NCH_3), 4.15 (2H, t,

^3J=7.4 Hz, NCH_2), 7.41 (1H, t, J=1.8 Hz) and 7.43 (1H, t, J=1.8 Hz) (both *CH*=*CH*), 9.09 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 10.4 (CH_2CH_3), 23.4 (CH_2CH_3), 36.3 (NCH_3), 51.5 (NCH_2), 122.1 and 123.6 (both *CH*=*CH*), 136.9 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.1 (2F, t*, J=14.2 Hz, 2CF_2-3), −122.7 (2F, m$_c$, 2CF_2-2), −115.9 (2F, t*, J=14.2 Hz, 2CF_2-1), −82.0 (3F, tt, J_1=9.9 Hz, J_2=2.7 Hz, 2CF_3); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m*/*z* (%): 125 [$C_7H_{13}N_2^+$] (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m*/*z* (%): 298.9 [$C_4F_9SO_3^-$] (100) and lighter fragments.

3.2.10. 1-Butyl-3-methylimidazolium nonafluorobutanesulfonate (2b). The title compound was prepared from *N*-methylimidazole (2.04 g, 24.9 mmol), Me$(CH_2)_3$Cl (2.42 g, 26.1 mmol) and the salt **B** (8.00 g, 23.7 mmol) as described in GP1; yield 8.52 g (82%) as a clear yellow viscous liquid. **2b**, ^{1}H NMR (400.23 MHz): δ 0.94 (3H, t, ^3J=7.4 Hz, CH_2CH_3), 1.35 (2H, sextet, ^3J=7.5 Hz, CH_2CH_3), 1.85 (2H, m$_c$, NCH_2CH_2), 3.96 (3H, s, NCH_3), 4.19 (2H, t, ^3J=7.5 Hz, NCH_2), 7.37 (1H, t, J=1.8 Hz) and 7.41 (1H, t, J=1.8 Hz) (both *CH*=*CH*), 9.13 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 13.1 (CH_2CH_3), 19.3 (CH_2CH_3), 31.9 (NCH_2CH_2), 36.2 (NCH_3), 49.8 (NCH_2), 122.2 and 123.6 (both *CH*=*CH*), 136.7 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.1 (2F, t*, J=14 Hz, 2CF_2-3), −122.7 (2F, m$_c$, 2CF_2-2), −115.9 (2F, t*, J=14 Hz, 2CF_2-1), −82.0 (3F, tt, J_1=9.9 Hz, J_2=2.7 Hz, 2CF_3); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m*/*z* (%): 139.1 [$C_8H_{15}N_2^+$] (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m*/*z* (%): 298.95 [$C_4F_9SO_3^-$] (100) and lighter fragments.

3.2.11. 1-Isopropyl-3-methylimidazolium nonafluorobutanesulfonate (2c). The title compound was prepared from *N*-methylimidazole (2.04 g, 24.9 mmol), Me_2CHBr (3.22 g, 26.2 mmol) and the salt **B** (8.00 g, 23.7 mmol) as described in GP1; yield 8.14 g (81%) as a clear yellowish viscous liquid. **2c**, ^{1}H NMR (400.23 MHz): δ 1.56 (6H, d, ^3J=6.7 Hz, Me_2CH), 3.97 (3H, s, NCH_3), 4.65 (1H, heptet, ^3J=6.7 Hz, N*CH*Me$_2$), 7.42 (1H, t, J=1.9 Hz) and 7.45 (1H, t, J=1.9 Hz) (both *CH*=*CH*), 9.12 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 22.6 (Me_2CH), 36.1 (NCH_3), 53.3 (N*CH*Me$_2$), 120.2 and 123.7 (both *CH*=*CH*), 135.3 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.1 (2F, t*, J=14.2 Hz, 2CF_2-3), −122.7 (2F, m$_c$, 2CF_2-2), −115.9 (2F, t*, J=14.2 Hz, 2CF_2-1), −82.0 (3F, tt, J_1=10.0 Hz, J_2=2.8 Hz, 2CF_3); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m*/*z* (%): 125 [$C_7H_{13}N_2^+$] (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m*/*z* (%): 298.9 [$C_4F_9SO_3^-$] (100) and lighter fragments.

3.2.12. 1-*sec*-Butyl-3-methylimidazolium nonafluorobutanesulfonate (2d). The title compound was prepared from *N*-methylimidazole (2.04 g, 24.9 mmol), $MeCH_2$-CH(Me)Br (3.58 g, 26.1 mmol) and the salt **B** (6.74 g, 19.9 mmol) as described in GP1; yield 6.89 g (79%) as a tawny crystalline solid, mp 42–43 °C. **2d**, ^{1}H NMR (400.23 MHz): δ 0.87 (3H, t, ^3J=7.4 Hz, CH_3CH_2), 1.55 (3H, d, ^3J=6.9 Hz, CH_3CH), 1.86 (2H, quintet, ^3J=7.4 Hz, CH_3CH_2), 3.98 (3H, s, NCH_3), 4.41 (1H, sextet, ^3J=6.9 Hz, N*CH*), 7.41 (1H, t, J=1.8 Hz) and 7.46 (1H, t, J=1.8 Hz) (both *CH*=*CH*), 9.17 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 9.9 (CH_2CH_3), 20.4 (CH_3CHN), 29.8 (CH_2CH_3), 36.2 (NCH_3), 59.1 (N*CH*), 120.2 and 123.8 (both *CH*=*CH*), 135.7 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.1 (2F, t*, J=14.2 Hz, 2CF_2-3), −122.7 (2F, m$_c$, 2CF_2-2), −115.9 (2F, t*, J=14.2 Hz, 2CF_2-1), −82.0 (3F, tt, J_1=9.9 Hz, J_2=2.7 Hz, 2CF_3); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m*/*z* (%): 139 [$C_8H_{15}N_2^+$] (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m*/*z* (%): 298.9 [$C_4F_9SO_3^-$] (100) and lighter fragments. HRMS (FAB negative, Cs, 20 keV, direct, glycerin, *m*/*z*), found: 298.9395. Calcd ($C_4F_9O_3S^-$): 298.9419.

3.3. Synthesis of *N*-propyl-*N*′-alkyl imidazolium bis-(nonafluorobutane-1-sulfonyl)imides (3) (see Scheme 5): general procedure (GP2)

Imidazole (1 equiv) was placed into the reaction flask and dried in HV (0.05 mbar, rt) to remove traces of moisture before adding a solution of MeONa (1.05 equiv) in MeOH (4.026 mmol/g, prepared from MeOH and Na). The reaction mixture was stirred for 15–20 min at rt, then MeOH was removed in vacuum followed by drying the residue in HV (0.05 mbar, rt) for 1 h. MeCN (0.5 mL per 1 mmol substrate) followed by the Me$(CH_2)_2$Br (1.0–1.1 equiv) were added to the resulting sodium imidazolide at 0 °C, and the reaction mixture was stirred for 5 h at 0 °C and 15 h at ambient temperature. After the completion of the first alkylation step (NMR-control), the volatiles were removed in vacuum followed by the addition of the second alkylating reagent. After the completion of the second alkylation step (NMR-control), the residue was combined with the salt **A** (0.95 equiv) in two-phase water/CH_2Cl_2 mixture and treated as described in GP1 furnishing the compounds **3a**,**b**.

3.3.1. 1-Propyl-3-ethylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (3a). The title compound was prepared from imidazole (1.00 g, 14.7 mmol), MeONa (0.83 g, 15.4 mmol) in MeOH (10 mL), Me$(CH_2)_2$Br (1.80 g, 14.7 mmol) as a first alkylating reagent in MeCN (8 mL), $(EtO)_2SO_2$ (2.16 g, 14.0 mmol) as a second alkylating reagent employed at 0 °C to rt for 17 h, and the salt **A** (8.61 g, 13.9 mmol), as described in GP2; yield 9.90 g (99%) as a clear yellow viscous liquid. **3a**, ^{1}H NMR (400.23 MHz): δ 0.94 (3H, t, ^3J=7.4 Hz, $CH_2CH_2CH_3$), 1.52 (3H, t, ^3J=7.4 Hz, NCH_2CH_3), 1.89 (2H, sextet, ^3J=7.4 Hz, $CH_2CH_2CH_3$), 4.14 (2H, t, ^3J=7.4 Hz, NCH_2CH_2), 4.25 (2H, q, ^3J=7.4 Hz, NCH_2CH_3), 7.32 (1H, t, J=1.8 Hz) and 7.35 (1H, t, J=1.8 Hz) (both *CH*=*CH*), 8.82 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 10.2 ($CH_2CH_2CH_3$), 15.0 ($CH_2CH_2CH_3$), 23.4 ($CH_2CH_2CH_3$), 45.2 (NCH_2CH_3), 51.5 (NCH_2CH_2), 121.9 and 122.3 (both *CH*=*CH*), 135.2 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.1 (4F, t*, J=14 Hz, 2CF_2-3), −122.2 (4F, m$_c$, 2CF_2-2), −114.0 (4F, br t, J=14 Hz, 2CF_2-1), −81.9 (6F, tt, J_1=9.9 Hz, J_2=2.4 Hz, 2CF_3); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m*/*z* (%): 139.1 [$C_8H_{15}N_2^+$] (100) and lighter

fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 580.0 [$(C_4F_9SO_2)_2N^-$] (100) and lighter fragments. HRMS (FAB negative, Cs, 20 keV, direct, glycerin, *m/z*), found: 579.8994. Calcd ($C_8F_{18}NO_4S_2^-$): 579.8976.

3.3.2. 1-Butyl-3-propylimidazolium bis(nonafluorobutane-1-sulfonyl)imide (3b). The title compound was prepared from imidazole (1.021 g, 15.0 mmol), MeONa (0.851 g, 15.8 mmol) in MeOH (10 mL), $Me(CH_2)_2Br$ (2.03 g, 16.5 mmol) as a first alkylating reagent in MeCN (7.5 mL), $Me(CH_2)_3Br$ (2.62 g, 19.1 mmol) as a second alkylating reagent employed for 3 h at 70 °C, and the salt **A** (8.30 g, 13.4 mmol), as described in GP2; yield 10.04 g (>99%) as a yellowish crystalline solid, mp 36–37 °C. **3b**, ^{1}H NMR (400.23 MHz): δ 0.936 and 0.940 (both 3H, t, ^3J=7.4 Hz, CH_2CH_3), 1.34 (2H, sextet, ^3J=7.4 Hz, CH_2CH_3 of *n*-C_4H_9), 1.83 (2H, m_c, NCH_2CH_2 of *n*-C_4H_9), 1.89 (2H, sextet, ^3J=7.4 Hz, NCH_2CH_2 of *n*-C_3H_7), 4.14 and 4.17 (both 2H, t, ^3J=7.4 Hz, NCH_2), 7.340 and 7.344 (both 1H, br s, *CH*=*CH*) 8.82 (1H, br s, N–*CH*=N). ^{13}C NMR (100.65 MHz): δ 10.2 and 13.0 (both CH_3), 19.2 and 23.4 (both CH_2CH_3), 32.0 (NCH_2CH_2 of *n*-C_4H_9), 49.9 and 51.5 (both NCH_2), 122.3 (both *CH*=*CH*), 135.5 (N–*CH*=N). ^{19}F NMR (376.59 MHz): δ −127.1 (4F, t*, J=14 Hz, $2CF_2$-3), −122.2 (4F, m_c, $2CF_2$-2), −114.0 (4F, br t, J=14 Hz, $2CF_2$-1), −81.9 (6F, tt, J_1=9.9 Hz, J_2=2.3 Hz, $2CF_3$); *further splitting due to the multiple ^{19}F,^{19}F couplings. MS (ESI positive, ion energy 0.3 eV), *m/z* (%): 167 [$C_{10}H_{19}N_2^+$] (100) and lighter fragments. MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 580 [$(C_4F_9SO_2)_2N^-$] (100) and lighter fragments.

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7. A careful analysis of the spectroscopic data of the products obtained under the conditions **a** and **b** showed that they consist of the salt **B** (60–70 mol%), $CH_3C(O)NNf^{\ominus}K^{\oplus}$ (25–40 mol%) and $KOSO_2(CF_2)_4H$ (up to 11 mol%, MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 280.93 [$H(CF_2)_4SO_3]^-$). The latter salt may result from the nucleophilic ring opening of perfluorosulfolane, see Ref. 4 and Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015–1025. No desired $KNNf_2$ **A** is detected in either of the experiments. $CH_3C(O)NNf^{\ominus}K^{\oplus}$, ^{1}H NMR (400.23 MHz, DMSO-d_6): 1.81 (3H, s, CH_3). ^{19}F NMR (376.59 MHz, DMSO-d_6): δ −128.0 (2F, m_c, CF_2-3), −123.5 (2F, m_c, CF_2-2), −115.8 (2F, m_c, CF_2-1), −82.75 (3F, tt, J_1=9.8 Hz, J_2=2.9 Hz, CF_3). MS (ESI negative, ion energy 0.3 eV), *m/z* (%): 339.94 [$C_4F_9SO_2NC(O)CH_3]^-$.
8. In fact, microanalysis data given for $KNNf_2$ (see Ref. 5) are in a better consistency with the elemental composition of KONf!.
9. O-Sulfonylation of metal enolates or N-sulfonylation of lithium dialkylamides with NfF occurs instantaneously even at −78 °C, see: (a) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Synlett* **2001**, 1293–1295. (b) Lyapkalo, I. M.; Reissig, H.-U.; Schäfer, A.; Wagner, A. *Helv. Chim. Acta* **2002**, *85*, 4206–4215, respectively, whereas no evidences of $F^{\ominus}$ release were noticed upon activation of NfF with highly nucleophilic 4-(*N*,*N*-dimethylamino)pyridine.
10. Et_3N failed to produce the desired $NNf_2^{\ominus}$ ion when used as a base for sulfonylation of amides $RC(O)NH_2$ with NfF (see Ref. 5).
11. At the later stage of the optimization of $KNNf_2$ synthesis, we found out that a similar method was used for preparation of $LiNNf_2$ by heating of liquid NH_3 with NfF in access of Et_3N as an auxiliary base and solvent at 90 °C in autoclave: Conte, L.; Gambaretto, G. P.; Caporiccio, G.; Alessandrini, F.; Passerini, S. *J. Fluorine Chem.* **2004**, *125*, pp 243–252. Our protocol looks more convenient as it simplifies dosing of ammonia (in form of solid NH_4Cl) and is carried out at smoother conditions in normal laboratory glassware giving a better yield of the intermediate $Et_3NH^{\oplus}NNf_2^{\ominus}$.
12. The ^{19}F NMR spectrum contains no detectable signal of side product(s) that might result from perfluorosulfolane (cf. Ref. 7).
13. The samples of the salts neither change appearance nor gain in wait upon storage in open vial for a long period of time.
14. The reaction progress was monitored by ^{1}H NMR spectroscopy; in all the cases full conversion of the starting *N*-methyl imidazole was observed. Up to 15–18 mol% of *N*-methyl imidazolium bromide was detected by ^{1}H NMR as a side product resulting from HBr elimination from secondary bromides. It was easily removed from ionic liquid by aqueous extraction on the following anion exchange step. Although at higher temperature primary branched and secondary alkyl bromides react faster, a contribution of the E2 elimination pathway increases significantly.

15. First representatives of the salts **1**, *N*,*N*′-dimethyl- and *N*-methyl-*N*′-ethylimidazolium bis(nonafluorobutane-1-sulfonyl)imides were obtained earlier in a different way: Zhang, J.; Martin, G. R.; DesMarteau, D. D. *Chem. Commun.* **2003**, *18*, 2334–2335.
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Arenediazonium *o*-benzenedisulfonimides as efficient reagents for Heck-type arylation reactions

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Abstract—Arenediazonium *o*-benzenedisulfonimides can be used as new and efficient reagents for Heck-type arylation reactions of some common substrates containing C–C multiple bonds, namely ethyl acrylate, acrylic acid, acroleyne, styrene and cyclopentene. The reactions were carried out in an organic solvent, in the presence of $Pd(OAc)_2$ as pre-catalyst, and gave rise to arylated products, for example, ethyl cinnamates, cinnamic acids, cinnamic aldehydes and stilbenes, possessing an (*E*)-configuration, and 1-arylcyclopentenes, in good to excellent yields. It is noteworthy that all the reactions led to the recovery, in greater than 80% yield, of *o*-benzenedisulfonimide, recyclable for the preparation of other diazonium salts.

1. Introduction

As part of a broader project aimed at exploring the synthetic potential of a family of arenediazonium salts that are stable in the dry state, that is, the arenediazonium *o*-benzenedisulfonimides **1**,[1a,b] in this paper we have focused our attention on the reactivity of the said salts **1** as electrophilic reagents in Heck-type carbon–carbon coupling reactions.

Since 1970 through to the present day, the palladium-catalyzed arylation of olefins, activated or not, by aryl halides or triflates (the Heck reaction), has undergone wide development,[2] not only on the laboratory scale but also on the industrial scale for fine chemical production.[3]

The first electrophiles alternative to halides and triflates, tested in Heck-type coupling reactions, were the arenediazonium salts.[2–4] Further studies, especially over the past 15 years, have led to a marked increase in the synthetic value of diazonium salts in Heck-type reactions, compared with that of conventional reagents.[5,6] Indeed, there are many advantages associated with diazonium salts, particularly the greater reactivity of these salts, due to the fact that the diazonium group is a better nucleofuge than the halide or triflate:[5e,f,j] (a) the reactions do not require a base, or additional ligands, whose addition instead leads to uncontrolled decomposition of the salts themselves; (b) diazonium salts function under mild temperature conditions and for this reason are also suitable for reactions with thermally labile olefins; (c) reaction times are usually short; (d) coupling products are always obtained in high yields; (e) there is the possibility of aqueous one-pot procedures (tandem diazotization—Heck reactions) starting directly from the anilines;[4a,5j,6e] (f) the wide and ready availability of the starting compounds, that is, anilines, compared with the corresponding halides or triflates.

It has been demonstrated that the Heck-type reactions of arenediazonium salts are highly dependent on the nature of the diazonium counter-anion.[5g] The most commonly used salts are, by far, the tetrafluoroborates and, more recently, also the trifluoroacetates.[5b] However, it has been reported that perchlorates and fluorides also give good results, while, instead, halides and sulphates are totally inefficient for the Heck reactions.

Our present work highlights that dry arenediazonium *o*-benzenedisulfonimides **1** are a useful alternative to arenediazonium tetrafluoroborates in Heck-type carbon–carbon coupling reactions.

2. Results and discussion

A few years ago,[1] we reported that salts **1** can be prepared easily in excellent yields, by diazotization of primary aromatic amines with *i*-pentyl nitrite in the presence of *o*-benzenedisulfonimide (**6**), in glacial acetic acid or formic acid, at 0–10 °C. These salts, which are easily isolated in

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the dry state, show excellent stability at rt, and can therefore be kept safely, ready for use, for an unlimited time.

In the study described herein, a great variety of salts **1** in the dry state were reacted with some of the more common substrates used in the Heck reactions, for example, ethyl acrylate (**2**), acrylic acid (**3**), acroleyne (**4**), styrene (**5**) and cyclopentene (**11**), to give the corresponding arylation products, and therefore, ethyl cinnamates **7**, cinnamic acids **8**, cinnamic aldehydes **9**, stilbenes **10**, possessing an (*E*)-configuration, and 1-arylcyclopentenes **12** (Schemes 1 and 2). All reactions were carried out in an organic solvent, in the presence of $Pd(OAc)_2$, 1 mol% with respect to the reacting salt **1**, as the pre-catalyst. Note that in the present work we did not test any other catalyst/pre-catalyst different from $Pd(OAc)_2$. As already reported in the literature for other diazonium salts, also in these reactions no ligands were necessary; only in the case of acrylic acid (**3**) and acroleyne (**4**) it was necessary to work in the presence of an inorganic base. Tables 1–3 show the working conditions and the results of the reactions.

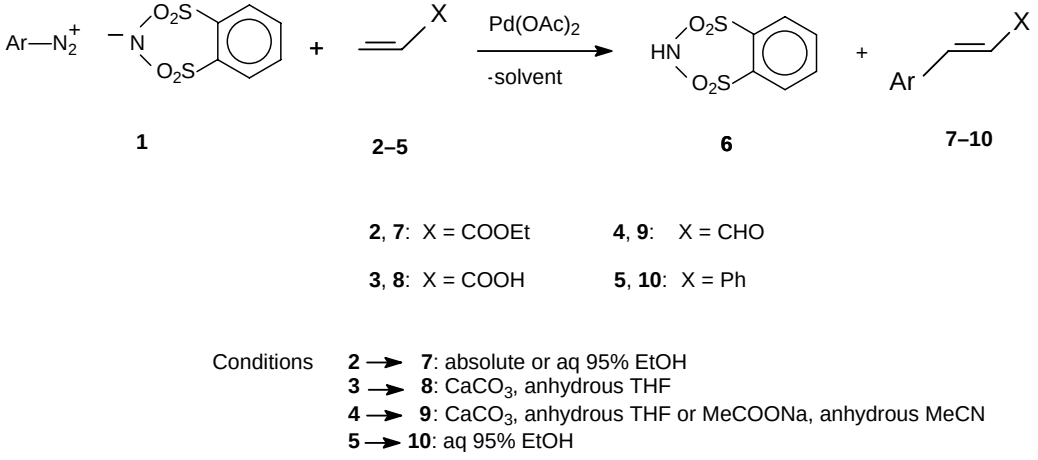
It is important to underline that all the reactions led to the recovery, in greater than 80% yield, of *o*-benzenedisulfonimide (**6**), recyclable for the preparation of other salts **1**.

2.1. Heck-type arylation of ethyl acrylate (2) with dry arenediazonium *o*-benzenedisulfonimides 1 to give (*E*)-ethyl cinnamates 7a–o

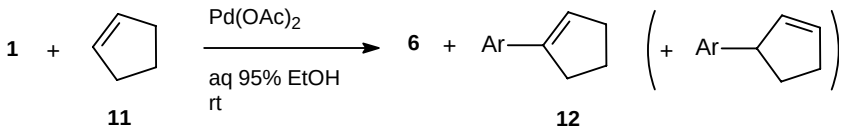
Cinnamic esters are compounds that are important industrially as UV absorbers, antioxidants in plastics and as key intermediates and starting materials in the synthesis of a great variety of pharmaceuticals, agrochemicals and fragrances.[7] Numerous methods for their preparation can be found in the literature. However, on an industrial scale, cinnamic esters are usually produced via Perkin and Claisen condensations of the corresponding aromatic aldehydes.[7b,8] An alternative and convenient synthesis of this class of compounds is the Heck arylation of acrylic esters with aryl halides.[2a] Such a reaction is also used on an industrial scale, for example, to prepare the most common UV-B sunscreen, namely 2-ethylhexyl 4-methoxycinnamate.[3]

It has been proposed that, instead of aryl halides in the Heck arylation to prepare cinnamic esters, arenediazonium salts could also be used,[4–6] mainly tetrafluoroborates, as such, or generated in situ starting from triazenes[5g,i] or anilines,[4a,c,6e] in the presence or absence of bases and with various palladium catalysts. As an alternative to the tetrafluoroborates, trifluoroacetates[5b] have also been proposed. Recently, (*E*)-cinnamic esters were also prepared by means of tandem Heck-esterification reactions, starting from arenediazonium tetrafluoroborates and acrylic acid in alcoholic solvents.[5h,6g]

In this work, numerous salts **1**, variously substituted, were reacted with ethyl acrylate (**2**), in a molar ratio of 1:1.2, in the presence of $Pd(OAc)_2$ (1 mol% with respect to salt **1**), as pre-catalyst. Two procedures for the preparation of ethyl cinnamates **7** were developed. The results can be found in Table 1. In procedure A the reactions were carried out in absolute EtOH, usually at 70 °C, and reached completion in short times of between 5 and 60 min (with the sole exception of entry 19 of Table 1, that required 2 h). Reaction completion was indicated by a negative test of azocoupling with 2-naphthol. Instead, in procedure B, the reactions were carried out in 95% aqueous EtOH at rt (20–25 °C) and the reaction times were much longer, varying from 30 min to 50 h. Both procedures proved to be general in that they gave positive results in the presence of both electron-withdrawing and electron-donating groups



Scheme 1. Heck-type arylation of ethyl acrylate (**2**), acrylic acid (**3**), acroleyne (**4**) and styrene (**5**).



Scheme 2. Heck-type arylation of cyclopentene (**11**).

Table 1. Ethyl cinnamates **7a–o**

Entry no.	Starting compound **1**	Ar in **1**, **7**	Procedure	*T* (°C)	Reaction time (min)	Product **7**	Yield (%)[a]	Yield (%) lit.[b]
1	**1a**	2-MeC_6H_4	A	70	5	**7a**	70	75–100[5g,6b]
2			B	rt	5 h		74	
3	**1b**	4-MeC_6H_4	A	70	30	**7b**	84	78–99[4c,5b,g,6b]
4			B	rt	2.5 h		95	
5	**1c**	2-$MeOC_6H_4$	A	70	15	**7c**	78[c]	75–97[5g,i,j]
6			A	rt	90		84	
7			B	rt	60		90	
8	**1d**	3-$MeOC_6H_4$	A	70	15	**7d**	29[d]	
9			A	rt	15 h		74	
10			B	rt	6 h		59	
11	**1e**	4-$MeOC_6H_4$	A	70	40	**7e**	84	68–98[5g–j]
12			B	rt	4 h		78	
13	**1f**	4-ClC_6H_4	A	70	15	**7f**	89	69–92[5h–j]
14			B	rt	30		89	
15	**1g**	3-BrC_6H_4	A	70	15	**7g**	87	
16			B	rt	30 h[e]		tr[f]	
17	**1h**	4-BrC_6H_4	A	70	60	**7h**	92	78–84[5g,j]
18			B	rt	30		92	
19	**1i**	4-IC_6H_4	A	70	2 h	**7i**	76	
20			B	rt	1.5 h		76	
21	**1j**	2-$NO_2C_6H_4$	A	70	15	**7j**	93	
22			B	rt	30		88	
23	**1k**	4-$NO_2C_6H_4$	A	70	5	**7k**	97	45–95[5b,6b]
24			B	rt	15		100	
25	**1l**	2-$HOOCC_6H_4$	A	70	45	**7l**	74	65[5j]
26			B	rt	5 h		88	
27	**1m**	4-CNC_6H_4	A	70	30	**7m**	73	
28			A	rt	17 h		97	
29			B	rt	51 h		42	
30	**1n**	2,4-$(NO_2)_2C_6H_3$	A	70	15	**7n**	80[g]	
31			B	rt	2.5 h		80[g]	
32	**1o**	2-MeOCO-3-thienyl	A	70	15	**7o**	81[h]	
33			B	rt	18 h		89	

[a] Yield of pure product after column chromatography.
[b] Range of yields reported in the literature, starting from tetrafluoroborates or trifluoroacetates.
[c] Ethyl 3,3-bis(2-methoxyphenyl)-2-propenoate was also isolated in 19% yield (0.09 g): MS *m/z* 312 (M^+); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34 (t, $J=7.1$ Hz, 3H), 3.70 (s, 6H), 4.29 (q, $J=7.1$ Hz, 2H), 6.45 (s,1H), 6.81–7.45 (m, 8H).
[d] Ethyl 3-methoxyphenyl ether was also isolated in 31% yield (0.07 g): MS *m/z* 152 (M^+).
[e] A test of azo coupling with 2-naphthol was still positive.
[f] tr=traces.
[g] 1,3-Dinitrobenzene was also isolated in 16% yield (0.07 g): MS *m/z* 168 (M^+).
[h] 2-Methoxycarbonylthiophene was also isolated in 10% yield (0.02 g): MS *m/z* 142 (M^+).

Table 2. Cinnamic acids **8a–d**, cinnamic aldehydes **9a–e** and stilbenes **10a–c**

Entry no.	Starting compound **1**	Ar in **1**, **8–10**	X in **3–5**, **8–10**	Solvent	Base	*T* (°C)	Reaction time (h)	Product **8–10**	Yield (%)[a]		
									8	**9**	**10**
1	**1b**	4-MeC_6H_4	COOH	THF	$CaCO_3$	60	12	**8a**	93		
2	**1e**	4-$MeOC_6H_4$	COOH	THF	$CaCO_3$	60	48[b]	**8b**	59		
3				MeCN	MeCOONa	60	6		67		
4	**1f**	4-ClC_6H_4	COOH	THF	$CaCO_3$	60	4.5	**8c**	96		
5	**1k**	4-$NO_2C_6H_4$	COOH	THF	$CaCO_3$	40	3.5	**8d**	55		
6	**1b**	4-MeC_6H_4	CHO	THF	$CaCO_3$	40	4.5	**9a**		95	
7	**1e**	4-$MeOC_6H_4$	CHO	THF	$CaCO_3$	40	26[b]	**9b**		tr[c]	
8				MeCN	MeCOONa	rt	3			83	
9	**1f**	4-ClC_6H_4	CHO	THF	$CaCO_3$	40	1.5	**9c**		92	
10	**1j**	2-$NO_2C_6H_4$	CHO	THF	$CaCO_3$	40	5.5	**9d**		87	
11	**1k**	4-$NO_2C_6H_4$	CHO	THF	$CaCO_3$	40	1	**9e**		91	
12	**1b**	4-MeC_6H_4	Ph	EtOH (95% aq)	—	70	14	**10a**			60[d]
13	**1e**	4-$MeOC_6H_4$	Ph	EtOH (95% aq)	—	70	40 min	**10b**			54[e]
14	**1k**	4-$NO_2C_6H_4$	Ph	EtOH (95% aq)	—	70	45 min	**10c**			83[f]

[a] Yield of pure product after column chromatography.
[b] The reaction was incomplete (a test of azo coupling with 2-naphthol was still positive).
[c] tr=traces.
[d] 1-(4-Tolyl)styrene was produced in 7% yield (see Section 4).
[e] 1-(4-Methoxyphenyl)styrene was produced in 16% yield (see Section 4).
[f] 1-(4-Nitrophenyl)styrene was produced in 6% yield (see Section 4).

Table 3. 1-Arylcyclopentenes **12a–i**

Entry no.	Starting compound **1**	Ar in **1**, **12**	Product **12**	Solvent	Reaction time at rt (min)	Yield (%)[a] of **12** (ratio 1-Ar:3-Ar)[b]		
						From **1**	From BF_4^-	From lit.
1	**1a**	2-MeC_6H_4	**12a**	EtOH (95% aq)	15	70 (97.4:2.6)		24 (0:100)[c,4c]
2	**1b**	4-MeC_6H_4	**12b**	EtOH (95% aq)	10	84 (100:0)	73 (94:6)	41 (70:30)[c,4a], 30 (54:46)[d,4a], 53 (50:50)[e,4a], 71 (50:50)[c,4c], 46 (10:90)[f,4c], 89 (5:95)[g,5b]
3	**1c**	2-$MeOC_6H_4$	**12c**	EtOH (95% aq)	10	81 (99:1)		
4	**1d**	3-$MeOC_6H_4$	**12d**	EtOH (95% aq)	20	77 (98.2:1.8)		
5	**1e**	4-$MeOC_6H_4$	**12e**	EtOH (95% aq)	15	89 (98.7:1.3)		30 (46:54)[c,4c], 31 (2:98)[f,4c]
6	**1f**	4-ClC_6H_4	**12f**	EtOH (95% aq)	10	83 (97.5:2.5)	73 (86:14)	35 (100:0)[f,4c], 75 (20:80)[h,5j], 72 (20:80)[g,5i], 10 (10:90)[d,4a], 49 (0:100)[c,4c]
7				MeCN	10	77 (31:63:6)[i]		
8				CH_2Cl_2	24 h[j]	[k]		
9	**1h**	4-BrC_6H_4	**12g**	EtOH (95% aq)	15	90 (100:0)		41 (99:1)[f,4c]
10	**1j**	2-$NO_2C_6H_4$	**12h**	EtOH (95% aq)	30	90 (100:0)		5 (0:100)[c,4c]
11	**1k**	4-$NO_2C_6H_4$	**12i**	EtOH (95% aq)	5	90 (100:0)	84 (79:21)	32 (5:95)[g,5b], 11 (0:100)[c,4a], 11 (0:100)[d,4c]
12				EtOH (absolute)	15	73 (100:0)		
13				THF	2.5 h[j]	89 (100:0)		

[a] Yield of pure product after column chromatography.
[b] Determined by GC analysis.
[c] From the tetrafluoroborate in MeCN, in the presence of $Pd(dba)_2$/MeCOONa.
[d] From the chloride in aqueous MeCN, in the presence of $LiPdCl_3$/HCOONa.
[e] As in note c, in the presence of $Pd(dba)_2$/HCOONa.
[f] As in note c, in CH_2Cl_2.
[g] From the trifluoroacetate in EtOH, in the presence of $Pd(dba)_2$.
[h] As in note g, starting from the tetrafluoroborate.
[i] GC ratio of regioisomers 1-Ar:3-Ar:4-Ar.
[j] At 40 °C.
[k] The reaction failed.

and independently of their position, whether *ortho*, *meta* or *para*, on the aromatic ring. In entries 6, 9 and 28, procedure A was carried out at rt: the reaction times were obviously longer, varying from 90 min to 17 h, but the arylation product yields were clearly much better. Procedure B failed in the case of 3-bromobenzenediazonium *o*-benzenedisulfonimide (**1g**; entry 16), and only in a few cases (entries 4, 7, 26 and 33), did it furnish higher yields with respect to those obtained with procedure A.

All the ethyl cinnamates **7a–o** were obtained exclusively with an (*E*)-configuration, in good to optimal yields. With procedure A the yields varied between 70 and 97% (the average yield on 15 considered examples was 84%), with procedure B the yields varied between 42 and 100% (the average yield on 14 considered examples was 81%). It is to be also noted that entries 15–20, involving salts containing a bromide or iodide substituent on the aromatic ring (**1g**,**h**,**i**), show high chemoselectivity in that the only diazonium group reacted, as demonstrated by the reaction products that were exclusively the ethyl 3- or 4-bromo(or iodo)cinnamates (**7g**,**h**,**i**); this is similar to that reported in the literature for the halide substituted tetrafluoroborates.[5e,f,j]

Still with regard to yields of ethyl cinnamates **7**, Table 1 shows that our yields, obtained using the dry arenediazonium *o*-benzenedisulfonimides **1**, are comparable with those reported in the literature starting from the corresponding arenediazonium tetrafluoroborates or trifluoroacetates, the sole exception being the 2-carboxybenzenediazonium *o*-benzenedisulfonimide (**1l**), which gave much higher yields (entries 25, 26). Furthermore, it is quite significant to note that all the nitrosubstituted benzenediazonium *o*-benzenedisulfonimides **1j**,**k**,**n** gave arylation products in excellent yields (81–100%, entries 21–24 and 30, 31). This stands in contrast with the difficulties reported in the literature starting from the corresponding nitrosubstituted tetrafluoroborates[4b,c,5a,j] or trifluoroacetates,[5b] in the presence of various palladium catalysts. To clarify this discordance we performed the Heck-arylation of ethyl acrylate (**2**) with 2-nitrobenzenediazonium and 4-nitrobenzenediazonium tetrafluoroborates under the same conditions as in entries 21 and, respectively, 23 and 24. These salts behaved in exactly the same way as the corresponding *o*-benzenedisulfonimides **1j** and **1k**, and ethyl cinnamates **7j** and **7k** were obtained in comparable yields (see Sections 4.8.1, 4.8.2 and 4.8.3). Note also that excellent yields were recently obtained on reacting 4-nitrobenzenediazonium tetrafluoroborate with acrylic esters using a new Pd(0) catalyst, that is, (*E*,*E*,*E*)-1-ferrocenylsulfonyl-6,11-bis[(4-methylphenyl)sulfonyl]-1,6,11-triazaciclopentadeca-3,8,13-trienepalladium(0), that is, however, of both elaborate and very expensive synthesis.[6b]

To substantiate the validity of the dry arenediazonium *o*-benzenedisulfonimides **1** as electrophiles in Heck-type arylations, reactions with other substrates containing C–C multiple bonds, that is, acrylic acid (**3**), acroleyne (**4**), styrene (**5**) and cyclopentene (**11**), were carried out.

2.2. Heck-type arylation of acrylic acid (3) and acroleyne (4) with dry arenediazonium *o*-benzenedisulfonimides 1 to give (*E*)-cinnamic acids 8a–d and (*E*)-cinnamic aldehydes 9a–e

There are few examples[5h,6g] of Heck-type coupling reactions of arenediazonium salts with acrylic acid (**3**). However, a recent patent[6e] reports the Heck arylation of **3** with various arenediazonium salts prepared in situ from the corresponding anilines; the aim of the patent was to prepare polyhalogenated cinnamic acids useful for the preparation of indanones, which are precursors of agro- and pharmaceutical chemicals, and of substances endowed with liquid-crystalline properties.

Some representative dry arenediazonium *o*-benzenedisulfonimides **1** were reacted with acrylic acid (**3**) in a molar ratio of 1:1.5 in anhydrous THF at 40–60 °C, in the presence of anhydrous $CaCO_3$ as the base (in equimolar amount with respect to the acid) and $Pd(OAc)_2$ (1 mol% with respect to the salt **1**) as pre-catalyst. The results are shown in Table 2 (entries 1–5). The reaction times were varied from 3.5 to 48 h. The use of anhydrous MeCN as the solvent, and of MeCOONa as the base, shortened the reaction times (compare entries 3 and 2). The cinnamic acids **8** were obtained exclusively in the (*E*)-configuration, the yields varying from 55 to 96% (the average yield on the five considered examples was 74%). The reaction of entry 2, carried out in the same reaction conditions but substituting THF with EtOH gave (*E*)-ethyl 4-methoxycinnamate (**7e**) via tandem Heck-esterification reactions (see Section 4.4.5), as reported in the literature starting from the tetrafluoroborates.[5h,6g]

Likewise, some representative (*E*)-cinnamic aldehydes **9** were prepared by reacting the dry salts **1** with acroleyne (**4**). The conditions and results are shown in Table 2 (entries 6–11). As can be seen, the reaction of 4-methoxybenzenediazonium *o*-benzenedisulfonimide (**1e**) failed in THF/$CaCO_3$ at 40 °C (entry 7), whereas there were good results in MeCN/MeCOONa at rt (entry 8). The average yield of the five considered examples was 90%.

With regard to the Heck arylation of acroleyne with diazonium salts, the only example reported in the literature is the one related to the synthesis of (*E*)-4-methoxycinnamic aldehyde (**9b**) that was obtained in 71% yield starting from 4-methoxybenzenediazonium tetrafluoroborate.[5a]

2.3. Heck-type arylation of styrene (5) with dry arenediazonium *o*-benzenedisulfonimides 1 to give (*E*)-stilbenes 10a–c

Amongst the most interesting substrates for Heck-type coupling reactions are styrene and the stilbenes, particularly in view of their use in the preparation of conjugated aromatic oligomers and polymers.[9] As stated for the acrylic esters, also many stilbenes have been prepared, always in good[4a,c,d,5b,e] to excellent[6b] yields, possessing an (*E*)-configuration, by the reaction of styrene with arenediazonium salts, mainly the tetrafluoroborates, as such[4c,5e,6b] or generated in situ by diazotization of anilines,[4a,d] but also trifluoroacetates,[5b] in the presence of various palladium catalysts/pre-catalysts.

In the present work, various salts **1** were reacted with styrene (**5**), in a molar ratio of 1:1.2, in the presence of $Pd(OAc)_2$, 1 mol% with respect to salt **1**, as pre-catalyst. The reactions, which were carried out in 95% aqueous EtOH at 70 °C, reached completion in times of between 40 min and 14 h, and were not completely regioselective. In fact, along with the stilbenes **10**, varying amounts of 1-arylstyrenes (6–16% yields) were also formed. However, column chromatography on the crude reaction mixtures, avoiding sunlight to prevent known photoisomerization,[9a] provided stilbenes **10a–c**, with an (*E*)-configuration exclusively, in good yields (from 54 to 83%). The results are shown in Table 2 (entries 12–14).

2.4. Heck-type arylation of cyclopentene (11) with dry arenediazonium *o*-benzenedisulfonimides 1 to give 1-arylcyclopentenes 12a–i

The palladium-catalyzed Heck-type arylations of cyclopentene with both aryl halides and arenediazonium salts usually result in a mixture of all the possible regioisomers, their formation being explained in terms of the isomerization of the initial arylation product that is the 3-arylcyclopentene.[4c]

To the best of our knowledge, the reactions carried out on the cyclopentene (**11**) with diazonium salts like the tetrafluoroborates,[4c,5j] chlorides[4a] or trifluoroacetates, as such[5b] or generated in situ,[5i] gave, in most cases, mixtures of two isomers, the 1-arylcyclopentenes and the 3-arylcyclopentenes, generally with a prevalence for the 3-aryl isomer, in low to modest yields. This is independent of the catalyst and the solvent used and of the type of substituent present on the diazonium salt (see Table 3). Only one report[4c] details the exclusive formation, or definite prevalence, of 1-aryl isomers, precisely 1-(4-chlorophenyl)cyclopentene (35% yield), and 1-(4-bromophenyl)cyclopentene (41% yield), 1-(3-tolyl)cyclopentene (27% yield) and 1-(3-chlorophenyl)cyclopentene (75% yield), contaminated, respectively, by 1, 6 and 10% of the 3-aryl isomers. These reactions were carried out on the tetrafluoroborates in CH_2Cl_2, at rt, in the presence of $Pd(dba)_2$/MeCOONa. For the reactions of salts **1** with **11**, we chose the conditions previously[5b,i,j] reported for the Heck reaction of cyclopentene, that is, at rt in EtOH and in the presence of $Pd(OAc)_2$. However, in the literature only five salts have been tested: 4-chlorobenzenediazonium tetrafluoroborate[5j] or trifluoroacetate[5i] and 4-(Boc-amino)benzenediazonium, 4-toluenediazonium and 4-nitrobenzenediazonium trifluoroacetates.[5b] The first two salts gave mixtures of the two isomers 1-aryl and 3-aryl, in a ratio of 1:5 (as shown by GC) in favor of the second, in yields of 75 and 72%, respectively. The other three salts gave 3-arylcyclopentenes contaminated by 5% (by ^{1}H NMR spectroscopy) of 1-aryl isomers, in yields of 77, 89 and 32%, respectively.

A variety of salts **1** were reacted with cyclopentene (**11**) in a molar ratio of 1:1.2, in 95% aqueous EtOH at rt in the presence of $Pd(OAc)_2$ (1 mol% with respect to salt **1**). The reactions proceeded to completion in short times (5–30 min) and gave the 1-arylcyclopentenes (**12**) as sole products (Table 3, entries 2, 9–13) or, in some cases, accompanied by small amounts of 3-arylcyclopentenes (GC analysis showed $<2.6\%$; entries 1, 3–6). The high selectivity of these

reactions were shown to be independent of the electron and steric effects of the substituents. Yields of the products **12** were excellent, varying between 70 and 90%; the average yield of the nine examples was 84%. To evaluate the effect of the solvent, 4-nitrobenzenediazonium *o*-benzenedisulfonimide (**1k**) was reacted with **11** also in absolute EtOH at rt, and in anhydrous THF at 40 °C (entries 12, 13). These reactions gave the sole isomer 1-(4-nitrophenyl)cyclopentene (**12i**), in yields just a little lower than or comparable to that of entry 11, carried out in 95% aqueous EtOH. With the same goal in mind, 4-chlorobenzenediazonium *o*-benzenedisulfonimide (**1f**) was reacted with **11** also in MeCN at rt and in CH_2Cl_2 at about 40 °C (entries 7, 8). The first reaction showed no selectivity in that it gave three isomers, that is, 1-aryl, 3-aryl and 4-aryl, in a ratio of 31:63:6 (as shown by GC) in favor of the 3-aryl. Instead the second reaction failed, probably because of the low solubility of the salt in the latter solvent. Also of particular note are the excellent yields (90%) obtained in entries 10 and 11 by reacting, respectively, 2-nitrobenzenediazonium and 4-nitrobenzenediazonium *o*-benzenedisulfonimides (**1j** and **1k**) with **11**. The literature, instead, reports that the Heck arylations of cyclopentene with nitrosubstituted arenediazonium salts always give low yields[4a,c,5b] (from 5 to 32%), the main reaction product always being nitrobenzene. To compare the reactivity of our salts **1** with that of the corresponding tetrafluoroborates, we always reacted some representative tetrafluoroborates, namelyl 4-toluenediazonium, 4-chlorobenzenediazonium and 4-nitrobenzenediazonium tetrafluoroborates, with **11**, in the conditions cited above for entries 2, 6, 11. In our hands, all three salts gave 1-aryl and 3-aryl isomer mixtures, with the first clearly prevailing; this is in disagreement with that reported in the literature. The results, shown in Table 3, highlight that, under the same reaction conditions, the selectivity of the tetrafluoroborates is lower than that of salts **1**.

3. Conclusion

In conclusion, this research has demonstrated the validity of a recent family of stable diazonium salts in the dry state, the arenediazonium *o*-benzenedisulfonimides **1**, as new and efficient reagents in Heck-type arylation reactions of several common substrates containing C–C multiple bonds, namely ethyl acrylate (**2**), acrylic acid (**3**), acroleyne (**4**), styrene (**5**) and cyclopentene (**11**). The proposed procedures are general in that they give positive results in the presence of both electron withdrawing and electron donating substituents, not suffering steric effects and affording arylation products, that is, ethyl cinnamates **7**, cinnamic acids **8**, cinnamic aldehydes **9**, stilbenes **10**, possessing an (*E*)-configuration, and 1-arylcyclopentenes **12**, in good to excellent yields. It is to be noted that in most of the reported reactions the salts **1** are in parallel[10] with the class of tetrafluoroborates, which are well-known from a long time, or the most recent trifluoroacetates. However, the use of the arenediazonium *o*-benzenedisulfonimides **1** has several advantages over the use of the other salts: (i) easy preparation and high stability, thus allowing them to be kept ready for use for long periods; (ii) possibility of recovery, at the end of the reactions, of *o*-benzenedisulfonimide (**6**), that unlike tetrafluoroboric or trifluoroacetic acids, is a non-risk acid that can be reused to prepare other salts **1**, with ecological and economic advantages. Once again it must be underlined that, with regard to the reactions of salts **1** with cyclopentene (**11**), our direct comparison of the two classes of salts, that is, salts **1** and the corresponding tetrafluoroborates, in the same reaction conditions, revealed still a parallel behavior, but there was a very clear synthetic superiority of the salts **1**, that led to the 1-arylcyclopentenes (**12**) with greater purity.

4. Experimental

4.1. General

All of the reactions were performed in oven-dried glassware when anhydrous solvent was used. No particular device was, however, adopted to exclude moisture or oxygen. Column chromatography and TLC were performed on Merck silica gel 60 (70–230 mesh ASTM) and GF 254, respectively. Petroleum ether refers to the fraction boiling in the range 40–60 °C and is abbreviated as PE. Room temperature (20–25 °C) is abbreviated as rt. Details for the reactions and yields of the pure (GC, GC–MS, TLC, ^{1}H NMR) isolated (*E*)-ethyl cinnamates **7a–o**, (*E*)-cinnamic acids **8a–d**, (*E*)-cinnamic aldehydes **9a–e**, (*E*)-stilbenes **10a–c**, and 1-arylcyclopentenes **12a–i** are listed in Tables 1–3. Structures and purity of all the products were confirmed by comparison of their physical (mp or bp) and spectral data (MS, ^{1}H NMR) with those reported in the literature or with those of the corresponding commercially available samples of analytical purity. All of the amines and olefins, solvents and all of the reference compounds were purchased from the Aldrich Chemical Co. Dowex 50X8 ion-exchange resin was purchased from Fluka.

4.2. Dry arenediazonium *o*-benzenedisulfonimides 1

Dry arenediazonium *o*-benzenedisulfonimides **1a–h**,**j**,**k**,[1a,b] **1i**,[11a] **1m**[11b] and **1n**[11c] were prepared as described previously. According to the same general procedure, the new salts 2-carboxybenzenediazonium *o*-benzenedisulfonimide (**1l**) and 2-methoxycarbonyl-3-tiophenediazonium *o*-benzenedisulfonimide (**1o**) were also prepared. The crude salts were pure (by ^{1}H NMR spectroscopy) and could be used in the subsequent Heck-type arylation, without further crystallization.

4.2.1. Dry 2-carboxybenzenediazonium *o*-benzenedisulfonimide (1l). Diazotization of 2-aminobenzoic acid (1.37 g, 10 mmol) was carried out with *i*-pentyl nitrite (1.29 g, 11 mmol) in HCOOH (30 ml), in the presence of *o*-benzenedisulfonimide (**6**; 2.63 g, 12 mmol), at 0–5 °C. The virtually pure (^{1}H NMR, dp=decomposition point) title compound was obtained in >99% yield (3.67 g). For analytical purposes, a sample was purified by dissolution in HCOOH and precipitation with anhydrous Et_2O after cooling: dp 135 °C; MS *m*/*z* 367 (M^+); ^{1}H NMR (200 MHz, CD_3CN/CD_3COCD_3): δ 7.64–7.78 (m, 4H), 8.14 (t, J=8.0 Hz, 1H), 8.34 (t, J=8.0 Hz, 1H), 8.44 (ddd, J=7.7, 1.5 Hz, 1H), 8.69 ppm (ddd, J=8.3, 1.2 Hz, 1H); ^{13}C NMR (D_2O/DCl): δ 115.5 (s), 122.4 (d, 2C), 132.8 (s), 134.7 (d), 135.3 (d, 2C), 136.6 (d, 2C), 141.2 (s, 2C), 142.3 (d), 163.6 (s). Anal. Calcd for $C_{13}H_9N_3O_6S_2$ (367.35): C,

42.51; H, 2.47; N, 11.44; S, 17.45. Found: C, 42.44; H, 2.51; N, 11.33; S, 17.40.

4.2.2. Dry 2-methoxycarbonyl-3-tiophenediazonium *o*-benzenedisulfonimide (1o). Yield: 97% (3.76 g); dp 161.6–162.8 °C; MS *m/z* 359 ($M^+ - N_2$); ^{1}H NMR (200 MHz, CD_3CN/CD_3COCD_3): δ 4.04 (s, 3H), 7.61–7.72 (m, 4H), 8.16 (d, $J=5.6$ Hz, 1H), 8.19 (d, $J=5.6$ Hz, 1H); ^{13}C NMR ($D_2O/DCl/CD_3COCD_3$): δ 51.4 (q), 103.6 (s), 118.0 (d, 2C), 125.4 (d), 131.0 (d, 2C), 132.5 (d), 135.6 (s, 2C), 145.4 (s), 154.3 (s). Anal. Calcd for $C_{12}H_9N_3O_6S_3$ (387.40): C, 37.20; H, 2.34; N, 10.85; S, 24.83. Found:C, 37.15; H, 2.28; N, 10.77; S, 24.77.

CAUTION! In our laboratory was no case of sudden decomposition during the preparation, purification, and handling of salts **1**. Nevertheless it must be born in mind that all diazonium salts in the dry state are potentially explosive. Therefore, they must be carefully stored and handled.

4.3. Heck-type reactions of dry arenediazonium *o*-benzenedisulfonimides 1 with ethyl acrilate (2); representative procedures

4.3.1. Procedure A. (*E*)-Ethyl 4-nitrocinnamate (7k). In entry 23 of Table 1, 4-nitrobenzenediazonium *o*-benzenedisulfonimide (**1k**; 0.55 g, 1.5 mmol) was added in one portion with stirring to a solution of ethyl acrilate (**2**; 0.18 g, 1.8 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in absolute EtOH (15 ml) and the reaction mixture was placed in an oil bath at 70 °C. The salt dissolved at once, and the resultant solution became temporarily deep red and then turned quickly to brown; simultaneously, a plentiful evolution of nitrogen took place. A test of azo coupling with 2-naphthol was negative 5 min after the addition of the salt. This confirmed a sudden reaction of **1k**. TLC (PE/Et_2O, 7:3), GC, and GC–MS analyses of the reaction mixture showed the presence of the title compound as major product, beside the unreacted ethyl acrilate. The reaction mixture was evaporated under reduced pressure and the residue was poured into Et_2O–H_2O (40 ml, 1:1). The aqueous layer was separated and extracted with Et_2O (2×20 ml). The combined organic extracts were washed with H_2O (20 ml), dried over Na_2SO_4, and evaporated under reduced pressure. The crude residue was chromatographed on a short column (PE/Et_2O, 7:3) to provide the pure (GC, GC–MS, TLC, ^{1}H NMR) title compound in 97% yield (0.32 g); mp 138.5–139 °C, from EtOH; MS *m/z* 221 (M^+); physical and ^{1}H NMR data identical to those of a commercially available sample of analytical purity.

The aqueous layer and aqueous washings were collected and evaporated under reduced pressure. The residue was passed through a column of Dowex 50X8 ion-exchange resin (1.6 g for 1 g of product), eluting with H_2O (about 35 ml). After removal of H_2O under reduced pressure, virtually pure (^{1}H NMR) *o*-benzenedisulfonimide (**6**) was recovered in 85% yield (0.28 g); mp 192–194 °C, from toluene (lit.[1a] mp 192–194 °C).

4.3.2. Procedure B. (*E*)-Ethyl 4-nitrocinnamate (7k). The procedure B differs from the former only for the solvent (95% aqueous EtOH) and for the reaction temperature (rt). The title compound obtained by chromatography of the crude residue, had physical and ^{1}H NMR spectroscopic data identical to those of the above product.

Details for the reactions and yields of products **7a–o** are listed in Table 1.

4.3.3. (*E*)-Ethyl 2-methylcinnamate (7a). Chromatographic solvent: PE/Et_2O, 9:1; colorless oil: bp 130 °C/1.5 mmHg (lit.[12] bp 148 °C/1.2 mmHg); MS *m/z* 190 (M^+); ^{1}H NMR spectroscopic data identical to that reported.[6b]

4.3.4. (*E*)-Ethyl 4-methylcinnamate (7b). Chromatographic solvent: PE/Et_2O, 9:1; colorless oil: bp 147 °C/2 mmHg; MS *m/z* 190 (M^+); physical and ^{1}H NMR spectroscopic data identical to those of a commercially available sample of analytical purity (Aldrich).

4.3.5. (*E*)-Ethyl 2-methoxycinnamate (7c). Chromatographic solvent: PE/Et_2O, 4:1; mp 33–34 °C, from PE (lit.[13] mp 35 °C); MS *m/z* 206 (M^+); ^{1}H NMR spectroscopic data identical to those reported.[14]

4.3.6. (*E*)-Ethyl 3-methoxycinnamate (7d). Chromatographic solvent: PE/Et_2O, 4:1; colorless oil: bp 145 °C/1.5 mmHg (lit.[12] bp 185–186 °C/15 mmHg); MS *m/z* 206 (M^+); ^{1}H NMR spectroscopic identical to that reported.[14]

4.3.7. (*E*)-Ethyl 4-methoxycinnamate (7e). Chromatographic solvent: PE/Et_2O, 7:3; mp 49.5–51 °C, from PE (lit.[12] mp 49–50 °C); MS *m/z* 206 (M^+); ^{1}H NMR spectroscopic data identical to that reported.[15]

4.3.8. (*E*)-Ethyl 4-chlorocinnamate (7f). Chromatographic solvent: PE/Et_2O, 9:1; colorless oil: bp 136–137 °C/0.8 mmHg (lit.[13] bp 160 °C/11 mmHg); MS *m/z* 210 (M^+); ^{1}H NMR spectroscopic data identical to that reported.[15]

4.3.9. (*E*)-Ethyl 3-bromocinnamate (7g). Chromatographic solvent: PE/Et_2O, 9:1; mp 37 °C, from EtOH (lit.[12,16] oil); MS *m/z* 254 (M^+); ^{1}H NMR spectroscopic data identical to that reported.[16]

4.3.10. (*E*)-Ethyl 4-bromocinnamate (7h). Chromatographic solvent: PE/Et_2O, 9:1; colorless oil: bp 158 °C/1.5 mmHg; MS *m/z* 254 (M^+); physical and ^{1}H NMR spectroscopic data identical to those of a commercially available sample of analytical purity.

4.3.11. (*E*)-Ethyl 4-iodocinnamate (7i). Chromatographic solvent: PE/Et_2O, 9:1; mp 35–36 °C, from PE (lit.[17] mp 38–39 °C); MS *m/z* 302 (M^+); ^{1}H NMR spectroscopic data identical to that reported.[17]

4.3.12. (*E*)-Ethyl 2-nitrocinnamate (7j). Chromatographic solvent: PE/Et_2O, 7:3; mp 42–43 °C, from EtOH (lit.[12] mp 44 °C); MS *m/z* 221 (M^+); ^{1}H NMR spectroscopic data identical to that reported.[15]

4.3.13. (*E*)-Ethyl 2-carboxycinnamate (7l). Chromatographic solvent: $CHCl_3$/MeOH, 9.5:0.5; mp 85.5–86.5 °C, from $CHCl_3$/PE (lit.[12] mp 95 °C); MS *m/z* 220 (M^+); ^{1}H

NMR ($CDCl_3$, 200 Hz): δ 1.41 (t, J=7.1 Hz, 3H), 4.36 (q, J=7.1 Hz, 2H), 6.39 (d, J=15.9 Hz, 1H), 8.63 (d, J=15.9 Hz, 1H), 7.61–7.70 (m, 3H), 8.19 (m, 1H).

4.3.14. (*E*)-Ethyl 4-cianocinnamate (7m). Chromatographic solvent: PE/Et_2O, 3:2; mp 69–69.3 °C, from EtOH; MS *m/z* 201 (M^+); physical and ^1H NMR spectroscopic data identical to those of a commercially available sample of analytical purity.

4.3.15. (*E*)-Ethyl 2,4-dinitrocinnamate (7n). Chromatographic solvent: PE/Et_2O, 3:2; mp 94.6–95.4 °C, from EtOH (lit.[12] mp 94 °C); MS *m/z* 266 (M^+); ^1H NMR spectroscopic data identical to that reported.[18]

4.3.16. (*E*)-Ethyl 3-(2-methoxycarbonyl-3-thienyl)pronenoate (7o). Chromatographic solvent: PE/Et_2O, 7:3; mp 65.5–66 °C, from PE; MS *m/z* 240 (M^+); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34 (t, J=7.1 Hz, 3H), 3.92 (s, 3H), 4.28 (q, J=7.1 Hz, 2H), 6.38 (d, J=15.8 Hz, 1H), 8.51 (d, J=15.8 Hz, 1H), 7.35 (d, J=5.3 Hz, 1H), 7.47 (d, J=5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.5 (q), 52.5 (q), 60.9 (t), 122.3 (d), 126.8 (d), 131.0 (d), 131.3 (s), 136.7 (d), 142.1 (s), 162.5 (s), 166.9 (s). Anal. Calcd for $C_{11}H_{12}O_4S$ (240.27): C, 54.99; H, 5.03; S, 13.34. Found C, 55.02; H, 5.06; S, 13.40.

4.4. Heck-type reactions of dry arenediazonium *o*-benzenedisulfonimides 1 with acrilic acid (3); representative procedures

4.4.1. (*E*)-4-Methylcinnamic acid (8a). In entry 1 of Table 2, the reaction mixture constituted of 4-toluenediazonium *o*-benzenedisulfonimide (**1b**; 0.51 g, 1.5 mmol), acrilic acid (**3**; 0.16 g, 2.25 mmol), anhydrous $CaCO_3$ (0.22 g, 2.25 mmol), and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in anhydrous THF (15 ml) and maintained under stirring, was placed in an oil bath at 60 °C. The reaction reached completion after 12 h (absence of azo coupling with 2-naphthol). The reaction mixture was evaporated under reduced pressure and then dissolved into a 5% aqueous NaOH solution (5–10 ml). The aqueous layer was extracted with Et_2O (3×20 ml) and then acidified with dil HCl until complete precipitation of **8a**, which was extracted with Et_2O (3×20 ml). The combined organic extracts were washed with H_2O (20 ml), dried over Na_2SO_4, and evaporated under reduced pressure. The title compound was obtained virtually pure in 88% yield (0.21 g); mp 195.0–196.5 °C, from MeCOMe; MS *m/z* 162 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity. Working as described above, pure *o*-benzenedisulfonimide (**6**) was recovered in 80% yield (0.26 g).

4.4.2. (*E*)-4-Methoxycinnamic acid (8b). In entry 3 of Table 2, the reaction mixture constituted of 4-methoxybenzenediazonium *o*-benzenedisulfonimide (**1e**; 0.53 g, 1.5 mmol), acrilic acid (**3**; 0.16 g, 2.25 mmol), anhydrous MeCOONa (0.25 g, 3.0 mmol), and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in anhydrous MeCN (10 ml) and maintained under stirring, was placed in an oil bath at 60 °C. The reaction reached completion after 6 h (absence of azo coupling with 2-naphthol). The above work-up provided the virtually pure title compound in 67% yield (0.18 g); mp 169.0–170.5 °C, from aqueous EtOH; MS *m/z* 178 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity. Pure *o*-benzenedisulfonimide (**6**) was recovered in 80% yield (0.26 g).

Details for the reactions and yields of products **8a–d** are listed in Table 2 (entries 1–5).

4.4.3. (*E*)-4-Chlorocinnamic acid (8c). Prepared according to the procedure described above for **8a**, starting from **1f**. Mp 249–250.3 °C, from EtOH; MS *m/z* 182 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity (Aldrich).

4.4.4. (*E*)-4-Nitrocinnamic acid (8d). Prepared according to the procedure described above for **8a**, starting from **1k**. Mp 291.5–292.6 °C, from EtOH (lit.[19] mp 286–287 °C); MS *m/z* 193 (M^+); ^1H NMR identical to that reported.[19]

4.4.5. (*E*)-Ethyl 4-methoxycinnamate (7e). According to the procedure A described above for the preparation of (*E*)-ethyl 4-nitrocinnamate (**7k**), a reaction mixture constituted of 4-methoxybenzenediazonium *o*-benzenedisulfonimide (**1d**; 0.53 g, 1.5 mmol), acrilic acid (**3**; 0.13 g, 1.80 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in absolute EtOH (15 ml) and maintained under stirring, was placed in an oil bath at 70 °C. The reaction was complete after 30 min (absence of azo coupling with 2-naphthol). TLC ($CHCl_3$), GC, and GC–MS analyses of the reaction mixture showed the presence of the title compound as major product. The crude residue, obtained after the usual work up, was chromatographed on a short column, eluting with $CHCl_3$. Compound **7e** was obtained pure in 52% yield (0.16 g); mp 49.5–51 °C, from PE; MS *m/z* 206 (M^+); physical and ^1H NMR data identical to those of the sample reported in Section 4.3.7.

4.5. Heck-type reactions of dry arenediazonium *o*-benzenedisulfonimides 1 with acroleyne (4); representative procedures

4.5.1. (*E*)-4-Methylcinnamic aldehyde (9a). In entry 6 of Table 2, the reaction mixture constituted of 4-toluenediazonium *o*-benzenedisulfonimide (**1b**; 0.51 g, 1.5 mmol), acroleyne (**4**; 0.13 g, 2.25 mmol), anhydrous $CaCO_3$ (0.22 g, 2.25 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in anhydrous THF (15 ml) and maintained under stirring, was placed in an oil bath at 40 °C. The reaction reached completion after 4.5 h (absence of azo coupling with 2-naphthol). TLC (PE), GC, and GC–MS analyses of the reaction mixture showed the presence of **9a** as major product, beside the unreacted starting acroleyne. A work-up identical to that decribed above for *E*-ethyl 4-nitrocinnamate (**7k**), afforded a crude residue that was chromatographed on a short column (PE/Et_2O, 4:1). The title compound **9a** was obtained pure in 95% yield (0.21 g); mp 43.4–44.5 °C, from aqueous EtOH; MS *m/z* 146 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity. Pure *o*-benzenedisulfonimide (**6**) was recovered in 80% yield (0.26 g).

4.5.2. (*E*)-4-Methoxycinnamic aldehyde (9b). In entry 8 of Table 2, the reaction mixture constituted of 4-methoxybenzenediazonium *o*-benzenedisulfonimide (**1e**; 0.53 g, 1.5 mmol), acroleyne (**4**; 0.13 g, 2.25 mmol), anhydrous MeCOONa (0.13 g, 1.5 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in anhydrous MeCN (10 ml) was stirred at rt for 3 h, until completion of the reaction (absence of azo coupling with 2-naphthol). The crude residue, obtained after the above work-up, was chromatographed through a short column (PE/Et_2O, 7:3) to provide the pure title compound **9b** in 83% yield (0.20 g); mp 58.5–59.8 °C, from PE; MS *m*/*z* 162 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity. Pure *o*-benzenedisulfonimide (**6**) was recovered in 85% yield (0.28 g).

4.5.3. (*E*)-4-Chlorocinnamic aldehyde (9c). Prepared as described above for **9a**, starting from **1f**. Chromatographic solvent: PE/Et_2O, 4:1; mp 61–62 °C, from EtOH; MS *m*/*z* 166 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity (Aldrich).

4.5.4. (*E*)-2-Nitrocinnamic aldehyde (9d). Prepared as described above for **9a**, starting from **1j**. Chromatographic solvent: PE/Et_2O, 3:2; mp 126.8–127.1 °C, from EtOH; MS *m*/*z* 177 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity (Aldrich).

4.5.5. (*E*)-4-Nitrocinnamic aldehyde (9e). Prepared as described above for **9a**, starting from **1k**. Chromatographic solvent: PE/Et_2O, 3:2; mp 137–138.2 °C, from $CHCl_3$/PE; MS *m*/*z* 177 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity (Aldrich).

Details for the reactions and yields of products **9a–e** are listed in Table 2 (entries 6–11).

4.6. Heck-type reactions of dry arenediazonium *o*-benzenedisulfonimides 1 with styrene (5); representative procedure

4.6.1. (*E*)-4-Nitrostilbene (10c). In entry 14 of Table 2, the reaction mixture constituted of 4-nitrobenzenediazonium *o*-benzenedisulfonimide (**1k**; 0.55 g, 1.5 mmol), styrene (**5**; 0.19 g, 1.8 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in 95% aqueous EtOH (15 ml) and maintained under stirring, was placed in an oil bath at 70 °C. The reaction reached completion after 45 min (absence of azo coupling with 2-naphthol). GC–MS analysis of the crude residue, obtained after a work-up identical to that described above for (*E*)-ethyl 4-nitrocinnamate (**7k**), showed the presence of three products: nitrobenzene, MS *m*/*z* 123 (M^+), 1-(4-nitrophenyl)-1-phenylethylene, MS *m*/*z* 225 (M^+), and (*E*)-4-nitrostilbene, MS *m*/*z* 225 (M^+), as major product. These were isolated by chromatography on a short column (PE/Et_2O, 4:1), sheltered from the sunlight. The first eluted product was nitrobenzene (0.02 g, 10% yield). The second eluted product was 1-(4-nitrophenyl)-styrene (0.02 g, 6% yield); ^1H NMR ($CDCl_3$, 200 MHz): δ 5.50 (s, 1H), 5.53 (s, 1H), 7.20–7.40 (m, 5H), 7.50 (d, J=9.0 Hz, 2H), 8.20 (d, J=9.0 Hz, 2H). The third eluted product was the title compound **10c** (0.28 g, 83%); mp 157.2–157.8, from EtOH (lit.[12] mp 155 °C); ^1H NMR identical to that reported.[5b] Pure *o*-benzenedisulfonimide (**6**) was recovered in 85% yield (0.28 g).

Details for the reactions and yields of products **10a–c** are listed in Table 2 (entries 12–14).

4.6.2. (*E*)-4-Methylstilbene (10a). Chromatographic solvent: PE/Et_2O, 3:2; mp 118.5–119 °C, from EtOH; MS *m*/*z* 194 (M^+); physical and ^1H NMR data identical to those of a commercially available sample of analytical purity. The by product 1-(4-tolyl)styrene was isolated in 7% yield (0.02 g); MS: *m*/*z*=194 (M^+); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.36 (s, 3H), 5.40 (d, J=1.6 Hz, 1H), 5.42 (d, J=1.6 Hz, 1H), 7.13 (d, J=8.3 Hz, 2H), 7.23 (d, J=8.30 Hz, 2H), 7.22–7.32 (m, 5H).

4.6.3. (*E*)-4-Methoxystilbene (10b). Chromatographic solvent: PE/Et_2O, 3:2; mp 136–136.5 °C, from EtOH (lit.[12] mp 137 °C); MS *m*/*z* 210 (M^+); ^1H NMR identical to that reported.[5b] The by product 1-(4-methoxyphenyl)-styrene was isolated in 16% yield (0.05 g); MS *m*/*z* 210 (M^+); ^1H NMR ($CDCl_3$, 200 MHz): δ 3.82 (s, 3H), 5.35 (d, J=1.7 Hz, 1H), 5.39 (d, J=1.7 Hz, 1H), 6.86 (d, J=8.7 Hz, 2H), 7.27 (d, J=8.7 Hz, 2H), 7.32–7.34 (m, 5H).

4.7. Heck-type reactions of dry arenediazonium *o*-benzenedisulfonimides 1 with cyclopentene (11); representative procedure

4.7.1. 1-(4-Nitrophenyl)cyclopentene (12i). In entry 11 of Table 3, the reaction mixture constituted of 4-nitrobenzenediazonium *o*-benzenedisulfonimide (**1k**; 0.55 g, 1.5 mmol), cyclopentene (**11**; 0.12 g, 1.8 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in 95% aqueous EtOH (15 ml) was stirred at rt until completion of the reaction (5 min; absence of azo coupling with 2-naphthol). TLC (PE/Et_2O, 9:1), GC, and GC–MS analyses of the crude residue, obtained after a work-up identical to that described above for (*E*)-ethyl 4-nitrocinnamate (**7k**), showed the presence of **12i**, as only arylation product. By chromatography on a short column (PE/Et_2O, 9:1), the title compound was obtained pure in 89.3% yield (0.25 g); mp 99.4–100 °C, from PE; MS *m*/*z* 189 (M^+); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.99–2.14 (apparent quintet, 2H), 2.56–2.60 (m, 2H), 2.70–2.78 (m, 2H), 6.42 (m, 1H), 7.54 (d, J=8.3 Hz, 2H), 8.16 (d, J=8.3 Hz, 2H). Anal. Calcd for $C_{11}H_{11}NO_2$ (189.21): C, 69.83; H, 5.86; N, 7.40. Found C, 69.79; H, 5.82; N, 7.35. Compound **12i** has been mentioned in the literature,[4a,e,5b] but it was not isolated and its physical and spectral data were not reported. Pure *o*-benzenedisulfonimide (**6**) was recovered in 85% yield (0.28 g).

Details for the reactions and yields and purity of products **12a–i** are listed in Table 3.

4.7.2. 1-(2-Tolyl)cyclopentene (12a). Chromatographic solvent: PE. GC and GC–MS analyses showed a slight contamination (2.6%) of the regioisomer 3-(2-tolyl)cyclopentene (confirmed by ^1H NMR). Colorless oil: bp 144 °C/4 mmHg (lit.[20] bp 122–123 °C/25 mmHg); MS *m*/*z* 158

(M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.96–2.07 (apparent quintet, 2H), 2.36 (s, 3H), 2.49–2.56 (m, 2H), 2.62–2.70 (m, 2H), 5.78 (m, 1H), 7.18–7.28 (m, 4H); identical to that reported.[21]

4.7.3. 1-(4-Tolyl)cyclopentene (12b). Chromatographic solvent: PE/Et_2O, 9.8:0.2; mp 51.8–52 °C, from EtOH (lit.[22] mp 50–51 °C); MS *m/z* 158 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.97–2.08 (apparent quintet, 2H), 2.33 (s, 3H), 2.44–2.60 (m, 2H), 2.60–2.76 (m, 2H), 6.13 (m, 1H), 7.12 (d, J=8.3 Hz, 2H), 7.33 (d, J=8.3 Hz, 2H); identical to that reported.[23]

4.7.4. 1-(2-Methoxyphenyl)cyclopentene (12c). Chromatographic solvent: PE/Et_2O, 9.8:0.2. GC and GC–MS analyses showed a slight contamination (1%) of the regioisomer 3-(2-methoxyphenyl)cyclopentene (confirmed by ^{1}H NMR). Colorless oil: bp 122 °C/1.8 mmHg (lit.[24] bp 65 °C/0.05 mmHg); MS *m/z* 174 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.85–2.10 (apparent quintet, 2H), 2.48–2.68 (m, 2H), 2.68–2.85 (m, 2H), 3.87 (s, 3H), 6.44 (m, 1H), 6.82–7.00 (m, 2H), 7.12–7.34 (m, 2H); identical to that reported.[24]

4.7.5. 1-(3-Methoxyphenyl)cyclopentene (12d). Chromatographic solvent: PE/Et_2O, 9.8:0.2. GC and GC–MS analyses showed a slight contamination (1.8%) of the regioisomer 3-(3-methoxyphenyl)cyclopentene (confirmed by ^{1}H NMR). Colorless oil: bp 143–144 °C/2 mmHg (lit.[25] bp 129–131 °C/13 mmHg); MS *m/z* 174 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.02–2.10 (apparent quintet, 2H), 2.50–2.65 (m, 2H), 2.65–2.85 (m, 2H), 3.86 (s, 3H), 6.22 (m, 1H), 6.75–6.85 (m, 1H), 6.98–7.12 (m, 2H), 7.20–732 (m, 1H); identical to that reported.[25]

4.7.6. 1-(4-Methoxyphenyl)cyclopentene (12e). Chromatographic solvent: PE/Et_2O, 9.8:0.2. GC and GC–MS analyses showed a slight contamination (1.3%) of the regioisomer 3-(4-methoxyphenyl)cyclopentene (confirmed by ^{1}H NMR). After crystallization from EtOH, the title compound was obtained pure: mp 90.9–91.3 °C (lit.[22] mp 89–90 °C); MS *m/z* 174 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.97–2.04 (apparent quintet, 2H), 2.47–2.58 (m, 2H), 2.63–2.70 (m, 2H), 3.81 (s, 3H), 6.04 (m, 1H), 6.84 (d, J=9.3 Hz, 2H), 7.37 (d, J=9.3 Hz, 2H); identical to that reported.[21]

4.7.7. 1-(4-Chlorophenyl)cyclopentene (12f). Chromatographic solvent: PE/Et_2O, 9.8:0.2. GC and GC–MS analyses showed a slight contamination (2.5%) of the regioisomer 3-(4-chlorophenyl)cyclopentene (confirmed by ^{1}H NMR). After crystallization from EtOH, the title compound was obtained pure: mp 73.2–73.6 (lit.[4c] mp 74–74.5 °C); MS *m/z* 178 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.89–2.03 (apparent quintet, 2H), 2.41–2.52 (m, 2H), 2.56–2.67 (m, 2H), 6.11 (m, 1H), 7.21 (d, J=8.6 Hz, 2H), 7.28 (d, J=8.6 Hz, 2H).

4.7.8. 1-(4-Bromophenyl)cyclopentene (12g). Chromatographic solvent: PE/Et_2O, 9.5:0.5; mp 94.6–95.4 °C, from EtOH (lit.[26] mp 97–98 °C); MS *m/z* 222 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.85–2.18 (apparent quintet, 2H), 2.44–2.60 (m, 2H), 2.60–2.76 (m, 2H), 6.18 (m, 1H), 7.29 (d, J=8.7 Hz, 2H), 7.42 (d, J=8.7 Hz, 2H).

4.7.9. 1-(2-Nitrophenyl)cyclopentene (12h). Chromatographic solvent: PE/Et_2O, 9:1; colorless liquid: bp 122 °C/1.5 mmHg; MS *m/z* 189 (M^+); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.99–2.06 (apparent quintet, 2H), 2.47–2.60 (m, 4H), 5.83 (m, 1H), 7.32–7.40 (m, 2H), 7.45–7.55 (m, 1H), 7.71–7.76 (m, 1H). Anal. Calcd for $C_{11}H_{11}NO_2$ (189.21): C, 69.83; H, 5.86; N, 7.40. Found C, 69.87; H, 5.90; N, 7.43.

4.8. Heck-type reactions of dry arenediazonium tetrafluoroborates with ethyl acrilate (2) and cyclopentene (11); representative procedures

4.8.1. (*E*)-Ethyl 4-nitrocinnamate (7k). According to procedure A described above for entry 23 of Table 1, 4-nitrobenzenediazonium tetrafluoroborate[27] (0.36 g, 1.5 mmol) was added in one portion with stirring to a solution of ethyl acrilate (**2**; 0.18 g, 1.8 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in absolute EtOH (15 ml) and the reaction mixture was placed in an oil bath at 70 °C. A test of azo coupling with 2-naphthol was negative 15 min after the addition of the salt. Usual work up provided the pure (GC, GC–MS, TLC, ^{1}H NMR) title compound in 93% yield (0.31 g); physical and ^{1}H NMR data were identical to those of the sample reported in Section 4.3.1.

4.8.2. (*E*)-Ethyl 4-nitrocinnamate (7k). According to procedure B described above for entry 24 of Table 1, the above reaction mixture in 95% aqueous EtOH (15 ml) was stirred at rt until absence of azo coupling with 2-naphthol (30 min). Usual work up provided the pure (GC, GC–MS, TLC, ^{1}H NMR) title compound in 100% yield (0.33 g); physical and ^{1}H NMR data were identical to those of the sample reported in Section 4.3.1.

4.8.3. (*E*)-Ethyl 2-nitrocinnamate (7j). According to procedure A described above for entry 21 of Table 1, a mixture constituted of 2-nitrobenzenediazonium tetrafluoroborate[27] (0.36 g, 1.5 mmol), ethyl acrilate (**2**; 0.18 g, 1.8 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in absolute EtOH (15 ml) and maintained under stirring, was placed in an oil bath at 70 °C, until completion of the reaction (15 min). Usual work up provided the pure (GC, GC–MS, TLC, ^{1}H NMR) title compound in 100% yield (0.33 g); physical and ^{1}H NMR data were identical to those of the sample reported in Section 4.3.12.

4.8.4. 1-(4-Tolyl)cyclopentene (12b). According to the general procedure described above for entry 11 of Table 3, a mixture constituted of 4-toluenediazonium tetrafluoroborate[27] (0.31 g, 1.5 mmol), cyclopentene (**11**; 0.12 g, 1.8 mmol) and $Pd(OAc)_2$ (1 mol%; 0.004 g, 0.015 mmol) in aqueous 95% EtOH (15 ml), was stirred at rt until completion of the reaction (10 min; absence of azo coupling with 2-naphthol). After the usual work up, the crude residue was column chromatographed, eluting with PE/Et_2O, 9.8:0.2, to afford a mixture (0.21 g, 73% yield) of the title compound **12b** and the regioisomer 3-(4-tolyl)cyclopentene (confirmed by ^{1}H NMR analysis), in a 94:6 GC ratio.

4.8.5. 1-(4-Chlorophenyl)cyclopentene (12f). The reaction was carried out as described above, starting from

4-chlorobenzenediazonium tetrafluoroborate[27] (0.34 g, 1.5 mmol) and was complete after 10 min at rt. After the usual work up, the crude residue was column chromatographed, eluting with PE/Et_2O, 9.5:0.5, to afford a mixture (0.19 g, 73% yield) of the title compound **12f** and the regioisomer 3-(4-chlorophenyl)cyclopentene, in a 86:14 GC ratio; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.55–1.70 (m, 1H), 1.89–2.03 (apparent quintet, 2H), 2.30–2.41 (m, 3H), 2.41–2.52 (m, 2H), 2.56–2.67 (m, 2H), 3.73–3.88 (m, 1H), 5.67–5.71 (m, 1H), 5.89–5.92 (m, 1H), 6.11 (m, 1H), 7.06 (d, J=8.8 Hz, 2H), 7.20 (d, J=8.8 Hz, 2H), 7.21 (d, J=8.6 Hz, 2H), 7.28 (d, J=8.6 Hz, 2H).

4.8.6. 1-(4-Nitrophenyl)cyclopentene (12i). The reaction was carried out as described above, starting from 4-nitrobenzenediazonium tetrafluoroborate[27] (0.36 g, 1.5 mmol) and was complete after 10 min at rt. After the usual work up, the crude residue was column chromatographed, eluting with PE/Et_2O, 9:1, to afford a mixture (0.24 g, 84% yield) of the title compound **12i** and the regioisomer 3-(4-nitrophenyl)cyclopentene, in a 79:21 GC ratio; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.67–1.83 (m, 1H), 1.99–2.14 (apparent quintet, 2H), 2.46–2.54 (m, 3H), 2.56–2.60 (m, 2H), 2.70–2.78 (m, 2H), 3.98–4.02 (m, 1H), 5.74–5.79 (m, 1H), 6.02–6.06 (m, 1H), 6.42 (m, 1H), 7.34 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.3 Hz, 2H), 8.15 (d, J=8.8 Hz, 2H), 8.16 (d, J=8.3 Hz, 2H).

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A facile synthesis of 9-dialkylamino-9*H*-pyrrolo[1,2-*a*]indoles via iminium salts generated from 2-(pyrrol-1-yl)-benzaldehydes and secondary amine hydrochlorides in the presence of NaI/TMSCl/Et_3N

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Abstract—The NaI/TMSCl/Et_3N-mediated condensation between 2-(pyrrol-1-yl)benzaldehydes and secondary amine hydrochlorides followed by intramolecular trapping of the resulting iminium carbon by the 2-position of the pyrrole ring afforded corresponding 9-dialkylamino-9*H*-pyrrolo[1,2-*a*]indoles generally in good yields.

1. Introduction

Recently, Rish et al. reported that reactions of secondary amines with aldehydes were mediated by NaI/TMSCl/Et_3N to generate the corresponding iminium salts, which were used for the in situ α-aminoalkylation of enamines to provide β-amino ketones.[1] We envisaged that 2-(pyrrol-1-yl)benzaldehydes **1**, which are easily prepared from the respective anthranilates as reported previously,[2,3] and secondary amine hydrochlorides would generate the respective iminium salts **2** under the Risch's conditions and that these iminium salts should undergo intramolecular cyclization to give 9-dialkylamino-9*H*-pyrrolo[1,2-*a*]indoles **3**. We wish to describe here the results of our investigation, which offer a simple and versatile method for preparing this class of molecules.[4] The 9*H*-pyrrolo[1,2-*a*]indole skeleton has held considerable interest, because it is the basic framework of cytostatic mytomycine derivatives.[5] The previous synthetic route to 9-amino-9*H*-pyrrolo[1,2-*a*]indole derivatives involved cyclization of *N*-alkyl-2-(pyrrol-1-yl)benzamide derivatives with phosphoryl chloride leading to the corresponding 9-alkylimino-9*H*-pyrrolo[1,2-*a*]indole derivatives, which was converted into 9-alkylamino-9*H*-pyrrolo[1,2-*a*]indole by $NaBH_4$ reduction.[6] Our new method enabled us to prepare a range of 9-dialkylamino derivatives from 2-(pyrrol-1-yl)benzaldehydes **1** in one-pot.

2. Results and discussion

We began our study examining a reaction of 2-(pyrrol-1-yl)benzaldehyde (**1a**) with dimethylamine hydrochloride in the presence of chlorotrimethylsilane, sodium iodide, and triethylamine in acetonitrile (Method A). It was found that the reaction mixture was stirred for a day at room temperature to give, after usual workup, 9-dimethylaminopyrrolo[1,2-*a*]indole (**3a**) in high yield, as shown in Scheme 1 and Table 1 (entry 1). Under the same reaction conditions 9-diethylaminopyrrolo[1,2-*a*]indole (**3b**) and 7-chloro-9-dimethylaminopyrrolo[1,2-*a*]indole (**3i**) were obtained in high yields (entries 2 and 9). When **1a** was allowed to react with free secondary amines, such as diisopropylamine, pyrrolidine, and morpholine, triethylamine hydrochloride was used (Method B); the corresponding desired amino-pyrrolo[1,2-*a*]indoles **3c–e** were obtained similarly (entries 3–5). While good yields of **3d** and **3e** were produced, the yield of **3c** was rather lower. This is thought to be attributable to the bulkiness of diisopropylamine. The use of this quaternary salt was found to be essential for the production of these products; in the absence of this salt the reactions gave intractable mixtures of products containing **1a**, and not a trace of the desired product was obtained in each case. It indicates that somewhat acidic media are essential for the generation of the iminium salts **2**.

Keywords: Iminium salt; Iodotrimethylsilane; Pyrrole; Pyrroloindole; Secondary amine.
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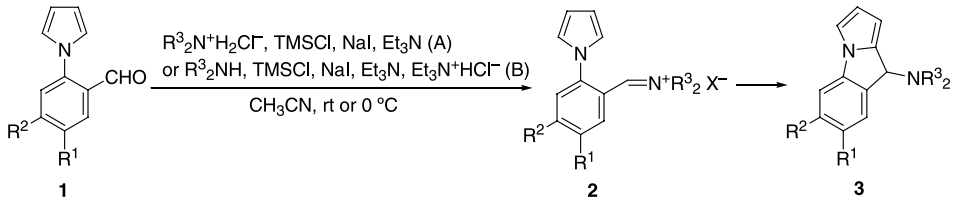

Scheme 1.

Table 1. Preparation of 9-dialkylamino-9*H*-pyrrolo[1,2-*a*]indoles **3**

Entry	**1**	$R^3{}_2NH$	Method	Temperature	**3** (Yield %)[a]
1	**1a** ($R^1=R^2=H$)	Me_2NH	A	rt	**3a** (84)
2	**1a**	Et_2NH	A	rt	**3b** (84)
3	**1a**	*i*-Pr_2NH	B	rt	**3c** (40)
4	**1a**	Pyrrolidine	B	rt	**3d** (80)
5	**1a**	Morpholine	B	rt	**3e** (77)
6	**1b** ($R^1=R^2=OMe$)	Me_2NH	A	0 °C	**3f** (82)
7	**1b**	Et_2NH	A	0 °C	**3g** (73)
8	**1b**	Piperidine	B	0 °C	**3h** (68)
9	**1c** ($R^1=Cl$, $R^2=H$)	Me_2NH	A	rt	**3i** (83)

[a] Isolated yields after chromatography on silica gel.

The reactions using 4,5-dimethoxy-2-(pyrrol-1-yl)benzaldehyde (**1b**) were conducted at 0 °C, in due consideration of the lability of methoxy moieties to iodotrimethylsilane generated in situ, to give the desired products **3f–h** in good yields (entries 6–8). Indeed, treatment of **1b** with dimethylamine hydrochloride at room temperature under the same conditions resulted in the formation of a rather complex mixture, from which only 21% yield of the desired product **3f** was isolated.

In summary, the reaction sequence outlined in Scheme 1 provides a facile route to a range of 9-dialkylamino-9*H*-pyrro[1,2-*a*]indole derivatives from 2-(pyrrol-1-yl)benzaldehydes via intramolecular cyclization of the corresponding iminium salts. This method may be of value in organic synthesis because of the ease of operation as well as the ready availability of the starting materials.

3. Experimental

3.1. General

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1600 Series FT IR spectrometer. The ^1H NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. The ^{13}C NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz in $CDCl_3$. Low resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use.

3.2. Starting materials

Methyl 2-(pyrrol-1-yl)benzoate was prepared according to the procedure reported by Josey et al.[7] 2-(Pyrrol-1-yl)benzyl alcohol was prepared by LAH reduction of methyl 2-(pyrrol-1-yl)benzoate under conditions reported by Garofalo et al.[3] All other chemicals used in this study were commercially available.

3.2.1. 2-(Pyrrol-1-yl)benzaldehyde (1a).[3] To a stirred solution of 2-(pyrrol-1-yl)benzyl alcohol (1.7 g, 10 mmol) in CH_2Cl_2 (60 mL) containing Celite (20 g) was added PCC (6.2 g, 29 mmol) portionwise. After 30 min, the mixture was filtered by suction. The filtrate was washed with 5% hydrochloric acid twice and then brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was distilled by Kugelrohr to give **6** (0.98 g, 60%) as a yellow liquid; bp 130 °C (bath temp)/0.45 Torr (lit.[3] bp 72 °C/0.05 Torr).

3.2.2. Methyl 4,5-dimethoxy-2-(pyrrol-1-yl)benzoate. This compound was prepared from methyl 2-amino-4,5-dimethoxybenzoate under conditions reported by Josey et al.[7] for the preparation of methyl 2-(pyrrol-1-yl)benzoate in 68% yield; a pale yellow solid; mp 93–94 °C (hexane–CH_2Cl_2); IR (KBr disk) 1725 cm^{-1}; ^1H NMR δ 3.68 (3H, s), 3.91 (3H, s), 3.96 (3H, s), 6.29 (2H, dd, $J=2.3$, 2.0 Hz), 6.77 (2H, dd, $J=2.3$, 2.0 Hz), 6.84 (1H, s), 7.38 (1H, s); MS *m/z* 261 (M^+, 100). Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.25; H, 6.05; N, 5.46.

3.2.3. 4,5-Dimethoxy-2-(pyrrol-1-yl)benzyl alcohol. This compound was prepared by LAH reduction of methyl 4,5-dimethoxy-2-(pyrrol-1-yl)benzoate under conditions reported by Garofalo et al.[3] for the preparation of 2-(1-pyrrolyl)benzyl alcohol in 93% yield; a pale-yellow solid; mp 100 °C (hexane–Et_2O); IR (KBr disk) 3518, 1612 cm^{-1}; ^1H NMR δ 1.57 (1H, t, $J=5.6$ Hz), 3.87 (3H, s), 3.95 (3H, s), 4.46 (2H, d, $J=5.6$ Hz), 6.31 (2H, dd, $J=2.3$, 2.0 Hz), 6.8195 (1H, dd, $J=2.3$, 2.0 Hz), 6.8201 (1H, s), 7.04

(1H, s). Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.01; H, 6.22; N, 5.91.

3.2.4. 4,5-Dimethoxy-2-(pyrrol-1-yl)benzaldehyde (1b). This compound was prepared from 4,5-dimethoxy-2-(pyrrol-1-yl)benzyl alcohol according to the procedure for the preparation of **1a** in 67% yield; a pale-yellow solid; mp 135–136 °C (hexane–CH_2Cl_2); IR (KBr disk) 2866, 2790, 1674 cm^{-1}; ^1H NMR δ 3.96 (3H, s), 3.97 (3H, s), 6.37 (2H, dd, $J=2.3$, 2.0 Hz), 6.86 (1H, s), 6.91 (2H, dd, $J=2.3$, 2.0 Hz), 7.45 (1H, s), 9.62 (1H, s). Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.51; H, 5.71; N, 6.05.

3.2.5. Ethyl 2-amino-5-chlorobenzoate.[8] To a solution of 2-amino-5-chlorobenzoic acid (1.7 g, 9.8 mmol) in EtOH (27 mL) was added concd H_2SO_4 (2 mL). The mixture was heated at reflux temperature for 18 h. The mixture was neutralized by adding saturated aqueous $NaHCO_3$, and the precipitate was collected by filtration. The crude product was recrystallization from hexane–Et_2O to give the title compound in a pure form (1.6 g, 80%) as a pale-yellow solid; mp 78–79 °C (hexane–Et_2O); IR (KBr disk) 3456, 3357, 1687, 1616 cm^{-1}; ^1H NMR δ 1.39 (3H, t, $J=7.3$ Hz), 4.33 (2H, q, $J=7.3$ Hz), 5.73 (2H, br s), 6.60 (1H, d, $J=8.9$ Hz), 7.20 (1H, dd, $J=8.9$, 2.6 Hz), 7.83 (1H, d, $J=2.6$ Hz).

3.2.6. Ethyl 5-chloro-2-(pyrrol-1-yl)benzoate. This compound was prepared from ethyl 2-amino-5-chlorobenzoate under conditions reported by Josey et al.[7] for the preparation of methyl 2-(pyrrol-1-yl)benzoate in 68% yield; a pale-yellow liquid; 156 °C/0.7 mmHg; IR (neat) 1720 cm^{-1}; ^1H NMR δ 1.14 (3H, t, $J=7.3$ Hz), 4.17 (2H, q, $J=7.3$ Hz), 6.30 (2H, dd, $J=2.3$, 2.0 Hz), 6.77 (2H, dd, $J=2.3$, 2.0 Hz), 7.31 (1H, d, $J=8.6$ Hz), 7.50 (1H, dd, $J=8.6$, 2.6 Hz), 7.77 (1H, d, $J=2.6$ Hz). Calcd for $C_{13}H_{12}ClNO$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.53; H, 4.94; N, 5.52.

3.2.7. 5-Chloro-2-(pyrrol-1-yl)benzyl alcohol. This compound was prepared by LAH reduction of ethyl 5-chloro-2-(pyrrol-1-yl)benzoate under conditions reported by Garofalo et al.[3] for the preparation of 2-(1-pyrrolyl)benzyl alcohol in 86% yield; colorless needles; mp 99–100 °C (hexane–Et_2O); IR (KBr disk) 3318 cm^{-1}; ^1H NMR δ 1.67 (1H, t, $J=5.9$ Hz), 4.54 (2H, d, $J=5.9$ Hz), 6.33 (2H, dd, $J=2.3$, 2.0 Hz), 6.80 (2H, dd, $J=2.3$, 2.0 Hz), 7.23 (1H, d, $J=8.6$ Hz), 7.33 (1H, dd, $J=8.6$, 2.3 Hz), 7.59 (1H, d, $J=2.3$ Hz). Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.32; H, 5.01; N, 6.52.

3.2.8. 5-Chloro-2-(pyrrol-1-yl)benzaldehyde (1c). This compound was prepared from 5-chloro-2-(pyrrol-1-yl)-benzyl alcohol according to the procedure for the preparation of **1a** in 68% yield; a yellow liquid; bp 170 °C (bath temp)/0.5 mmHg; IR (neat) 2863, 2745, 1694 cm^{-1}; ^1H NMR δ 6.40 (2H, t, $J=2.3$, 2.0 Hz), 6.90 (2H, t, $J=2.3$, 2.0 Hz), 7.39 (1H, d, $J=8.6$ Hz), 7.62 (1H, dd, $J=8.6$, 2.6 Hz), 7.95 (1H, d, $J=2.6$ Hz), 9.75 (1H, s); MS *m/z* 205 (M^+, 19), 177 (48), 115 (100). Calcd for $C_{11}H_8ClNO$: C, 64.25; H, 3.92; N, 6.81. Found: C, 64.23; H, 4.13; N, 6.76.

3.3. Typical procedure for the preparation of 3 (Method A at room temperature)

3.3.1. 9-Dimethylamino-9*H*-pyrrolo[1,2-*a*]indole (3a). To a stirred mixture of NaI (0.34 g, 2.3 mmol), dimethylamine hydrochloride (92 mg, 1.1 mmol), Et_3N (0.23 g, 2.3 mmol), and Me_3SiCl (0.25 g, 2.3 mmol) in acetonitrile (2.3 mL) (Risch's conditions)[1] at room temperature was added 2-(pyrrol-1-yl)benzaldehyde (**1a**) (0.15 g, 0.90 mmol). The mixture was stirred for a day at the same temperature and diluted with CH_2Cl_2 (20 mL). The resulting mixture was washed with saturated aqueous $NaHCO_3$ and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was subjected to chromatography on SiO_2 (1:3 EtOAc/hexane) to give **3a** (0.15 g, 84%) as a pale-yellow solid; mp 64–65 °C (hexane); IR (KBr disk) 1617 cm^{-1}; ^1H NMR δ 2.23 (6H, s), 4.91 (1H, s), 6.22 (1H, ddd, $J=3.3$, 1.3, 1.0 Hz), 6.35 (1H, dd, $J=3.3$, 3.0 Hz), 7.05 (1H, dt, $J=3.0$, 1.0 Hz), 7.10 (1H, td, $J=7.6$, 1.0 Hz), 7.19 (1H, d, $J=7.6$ Hz), 7.31 (1H, t, $J=7.6$ Hz), 7.50 (1H, d, $J=7.6$ Hz); MS *m/z* 198 (M^+, 41), 154 (100). Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.74; H, 7.24; N, 13.94.

3.3.2. 9-Diethylamino-9*H*-pyrrolo[1,2-*a*]indole (3b). A pale-yellow oil; R_f 0.33 (1:5 EtOAc/hexane); IR (neat) 1618 cm^{-1}; ^1H NMR δ 1.06 (6H, t, $J=7.3$ Hz), 2.35–2.55 (4H, m), 5.09 (1H, s), 6.17 (1H, dt, $J=3.3$, 1.0 Hz), 6.34 (1H, dd, $J=3.3$, 2.6 Hz), 7.04 (1H, d, $J=3.0$ Hz), 7.09 (1H, ddd, $J=7.6$, 7.3, 1.0 Hz), 7.18 (1H, d, $J=7.6$ Hz), 7.29 (1H, t, $J=7.6$ Hz), 7.50 (1H, d, $J=7.3$ Hz); MS *m/z* 226 (M^+, 56), 154 (100). Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.58; H, 8.08; N, 12.37.

3.3.3. 7-Chloro-9-dimethylamino-9*H*-pyrrolo[1,2-*a*]indole (3i). A pale-yellow oil; R_f 0.39 (1:3 EtOAc/hexane); IR (neat) 1615 cm^{-1}; ^1H NMR δ 2.22 (6H, s), 4.89 (1H, s), 6.23 (1H, ddd, $J=3.3$, 1.3, 1.0 Hz), 6.36 (1H, dd, $J=3.3$, 3.0 Hz), 7.02 (1H, d, $J=3.0$ Hz), 7.10 (1H, $J=8.2$ Hz), 7.28 (1H, dd, $J=8.2$, 1.6 Hz), 7.48 (1H, d, $J=1.6$ Hz); MS *m/z* 232 (M^+, 43), 188 (100). Calcd for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 66.95; H, 5.61; N, 12.11.

3.4. Typical procedure for the preparation of 3 (Method B at room temperature)

3.4.1. 9-Pyrrolidino-9*H*-pyrrolo[1,2-*a*]indole (3d). To a stirred mixture of NaI (0.34 g, 2.2 mmol), pyrrolidine (72 mg, 1.0 mmol), Et_3N (0.10 g, 1.0 mmol), triethylamine hydrochloride (0.15 g, 1.1 mmol), and Me_3SiCl (0.24 g, 2.2 mmol) in acetonitrile (2.2 mL) at room temperature was added 2-(pyrrol-1-yl)benzaldehyde (**1a**) (0.16 g, 0.96 mmol). The mixture was stirred at the same temperature for a day. Work-up and purification were carried out in a manner similar to those described for the preparation of **3a** to afford **3d** (0.17 g, 80%) as a pale-yellow solid; mp 64–65 °C (hexane–Et_2O); IR (KBr disk) 1616 cm^{-1}; the ^1H NMR data for this product were identical to those described in the literature.[6a]

3.4.2. 9-Diisopropylamino-9*H*-pyrrolo[1,2-*a*]indole (3c). A pale-yellow solid; mp 37–39 °C (hexane–Et_2O); IR (KBr disk) 1616 cm^{-1}; ^1H NMR δ 1.04 (6H, d, $J=6.6$ Hz), 1.12

(6H, d, J=6.6 Hz), 2.85–3.0 (2H, m), 5.02 (1H, s), 6.13 (1H, dt, J=3.3, 1.3 Hz), 6.34 (1H, dd, J=3.3, 2.7 Hz), 7.0–7.15 (2H, m), 7.17 (1H, d, J=7.3 Hz), 7.27 (1H, t, J=7.3 Hz), 7.41 (1H, d, J=7.3 Hz); MS m/z 254 (M^+, 7.8), 154 (100). Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.15; H, 9.00; N, 11.01.

3.4.3. 9-Morpholino-9*H*-pyrrolo[1,2-*a*]indole (3e). A pale-yellow solid; mp 138–140 °C (hexane–Et_2O); IR (KBr disk) 1616 cm^{-1}; ^1H NMR δ 2.51 (4H, t, J=5.6 Hz), 3.68 (4H, t, J=5.6 Hz), 4.89 (1H, s), 6.23 (1H, ddd, J=3.3, 1.3, 1.0 Hz), 6.35 (1H, dd, J=3.3, 3.0 Hz), 7.05 (1H, dt, J=3.0, 1.0 Hz), 7.10 (1H, td, J=7.6, 1.0 Hz), 7.18 (1H, d J=7.6 Hz), 7.31 (1H, td, J=7.6, 1.0 Hz), 7.51 (1H, d, J=7.6 Hz); MS m/z 240 (M^+, 13), 154 (100). Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.23; H, 6.63; N, 11.53.

3.5. Typical procedure for the preparation of 3 (Method A at 0 °C)

3.5.1. 9-Dimethylamino-6,7-dimethoxy-9*H*-pyrrolo[1,2-*a*]indole (3f). To a stirred mixture of NaI (0.33 g, 2.2 mmol), dimethylamine hydrochloride (81 mg, 0.99 mmol), Et_3N (0.20 g, 2.0 mmol), and Me_3SiCl (0.24 g, 2.2 mmol) in acetonitrile (2.2 mL) at 0 °C was added a solution of 4,5-dimethoxy-2-(pyrrol-1-yl)benzaldehyde (**1b**) (0.22 g, 0.95 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at the same temperature for 2 days. Work-up and purification were carried out in a manner similar to those described for the preparation of **3a** to afford **3f** (0.20 g, 82%) as a pale-yellow solid; mp 157–158 °C (hexane–Et_2O); IR (KBr disk) 1622 cm^{-1}; ^1H NMR δ 2.22 (6H, s), 3.90 (3H, s), 3.95 (3H, s), 4.84 (1H, s), 6.21 (1H, ddd, J=3.3, 1.3, 1.0 Hz), 6.32 (1H, dd, J=3.3, 2.6 Hz), 6.80 (1H, s), 7.00 (1H, d, J=2.6 Hz), 7.09 (1H, s); ^{13}C NMR δ 40.70, 56.29, 56.53, 64.33, 94.79, 105.52, 109.88, 110.19, 112.09, 127.00, 134.39, 134.58, 145.81, 149.58; MS m/z 258 (M^+, 28), 214 (100). Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.52; H, 7.01; N, 11.01.

3.5.2. 9-Diethylamino-6,7-dimethoxy-9*H*-pyrrolo[1,2-*a*]indole (3g). A pale-yellow solid; mp 106–107 °C (hexane–Et_2O); IR (KBr disk) 1620 cm^{-1}; ^1H NMR δ 1.08 (6H, t, J=7.3 Hz), 2.35–2.6 (4H, m), 3.91 (3H, s), 3.95 (3H, s), 5.02 (1H, s), 6.15 (1H, ddd, J=3.3, 1.3, 1.0 Hz), 6.30 (1H, t, J=3.0 Hz), 6.80 (1H, s), 6.99 (1H, d, J=2.6 Hz), 7.08 (1H, s); ^{13}C NMR δ 13.88, 44.92, 56.28, 56.59, 60.12, 94.73, 104.75, 109.79, 109.95, 112.07, 128.25, 134.56, 136.03, 145.76, 149.39; MS m/z 286 (M^+, 17), 214 (100). Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.11; H, 7.76; N, 9.73.

3.5.3. 6,7-Dimethoxy-9-piperidino-9*H*-pyrrolo[1,2-*a*]indole (3h) (Method B at 0 °C). To a stirred mixture of NaI (0.35 g, 2.3 mmol), piperidine (90 mg, 1.1 mmol), Et_3N (0.11 g, 1.1 mmol), triethylamine hydrochloride (0.15 g, 1.1 mmol), and Me_3SiCl (0.26 g, 2.4 mmol) in acetonitrile (2.3 mL) at 0 °C was added a solution of 4,5-dimethoxy-2-(pyrrol-1-yl)benzaldehyde (**1b**) (0.23 g, 1.0 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at the same temperature for 36 h. Work-up and purification were carried out in a manner similar to those described for the preparation of **3a** to afford **3h** (0.20 g, 68%) as a pale-yellow solid; mp 160–161 °C (hexane–Et_2O); IR (KBr disk) 1620 cm^{-1}; ^1H NMR δ 1.35–1.45 (2H, m), 1.5–1.65 (4H, m), 2.4–2.5 (4H, m), 3.91 (3H, s), 3.94 (3H, s), 4.81 (1H, s), 6.18 (1H, dt, J=3.3, 1.0 Hz), 6.31 (1H, dd, J=3.3, 2.6 Hz), 6.78 (1H, s), 6.98 (1H, d, J=2.6 Hz), 7.12 (1H, s); ^{13}C NMR δ 24.45, 26.16, 49.70, 56.30, 56.67, 64.85, 94.70, 105.39, 109.91, 110.28, 111.96, 127.08, 134.70, 135.43, 145.71, 149.46; MS m/z 298 (M^+, 25), 214 (100). Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.38; H, 7.58; N, 9.35.

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