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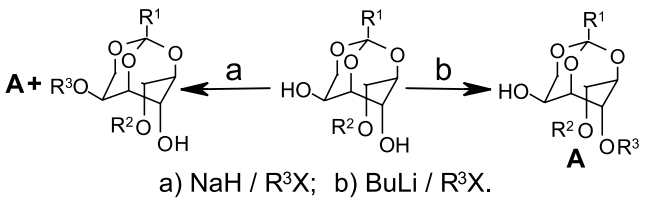
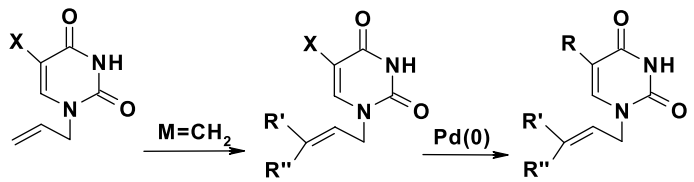
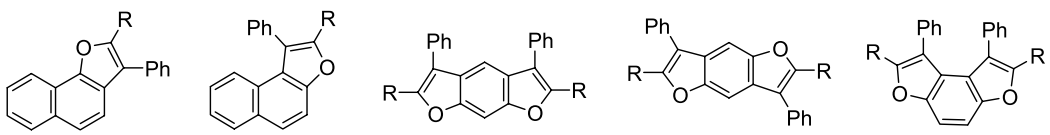
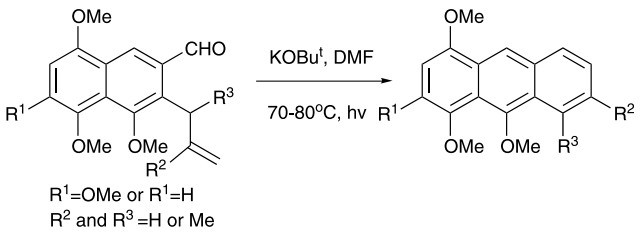
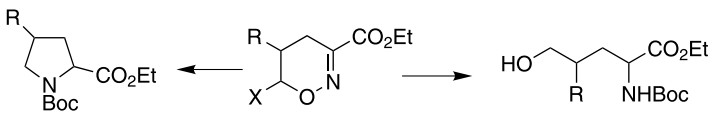


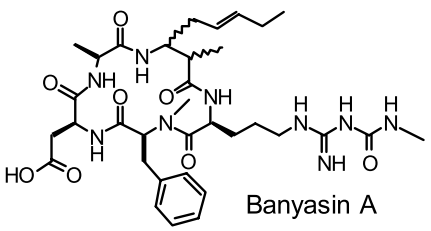


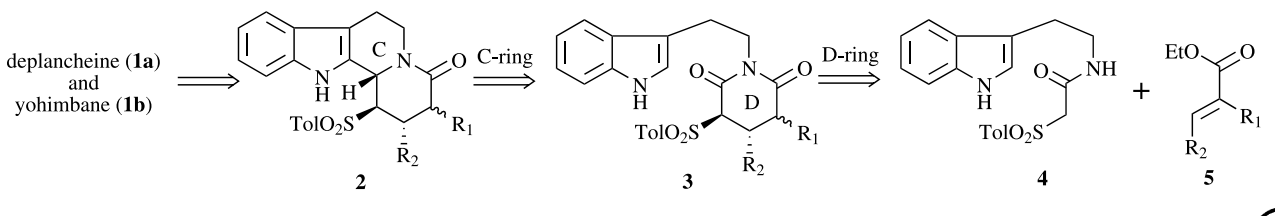
Novel acyclonucleosides (**9a–d**, **10a–d**, **18a**,**b** and **19a**,**b**) were prepared using Pd(0) and cross-metathesis methodologies. The allylic *N*-alkylation under Tsuji–Trost conditions was used to introduce the nucleobase, meanwhile the Suzuki–Miyaura reaction afforded C-5 substituted uracil analogues. A ruthenium-based cross-metathesis reaction was used to synthesize new acycloalkenyl nucleosides.

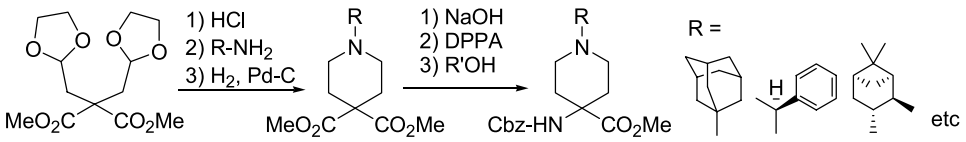


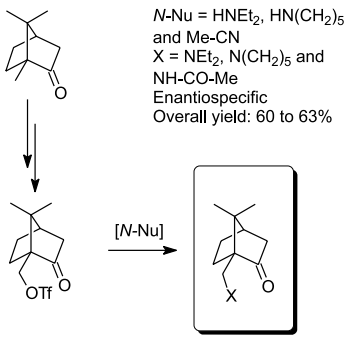


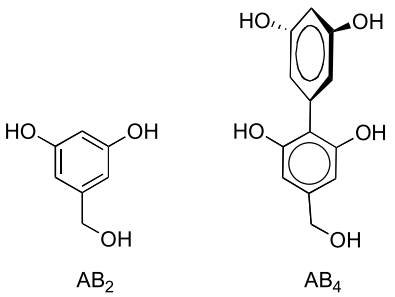


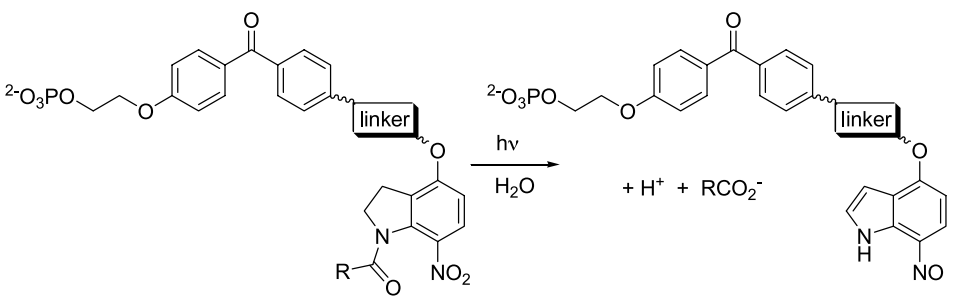


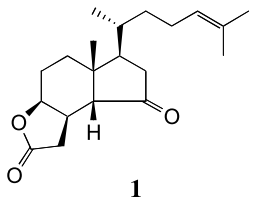






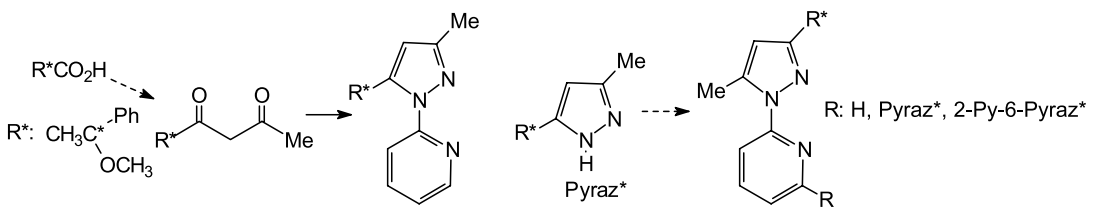


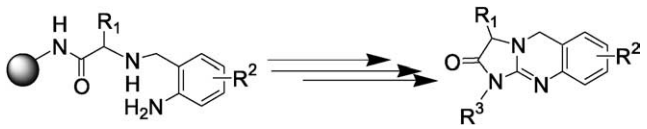


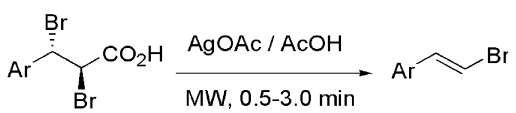


1

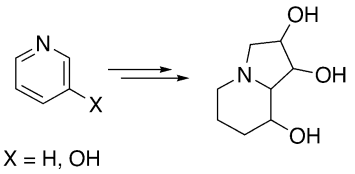
Two novel degraded sterols, e.g. aplykurodinone-1 (**1**), have been isolated from the skin of sea hare *S. geographica* from Greek coasts. The structure and the absolute stereochemistry have been established by spectral methods and chemical correlation with related compounds.

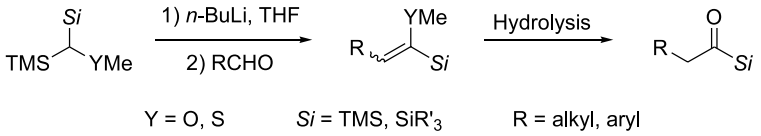


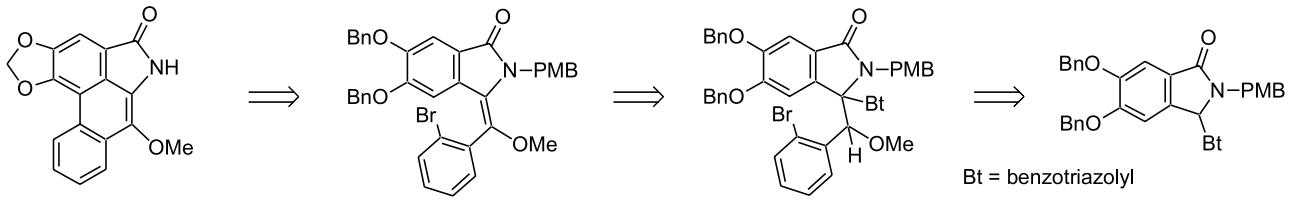


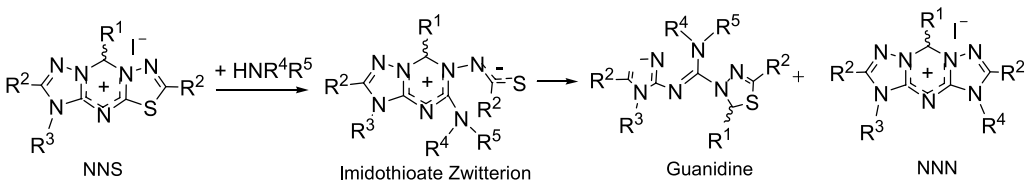


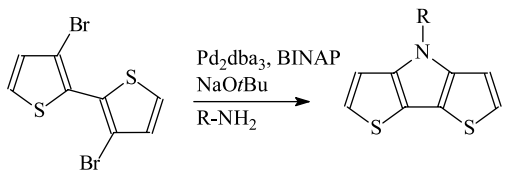
(*E*)-β-Arylvinyl bromides were stereoselectively prepared in high yields by microwave irradiation of the corresponding *anti*-3-aryl-2,3-dibromo-propanoic acids in AcOH in the presence of AgOAc for 0.5–3.0 min.

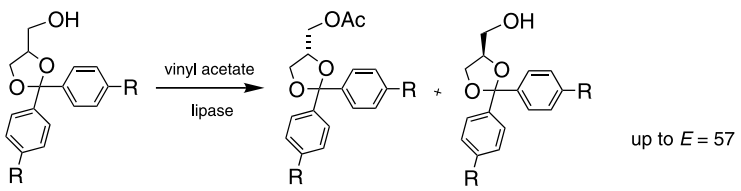


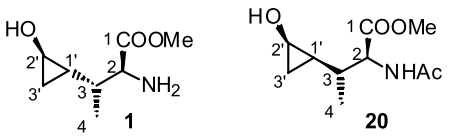




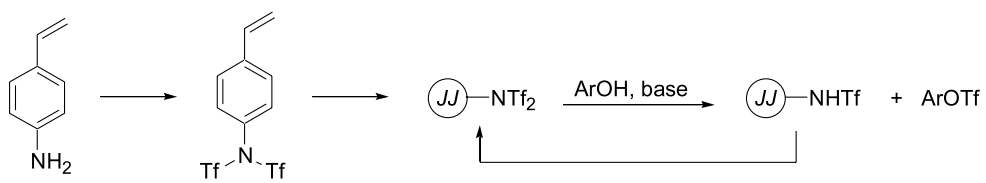


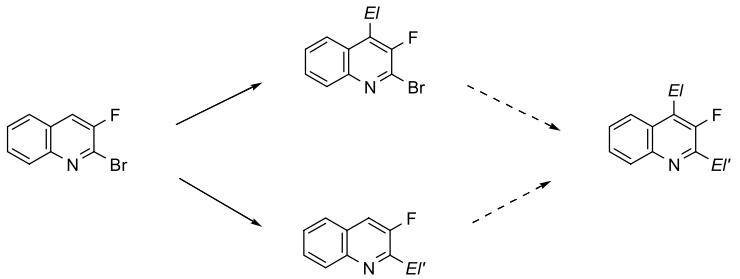


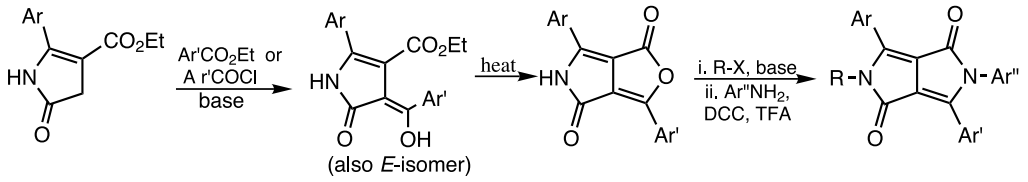




Novel conformationally restricted analogues of glutamic acid have been synthetised.







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ⓘ+ Supplementary data available via ScienceDirect

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Chelation controlled regiospecific O-substitution of *myo*-inositol orthoesters: convenient access to orthogonally protected *myo*-inositol derivatives

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Abstract—A general method for the completely regioselective protection of the three secondary hydroxyl groups of orthoester derivatives of *myo*-inositol, utilizing the subtle differences in reactivity exhibited by its alkali metal alkoxides due to differences in their ability to form chelates, is described. This method provides convenient access to orthogonally protected *myo*-inositol derivatives. A comparison of the methylation of racemic 4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate in the presence of sodium or lithium ions showed that stabilization of the C4-alkoxide by chelation with lithium overrides steric hindrance offered by the C6-axial substituent in deciding the regioselectivity during the nucleophilic O-substitution.

1. Introduction

Protection of hydroxyl groups is routinely encountered in the synthesis of cyclitol and carbohydrate derivatives. Understanding the reasons that govern differences in reactivity of different functional groups in the same molecule is the key for successful regioselective functionalization of complex organic molecules. Such an understanding becomes crucial while working with molecules having non-equivalent functional groups of the same kind (polyols, polyamines, polyacids, etc.).[1] Phosphorylated cyclitols and their analogs have attracted the attention of chemists and biologists in the last two decades due to their involvement in various biological phenomena[2] such as cellular signal transduction, calcium mobilization, insulin stimulation, exocytosis, cytoskeletal regulation, intracellular trafficking of vesicles and anchoring of certain proteins to cell membranes. Although regio- and enantioselective functionalization of inositols or their derivatives are being attempted[3] and appear to show promise for the synthesis of biologically relevant molecules, a very useful and practical strategy for the synthesis of cyclitol derivatives would be the regiospecific orthogonal protection of all the six hydroxyl groups, wherein one hydroxyl group is protected in each step. As a step towards achieving this goal, we herein report a general method for the completely regioselective protection of the three secondary hydroxyl groups of *myo*-inositol orthoesters, utilizing the subtle differences in reactivity exhibited by its alkali metal alkoxides.

myo-Inositol orthoesters (Scheme 1, **1**, **2**) have been used extensively for the synthesis of phosphoinositols, their derivatives and other compounds with interesting properties.[1–4] However, the overall yield of the required protected *myo*-inositol derivative is usually not good due to: (a) formation of isomeric *myo*-inositol orthoester derivatives and/or (b) use of transient protecting groups (esters, sulfonates, allyl ether, etc.) which increase the number of steps and decrease the overall yield. In fact, there is no general method for the orthogonal protection of the three hydroxyl groups of *myo*-inositol orthoesters (especially as ethers) which generates only one regioisomer in each step, in respectable yields. Such a method would provide orthogonally protected *myo*-inositol orthoesters, which are the key intermediates for the synthesis of biologically important inositol derivatives.

The differences in the observed reactivity of the three hydroxyl groups (and hence the observed regioselectivity) of *myo*-inositol orthoesters have been attributed to various factors shown in Scheme 1 and other parameters such as nature of the electrophile,[5] strength of the base used,[5,6] solvent used for the reaction,[6b,7] presence or absence of metal ions,[7,8] steric bulk of the reagent[5,9] and the catalyst used.[10] These variations were utilized to obtain either

Keywords: Regioselectivity; Inositol; Cyclitol; Lithium; Chelation.
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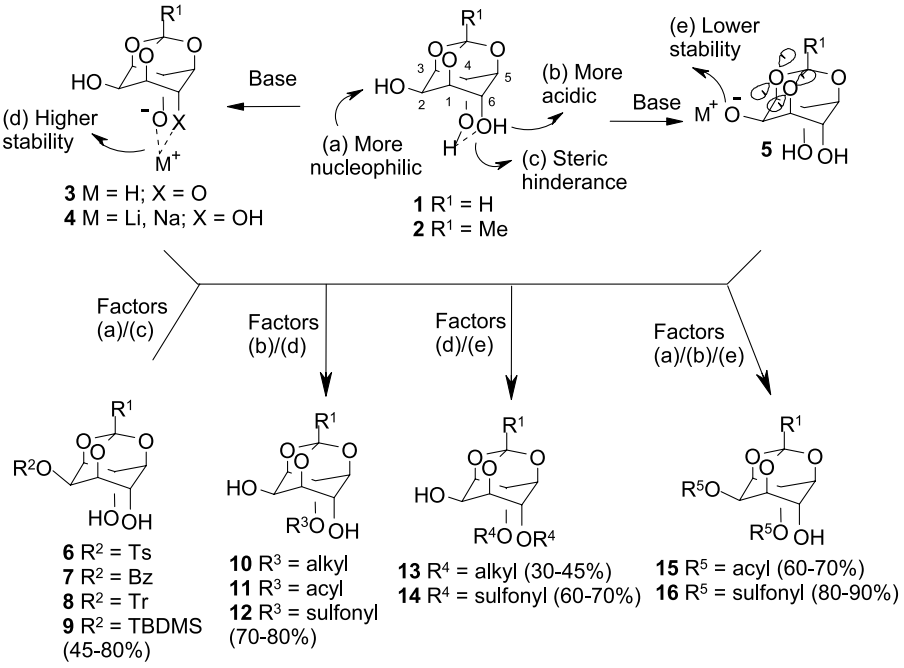


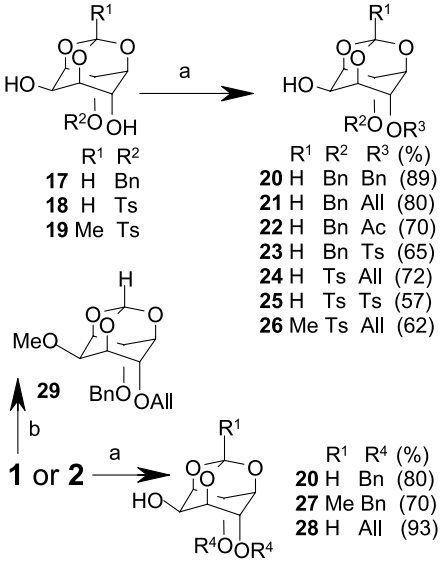
Scheme 1.

mono-O-substituted derivatives (**6**–**12**, Scheme 1) or di-O-substituted derivatives (**13**–**16**) in poor to good isolated yields. O-Alkylation[7] and O-acylation[8] of *myo*-inositol orthoesters **1** and **2** in the presence of sodium hydride are particularly interesting due to the very high regioselectivity observed, which was thought to be due to the involvement of chelates such as **4**.[11,12] We wondered whether this property of *myo*-inositol derivatives could be exploited to develop a general method for the regioselective sequential protection of the three hydroxyl groups wherein a single isomer is formed in each step. Our results show that chelation of the metal ion by *myo*-inositol orthoesters can override steric effects to some extent in deciding the observed regioselectivity during O-substitution.

2. Results and discussion

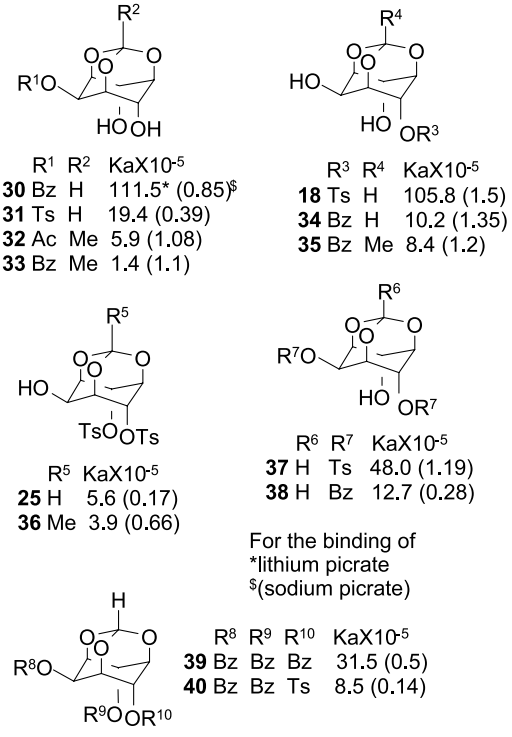
Although the O-alkylation[7] of *myo*-inositol orthoesters (such as **1** or **2**) with alkyl halides in the presence of 1 equiv of sodium hydride resulted in exclusive reaction at the C4(6)–O-position,[13] reaction of these triols with 2 equiv of alkyl halide[7,14] in the presence of 2 equiv of sodium hydride resulted in the formation of a mixture of 2,4- and 4,6-diethers. However, the reaction of the C4-monoether (such as **10**) with alkyl halide in the absence of metal ions provided the unsymmetrical diether (such as **15**, R^5 = alkyl) as the major product.[15] These results give credence to the postulated chelation[7] of the metal ion with 4,6-diaxial oxygens, during O-substitution of the axial monoether **10**, since acidity of the two hydroxyl groups in this monoether is expected to be comparable in the absence of the strong intramolecular hydrogen bond[12] as present in the corresponding triols (**1** and **2**). We postulated that if chelation of the metal ions was indeed operational in these O-substitution reactions, use of lithium instead of sodium ions must result in better regioselectivity, resulting in the formation of greater amounts of the 4,6-di-O-substituted derivatives **13** as compared to the 2,4-di-O-substituted derivatives **15** (R^5 = alkyl). This is expected since lithium, being smaller and a better ion for coordination[16] with oxygen atoms, would stabilize the oxyanion at the C6(4)–O-position in axial C4(6)–O-monosubstituted *myo*-inositol orthoesters (**10**).

The results of O-substitution in *myo*-inositol orthoesters **1** and **2** in the presence of lithium ions are summarized in Scheme 2. The reaction of the monobenzyl ether **17** with benzyl bromide in the presence of lithium hydride resulted in the formation of the corresponding symmetrical diether **20** without any trace of the unsymmetrical 2,4(6)-diether.



Scheme 2. (a) LiH or BuLi, THF–DMF, alkyl halide, acyl chloride or sulfonyl chloride. (b) (i) NaH, BnBr, DMF; (ii) BuLi, AllBr, THF–DMF; NaH, MeI.

However, the reaction was sluggish due to the low basicity of lithium hydride. Hence, in future experiments *n*-butyllithium was used as a base to generate the inositol orthoester oxyanions. Accordingly, the BuLi assisted reaction of various electrophiles with *myo*-inositol orthoesters (**1** or **2**) and their 4-O-substituted derivatives **17**–**19** (Scheme 2) proceeded smoothly to afford the corresponding 4,6-di-O-substituted derivatives **20**–**28** in good to excellent isolated yields along with minor amounts (5–10%) of tri-O-substituted derivatives. Since we isolate tri-O-substituted derivatives but no 2,4-di-O-substituted products, it appears that tri-O-substituted products result from the initially formed 4,6-di-O-substituted derivatives. The method being described here is sufficiently flexible to allow the preparation of 4,6-diethers and any combination of ether, ester and sulfonate derivatives. The protocol for best results is the generation of the lithium alkoxide of *myo*-inositol orthoester in dry THF followed by the addition of the appropriate electrophile in dry DMF. The yield of ditosylate **25** was not as high as those obtained for dialkylethers, but the unsymmetrical 2,4-ditosylate was not formed. This method is not suitable for the preparation of 4,6-diesters since alkoxides of C4(6)–monoesters **11** undergo isomerization to the corresponding C2-esters[8] faster than substitution at C6–O-position. The versatility of this method is demonstrated by the rapid and efficient preparation of an unsymmetrical tri-O-substituted derivative **29** (Scheme 2). To the best of our knowledge, completely regiospecific sequential tri-O-substitution of *myo*-inositol orthoesters is not reported. Earlier methods[7,14] for the preparation of 4,6-di-O-substituted derivatives of **1** or **2** either resulted in a mixture of products or were restricted to the preparation of disulfonates[6b] or the dibenzyl ether **20** via a circuitous route.[17]

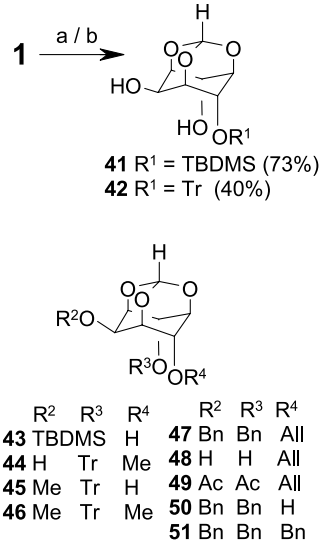


Scheme 3.

That the *myo*-inositol derivatives indeed bind lithium ions better than sodium ions as postulated above, was suggested by the picrate extraction experiments[18] (Scheme 3). Most of the orthoester derivatives shown in Scheme 3 bind lithium picrate 10–100 times better than sodium picrate and the diol **30** exhibits the highest binding constant for lithium picrate. These results give credence to the suggestion that the extent of chelation of metal ions by inositol derivatives is a major factor in deciding the observed regioselectivity (see below) for the O-substitution reactions shown in Scheme 2.

We also investigated the extent to which steric hindrance due to the presence of 4,6-diaxial substituents (in **1**, **2** and their derivatives) dictate the course of the reaction and decide the observed regioselectivity. To understand this, we carried out (a) the reaction of the triol **1** with bulky electrophiles (TBDMSCl, TrCl) and (b) the O-substitution of *myo*-inositol orthoester carrying a bulky protecting group (trityl) at the C4–O-position, with a small electrophile (methyl iodide).

The reaction of **1** with TBDMSCl (1 equiv)/BuLi led to the formation of the C4–O-protected derivative **41** (Scheme 4) as the major product, and C2-silyl ether was not formed. Reaction of the triol **1** with 2 equiv of TBDMSCl/LiH led to the formation of the racemic 2,4-di-O-substituted derivative **43**. This is in contrast to the corresponding reaction of the triol **1** with alkyl halides (not having bulky alkyl groups) which afforded the 4,6-diethers as the major product. The difference in the observed regioselectivity in these two reactions can be attributed to the steric hindrance offered by the C4–O–TBDMS group for the entry of another bulky TBDMS group at the 6-O-position. Similar steric hindrance is also reflected in the low yield of the trityl derivative **42** obtained by tritylation of the triol **1** (as compared to the yield of **10** on alkylation of **1** with normal alkyl halides[7]).

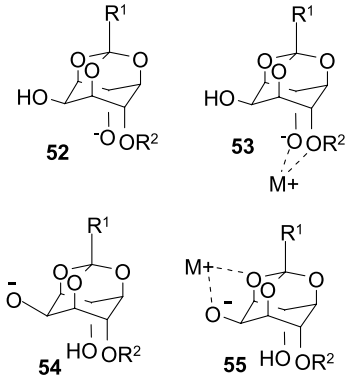


Scheme 4. (a) BuLi/THF, TBDMSCl (for **41**); (b) NaH, DMF, TrCl (for **42**).

The reaction of the trityl ether **42** with butyllithium followed by methyl iodide gave a mixture of products consisting of isomeric monomethyl ethers **44** and **45** as well as the

dimethyl ether **46** (Scheme 4). The racemic C6-ether **44** was formed in a higher proportion compared to the corresponding C2-methyl ether **45** (**44/45**=61:39). The use of sodium hydride for the same reaction also resulted in a mixture of products (**44**–**46**) but **45** was present in larger proportion as compared to **44** (**44/45**=11:89). The structure of the two monomethyl ethers **44** and **45** were established by unambiguous synthesis of **45** starting from the known ditosylate **25**.

In principle, reaction of 2,4-diols with butyllithium or sodium hydride can result in the formation of two anions **52** and **54** (Scheme 5). Higher isolated yields of the 4,6-disubstituted products (Scheme 2) suggest that **52** is preferentially formed. This could be a result of greater stabilization of the anion **52** by metal ions due to chelation (**53**) with two diaxially oriented oxygen atoms as compared to the stabilization of the anion **54** due to chelation (**55**) with the oxygen atoms in axial–equatorial orientation. This is analogous to the formation of a strong intramolecular hydrogen bond between the 4,6-diaxial hydroxyl groups in **1** which has been observed in its crystals, while the *cis*-1,2-hydroxyl groups result in a comparatively weaker intramolecular hydrogen bond.[12,19] Increase in the yield of the 4,6-di-O-substituted derivatives and non-formation of the 2,4-di-O-substituted derivatives (Scheme 2) in the BuLi assisted reaction as compared to the NaH assisted reaction suggests that Li^+ stabilizes the anion **52** better than Na^+ does.

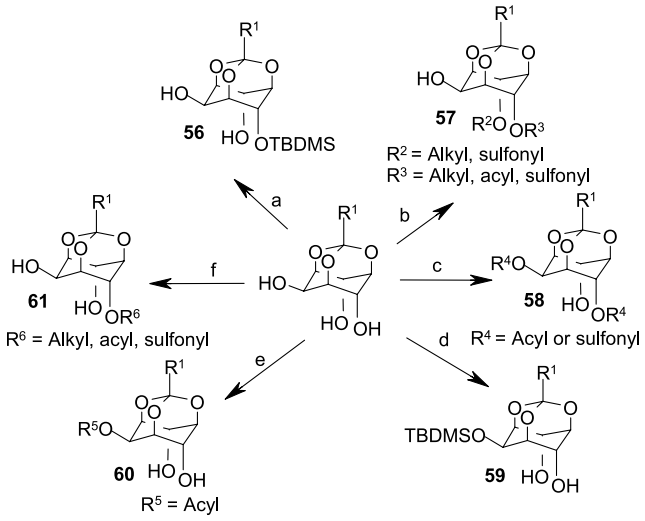


Scheme 5.

It is of relevance to compare the results of alkylation of the C4-benzyl (**17**) and C4-trityl (**42**) ethers in the presence of Na^+ and Li^+, which could throw light on the possibility of the relative ease of formation/stabilization of **52** and **54** under the conditions of alkylation. Since monobenzylation of the triol **1** with NaH/BnBr yields **17** exclusively, it can be inferred that dibenzylation of the triol **1** proceeds exclusively via the 4-benzyl ether **17** to yield a mixture of products consisting of 2,4 and 4,6 diethers (**50**, **20**) in the ratio 1:5 and the tribenzyl ether **51**.[7] On increasing the steric bulk of the alkyl group at the 4-O-position with a trityl group, predominant methylation takes place at the 2-O-position (to give **45**) which reflects the steric crowding at the 6 position. Alkylation of **17** with BuLi/BnBr on the other hand provides the 4,6-diether **20** exclusively and the corresponding trityl ether gives the 6-methylether **44** as the major product, unlike in the reaction assisted by Na^+. These results give credence to our postulate that in Li^+ assisted reactions stabilization of the anion **52** by chelation plays a dominant role over steric effect of the trityl group. However, yet another possibility which cannot be ruled out is the inability of the larger Na^+ to chelate at the 4,6-positions (in **42**) due to the presence of bulky trityl group while the smaller Li^+ can still form a chelate at the 4,6 positions due to its smaller size. These results strongly suggest that stabilization of the oxyanion by chelation with lithium (**53**) overrides steric hindrance offered by the *cis*-axial substituent in deciding the regioselectivity during the nucleophilic O-substitution in *myo*-inositol orthoesters. Hence, it appears that the major factor that controls regioselectivity during the di-O-substitution of *myo*-inositol orthoesters in the presence of metal ions is the extent of chelation that exists between the metal ion and the two diaxial oxygen atoms.

It is of interest to examine if the regioselectivity observed (exclusive reaction at the C4–O-position) during the mono-O-substitution[7] of the triol (**1** or **2**) in the presence of Na^+ and Li^+, should also be attributed to chelation by the metal ion (Scheme 1, **4**). Alkylation,[7] acylation[8] or silylation of the triol **1** in the presence of NaH or BuLi results in the exclusive formation of the 4-O-substituted derivatives. The triol **1** did not undergo alkylation with benzyl bromide in the presence of DBU. However, use of more reactive electrophiles (acyl halides) in the presence of tertiary amines (e.g., triethylamine, $pKa_H=10.8$[20]) is known[5,6a] to give the corresponding C4–O-acylated derivatives. Benzylation of **1** in the presence of potassium carbonate resulted in the exclusive alkylation at the 4-O-position to yield the benzyl ether **17** in 72% isolated yield. These results imply that chelation with metal ions is not a necessary condition for the mono-O-substitution at the 4-positon in the triol **1**. The observed regioselectivity can be rationalized by considering the intramolecular hydrogen bonding that is present[12] in these triols, which results in an increase of the acidity of the C4(6)–hydroxyl group.[13] If the base used is strong enough to form even minor amounts of the anion at C4–O-position, which is stabilized by intramolecular hydrogen bonding, reaction brought about by such bases result in substitution at the C4–O-position. Hence, during the mono-O-substitution of these triols (**1** and **2**), in our opinion, there is no need to invoke either chelation (Scheme 1, **4**) with metal ions or steric effect of the two axial hydroxyl groups[5] to rationalize the experimental observations, since hydrogen present in the *cis*-axial hydroxyl group is a good acceptor of hydrogen bond which could stabilize the anion (Scheme 1, **3**). Weaker bases bring about substitution at the 2-O-position as exemplified by benzoylation[5] of **1** in the presence of pyridine ($pKa_H=5.2$[20]), alkylation of **1** under phase transfer catalytic conditions[15] and silylation[21] of **1** in the presence of imidazole. Also, silylation of **1** in the presence of metals (palladium)[22] that are not basic enough to form the 4-anion result in a mixture of products consisting of different regioisomers. The predominant formation of 2-O-substituted derivatives in the presence of weaker bases could be due to the relatively higher nucleophilicity of the C2–OH as compared to the C4(6)–OH under unionized conditions, due to the involvement of the latter in intramolecular H-bonding.

In conclusion, we have developed a general method for the orthogonal O-substitution of the three hydroxyl groups of *myo*-inositol orthoesters wherein each step in the scheme of reactions proceed with very high regioselectivity. We have also shown that chelation of the metal ions with inositol orthoester derivatives play a major role in deciding the regioselectivity in these reactions. These results coupled with other regioseletive reactions reported in the literature provide convenient access to any O-substituted *myo*-inositol orthoester derivative (Scheme 6). We are now working towards the realization of a similar scheme of reactions that allows the nucleophilic substitution of one hydroxyl group of *myo*-inositol at a time that leads to orthogonally hexa-O-substituted *myo*-inositol derivatives.



Scheme 6. (a) and (b) Present work; (c) Refs. 5 and 6b; (d) Ref. 21; (e) Ref. 8; (f) Refs. 6b, 7 and 8.

3. Experimental

3.1. General

All the solvents used were purified according to literature procedures.[23] All the reactions were carried out in an atmosphere of argon. Dry DMF and dry THF were used as solvents in all the experiments involving metal hydrides or *n*-butyllithium. Sodium hydride used in experiments was 60% suspension in mineral oil. A stock solution of *n*-butyllithium (1.4–1.7 M) in dry hexanes was prepared and used in all the experiments. *myo*-Inositol derivatives **1**,[21] **2**,[24] **17**,[7] **18**,[6b] **30–40**[6b,8,11,25] were prepared according to literature procedures. Thin layer chromatography was performed on E. Merck pre-coated 60 F_{254} plates and the spots were rendered visible either by shining UV light or by charring the plates with concd H_2SO_4. Column chromatographic separations were carried out on silica gel (100–200 mesh) while flash column chromatographic separations were carried out on silica gel (230–400 mesh) with light petroleum–ethyl acetate mixtures as eluent. 'Usual work-up' implies washing of the organic layer with water followed by brine, drying over anhydrous sodium sulfate followed by removal of the solvent under reduced pressure using a rotary evaporator. The compounds previously reported in the literature were characterized by comparison of their melting points and/or ^{1}H NMR spectra with reported data. IR spectra were recorded in $CHCl_3$ solution or as nujol mull. NMR spectra were recorded at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C unless otherwise mentioned. All the asymmetrically substituted *myo*-inositol derivatives reported are racemic; however, only one of the enantiomers in shown in all the schemes.

3.1.1. Racemic 4-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (17). The triol **1** (0.100 g, 0.53 mmol) and benzyl bromide (0.63 mL, 5.26 mmol) were dissolved in DMF (4 mL) and stirred with potassium carbonate (0.727 g, 5.26 mmol) at 106 °C for 26 h. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate and worked up as usual. The known benzyl ether **17**[7] (0.106 g, 72%) was isolated after filtration of the crude product on a short column of silica gel.

3.1.2. Racemic 4-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoacetate (19). To a solution of the triol **2**[24] (0.650 g, 3.20 mmol) in dry DMF (6 mL) sodium hydride (0.154 g, 3.84 mmol) was added and stirred for 0.5 h. Then a solution of tosyl chloride (0.730 g, 3.84 mmol) in DMF (6 mL) was added in one lot and stirred for 0.5 h. The reaction mixture was worked up with ethyl acetate as usual and the solid obtained was filtered through a short column of silica gel to get **19** (0.837 g, 73%) as a colorless solid. Mp 137–139 °C. IR (ν): 3078–3533 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.75–7.90 (d, 2H, J=7.8 Hz), 7.35–7.50 (d, 2H, J=7.8 Hz), 5.06–5.18 (m, 1H), 4.47–4.60 (m, 1H), 4.15–4.31 (m, 2H), 3.96–4.13 (m, 2H), 2.90–3.15 (br s, 1H, D_2O exchangeable), 2.30–2.80 (br, 1H D_2O exchangeable), 2.48 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($(CD_3)_2CO$): δ 145.8, 133.7, 130.4, 128.1, 108.9, 75.1, 74.4, 73.2, 69.7, 66.8, 58.7, 23.8, 20.9. Anal. Calcd for $C_{15}H_{18}O_8S$: C, 50.27; H, 5.06. Found: C, 50.08; H, 5.06.

3.2. Synthesis of 4,6-di-O-substituted-*myo*-inositol 1,3,5-orthoesters

Procedure A. The required 4-O-substituted *myo*-inositol orthoester (1 mmol) was taken in dry THF (4 mL) and cooled to 0 °C. *n*-Butyllithium (1.5 mmol) was added dropwise using a syringe followed by a solution of the required alkyl halide, acyl halide or sulfonyl halide (1.2 mmol) in DMF (2 mL). The reaction mixture was stirred for 22–28 h and worked up with ethyl acetate. The products were separated by column chromatography using 10–20% ethyl acetate–light petroleum as the eluent.

Procedure B. The required 4-O-substituted *myo*-inositol orthoester (1 mmol) was taken in DMF (3–4 mL) and stirred for 2 h with lithium hydride (2 mmol). A solution of the alkyl halide in DMF (2 mL) was added and the mixture stirred for 36–40 h. The reaction mixture was then worked up with ethyl acetate and the products were separated as in procedure A.

Procedure C. The required triol **1** or **2** (1 mmol) was taken in THF (5 mL) and *n*-butyllithium (2.3 mmol) was added at 0 °C. A solution of the appropriate alkyl halide (2.2 mmol) in DMF (1 mL) was added and the mixture stirred for 36–45 h. The resulting mixture was then worked up with

ethyl acetate. The products were separated by column chromatography as in procedure A.

Procedure D. The required triol **1** or **2** (1 mmol) was taken in DMF (2–3 mL) and lithium hydride (4 mmol) was added at ambient temperature. A solution of the appropriate alkyl halide (2.2 mmol) in DMF (1 mL) was added and the mixture was stirred for 36–45 h. The reaction mixture was then worked up with ethyl acetate and the products separated as in procedure A.

3.2.1. 4,6-Di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (20). The monobenzyl ether **17** (0.283 g, 1 mmol) was benzylated by procedure A to obtain the known dibenzyl ether **20** (0.328 g, 89%). Mp 118–120 °C, (lit.[7] Mp 124–125 °C).

3.2.2. Racemic 4-*O*-benzyl-6-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (21). The monobenzyl ether **17** (0.283 g, 1 mmol) was allylated by procedure A to obtain the 6-allyl ether **21** (0.256 g, 80%) as gum. IR (ν): 3220–3600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.33 (s, 5H), 5.75–6.00 (m, 1H), 5.47 (s, 1H), 5.16–5.35 (m, 2H), 4.50–4.70 (AB q, 2H, $J=$ 11.8 Hz), 4.38–4.49 (m, 1H), 4.26–4.37 (m, 2H), 3.95–4.25 (m, 5H), 3.15–3.30 (d, 1H, $J=11.2$ Hz, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 137.9, 134.3, 128.7, 128.1, 127.8, 117.8, 103.6, 73.9, 73.3, 71.7, 71.0, 68.0, 61.7. Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.83; H, 6.47. The monoallyl ether **21** obtained above was converted to the known[7] racemic dibenzyl ether **47** as follows: to a solution of **21** (0.050 g, 0.20 mmol) in DMF (1 mL), sodium hydride (0.016 g, 0.40 mmol) was added and stirred for 5 min. Benzyl bromide (0.068 g, 0.40 mmol) was added and the mixture stirred for 0.5 h and worked up as usual to obtain **47** (0.062 g, 97%).

3.2.3. Racemic 4-*O*-benzyl-6-*O*-acetyl-*myo*-inositol 1,3,5-orthoformate (22). The monobenzyl ether **17** (0.286 g, 1 mmol) was acetylated (procedure B, reaction time 4 h), with acetic anhydride (0.125 g, 1.20 mmol) to obtain the racemic **22** (0.230 g, 70%). Mp 102–104 °C. IR (ν): 3300–3570, 1737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.16–7.45 (m, 5H), 5.51 (s, 1H), 5.35–5.46 (m, 1H), 4.62–4.72 (m, 1H), 4.57 (s, 2H), 4.05–4.43 (m, 4H), 3.20–3.40 (d, 1H, $J=11.8$ Hz, D_2O exchangeable), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.2, 137.5, 128.8, 128.4, 127.7, 103.5, 73.6, 72.8, 72.2, 68.6, 66.6, 61.6, 20.9. Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.91; H, 5.65.

3.2.4. Racemic 4-*O*-benzyl-6-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoformate (23). The monobenzyl ether **17** (0.278 g, 1 mmol) was sulfonylated (procedure B, reaction time 4 h), with *p*-toluenesulfonyl chloride (0.228 g, 1.20 mmol) to obtain the 6-tosylate **23** (0.283 g, 65%). Mp 160–162 °C. IR (ν): 3300–3600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.70–7.80 (d, 2H, $J=8.3$ Hz), 7.20–7.40 (m, 7H), 5.43 (s, 1H), 5.13–5.25 (m, 1H), 4.48–4.70 (AB q, 2H, $J=11.7$ Hz), 4.40–4.47 (m, 1H), 4.27–4.39 (m, 1H), 4.15–4.24 (m, 1H), 3.96–4.14 (m, 2H), 3.05–3.16 (d, 1H, $J=11.7$ Hz, D_2O exchangeable), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 145.7, 137.4, 133.1, 130.3, 128.7, 128.1, 127.9, 103.3, 73.0, 72.9, 72.8, 72.3, 71.8, 67.5, 60.9, 21.9. Anal. Calcd for $C_{21}H_{22}O_8S$: C, 58.06; H, 5.10. Found: C, 58.10; H, 4.80.

3.2.5. Racemic 4-*O*-(*p*-toluenesulfonyl)-6-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (24). The racemic 4-tosylate **18**[6b] (0.344 g, 1 mmol) was allylated (procedure B), with allyl bromide (0.145 g, 1.20 mmol) to obtain **24** (0.278 g, 72%) as gum. IR (ν): 3200–3600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75–7.85 (d, 2H, $J=8.3$ Hz), 7.30–7.45 (d, 2H, $J=$ 8.3 Hz), 5.75–6.00 (m, 1H), 5.44 (s, 1H), 5.05–5.38 (m, 3H), 4.35–4.50 (m, 1H), 3.95–4.34 (m, 6H), 3.10–3.25 (d, 1H, $J=10.3$ Hz, D_2O exchangeable), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 145.8, 133.9, 130.3, 128.2, 118.1, 103.3, 72.8, 72.3, 70.8, 67.5, 60.9, 21.9. The tosylate **24** obtained above was converted to the known[7] 4-allyl ether **48** as follows: the racemic **24** (0.050 g, 0.13 mmol) and sodium methoxide (0.070 g, 1.30 mmol) were refluxed in dry methanol (2 mL) for 2 h. The reaction mixture was cooled to ambient temperature and worked up as usual to obtain racemic **48** (0.026 g, 87%) as a gum. The monoallyl ether **48** (0.026 g) was characterized as its diacetate **49** (0.031 g, 89%) obtained by acetylation with acetic anhydride (0.046 g, 0.45 mmol) in pyridine (1 mL) for 12 h to get a colorless solid. Mp 87–89 °C. IR (ν): 1742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.79–5.94 (m, 1H), 5.57 (d, 1H, $J=$ 1 Hz), 5.38–5.43 (m, 1H), 5.31–5.35 (m, 1H), 5.19–5.29 (m, 2H), 4.61–4.66 (m, 1H), 4.35–4.40 (m, 1H), 4.27–4.33 (m, 2H), 4.03–4.10 (m, 2H), 2.22 (s, 3H), 2.06 (s, 3H). Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.70; H, 5.73.

3.2.6. 4,6-Di-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoformate (25). The racemic 4-tosylate **18** (0.500 g, 1.45 mmol) was taken in THF (8 mL) and *n*-butyllithium (1.60 mmol) was added at −78 °C. A solution of tosyl chloride (0.332 g, 1.75 mmol) in THF (2 mL) was added and the mixture stirred for 2 h during which the reaction temperature was allowed to come to ambient temperature. The resulting mixture was then worked up with ethyl acetate. The known ditosylate **25** (0.412 g, 57%) was separated by column chromatography. Mp 181–182 °C, (lit.[25] Mp 183–185 °C).

3.2.7. Racemic 4-*O*-(*p*-toluenesulfonyl)-6-*O*-allyl-*myo*-inositol 1,3,5-orthoacetate (26). The racemic 4-tosylate **19** (0.358 g, 1 mmol) was allylated (procedure B), with allyl bromide (0.146 g, 1.20 mmol) to obtain **26** (0.246 g, 62%) as gum. IR (ν): 3300–3590 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.75–7.84 (d, 2H, $J=8.3$ Hz), 7.30–7.43 (d, 2H, $J=8.3$ Hz), 5.75–6.00 (m, 1H), 5.15–5.40 (m, 2H), 5.00–5.12 (m, 1H), 4.34–4.39 (m, 1H), 3.94–4.28 (m, 6H), 2.89–3.10 (br s, 1H, D_2O exchangeable), 2.47 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 145.6, 134.0, 133.4, 130.3, 128.2, 117.9, 109.4, 73.5, 73.2, 72.9, 72.7, 70.8, 67.5, 60.0, 24.3, 21.8. Anal. Calcd for $C_{18}H_{22}O_8S$: C, 54.26; H, 5.57. Found: C, 54.12; H, 5.55.

3.2.8. 4,6-Di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (20). The triol **1** (0.190 g, 1 mmol) was benzylated using benzyl bromide (0.376 g, 2.20 mmol) and *n*-butyllithium (procedure C) to obtain the known **20**[7] (0.296 g, 80%). Mp 118–120 °C.

3.2.9. 4,6-Di-*O*-benzyl-*myo*-inositol 1,3,5-orthoacetate (27). The triol **2** (0.204 g, 1 mmol) was benzylated using benzyl bromide (0.359 g, 2.20 mmol) and *n*-butyllithium

(procedure C) to obtain **27** (0.268 g, 70%) as a solid. Mp 88–90 °C. IR (ν): 3300–3600 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.28 (s, 10H), 4.52–4.71 (AB q, 4H, $J=11.7$ Hz), 4.08–4.46 (m, 6H), 2.95–3.10 (d, 1H, $J=11.7$ Hz, D_2O exchangeable), 1.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 137.7, 128.5, 127.9, 127.7, 109.3, 73.8, 73.6, 71.7, 67.9, 60.4, 24.4. Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.97; H, 6.14.

3.2.10. 4,6-Di-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (28). The triol **1** (0.190 g, 1 mmol) was allylated using allyl bromide (0.278 g, 2.30 mmol) and lithium hydride (procedure D) to obtain **28** (0.251 g, 93%) as a gum. IR (ν): 3250–3700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.82–5.93 (m, 2H), 5.48 (s, 1H), 5.26–5.33 (dd, 2H, $J=1.4$, 17.0 Hz), 5.17–5.23 (dd, 2H, $J=1.4$, 10.0 Hz), 4.39–4.44 (m, 1H), 4.26–4.31 (t, 2H, $J=3.2$ Hz), 4.18–4.23 (m, 2H), 4.03–4.15 (m, 5H), 3.08–3.20 (d, 1H, $J=10$ Hz, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 134.3, 117.5, 103.5, 73.8, 73.2, 70.7, 68.0, 61.5. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.60; H, 7.04.

3.2.11. Racemic 2-*O*-methyl-4-*O*-benzyl-6-*O*-allyl-*myo*-inositol 1,3,5-orthoformate (29). Racemic **17** (0.281 g, 1 mmol) was taken in THF (4 mL) and cooled to 0 °C. *n*-Butyllithium (1.1 mL, 1.50 mmol) was added slowly followed by allyl bromide (0.145 g, 1.20 mmol) in dry DMF (2 mL) and the mixture stirred for 22 h. Then excess sodium hydride (0.100 g, 2.50 mmol) and methyl iodide (0.355 g, 2.50 mmol) were added and the mixture stirred for 4 h and worked up with ethyl acetate. The triether **29** (0.267 g, 80%) was separated (as gum) by flash column chromatography. ^1H NMR ($CDCl_3$): δ 7.20–7.50 (m, 5H), 5.75–6.05 (m, 1H), 5.51 (s, 1H), 5.14–5.40 (m, 2H), 4.51–4.76 (AB q, 2H, $J=11.7$ Hz), 4.24–4.50 (m, 5H), 4.00–4.23 (m, 2H), 3.78 (s, 1H), 3.48 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 137.9, 134.4, 128.7, 128.1, 127.8, 117.9, 103.4, 74.2, 74.0, 71.9, 71.1, 70.2, 70.0, 69.6, 68.3, 56.9. Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.76; H, 6.89.

3.2.12. Racemic 4-*O*-(*t*-butyldimethylsilyl)-*myo*-inositol 1,3,5-orthoformate (41). The triol **1** (0.500 g, 2.63 mmol) was silylated (procedure A) in THF (25 mL) using *n*-butyllithium (1.7 mL, 2.63 mmol) and a solution of TBDMSCl (0.476 g, 3.15 mmol) in THF (5 mL). The known racemic **41** (0.584 g, 73%) was isolated by column chromatography. Mp 74–76 °C, (lit.[22] Mp 73–74 °C).

3.2.13. Racemic 4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate (42). To a solution of the triol **1** (1 g, 5.30 mmol) in DMF (15 mL) was added sodium hydride (0.233 g, 5.83 mmol) and stirred for 0.5 h. A solution of trityl chloride (1.630 g, 5.83 mmol) in DMF (8 mL) was added drop-wise and the mixture stirred for 1 h. The reaction mixture was worked up with ethyl acetate and the crude product was purified by filtration over a short column of silica gel to obtain **42** (0.900 g, 40%) as a solid. Mp 217–218 °C. IR (ν): 3350–3700 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.20–7.60 (m, 15H), 5.28 (s, 1H), 4.53–4.62 (m, 1H), 4.16–4.40 (m, 3H), 3.84–3.89 (d, 1H, $J=9.8$ Hz, D_2O exchangeable), 3.69–3.77 (m, 1H), 3.02–3.20 (m, 2H, 1H D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 142.6, 128.4, 128.2, 128.0, 102.3, 89.8, 74.1, 73.1, 70.1, 67.7, 67.4, 60.9. Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.19; H, 5.73.

3.2.14. Racemic 2,4-di-*O*-(*t*-butyldimethylsilyl)-*myo*-inositol 1,3,5-orthoformate (43). The triol **1** (0.150 g, 0.80 mmol) was silylated (procedure D) in dry DMF (2 mL) using lithium hydride (0.260 g, 3.20 mmol) and *t*-butyldimethylsilyl chloride (0.253 g, 1.68 mmol) to obtain the known racemic **43** (0.174 g, 52%) as a solid. Mp 79–81 °C, (lit.[26] Mp 75–78 °C).

3.2.15. Methylation of racemic 4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate (42). Racemic **42** (0.600 g, 1.40 mmol) was methylated (procedure A) in THF (6 mL) using *n*-butyllithium (1 mL, 1.68 mmol) and methyl iodide (0.12 mL, 1.68 mmol) to obtain the 6-methyl ether **44** (0.147 g, 24%), the 2-methyl ether **45** (0.036 g, 6%) and the dimethyl ether **46** (0.183 g, 29%). Data for **44**: Mp 165–166 °C. IR (ν): 3323–3541 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.43–7.55 (m, 6H), 7.23–7.40 (m, 9H), 5.29 (s, 1H), 4.43–4.52 (m, 1H), 4.02–4.10 (m, 1H), 4.14–4.24 (m, 2H), 3.72–3.83 (m, 1H), 3.46 (s, 3H), 3.08–3.18 (m, 1H), 2.85 (br s, 1H, D_2O exchangeable). ^{13}C NMR ($CDCl_3$): δ 143.8, 128.6, 128.0, 127.5, 102.8, 88.0, 75.8, 73.7, 72.4, 69.0, 68.0, 61.3, 57.6. Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.30; H, 6.10. Data for **45**: mp 191–193 °C. IR (ν): 3304–3541 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.25–7.50 (m, 15H), 5.32 (d, 1H, $J=1.1$ Hz), 4.54–4.62 (m, 1H), 4.31–4.45 (m, 2H), 3.79–3.89 (m, 2H, 1H D_2O exchangeable), 3.57–3.65 (m, 1H), 3.48 (s, 3H), 3.41–3.51 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 142.7, 128.5, 128.2, 128.1, 102.3, 89.9, 71.1, 70.3, 69.9, 69.0, 68.1, 67.8, 56.9. Anal. Calcd for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.43; H, 5.44. Data for **46**: mp 251–253 °C. ^1H NMR ($CDCl_3$): δ 7.45–7.55 (m, 5H), 7.20–7.40 (m, 10H), 5.34 (s, 1H), 4.44–4.52 (m, 1H), 4.28–4.36 (m, 1H), 4.08–4.15 (m, 1H), 3.99–4.07 (m, 1H), 3.74–3.80 (m, 1H), 3.53 (s, 3H), 3.31 (s, 3H), 3.07–3.14 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 143.9, 128.6, 128.1, 127.5, 102.8, 88.0, 75.9, 70.1, 69.7, 69.4, 69.2, 68.5, 57.7, 56.7. Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.03; H, 6.13. Found: C, 72.99; H, 6.10. The proportion of **44** and **45** formed on using butyllithium and sodium hydride for the methylation of **42** were estimated as follows: racemic **42** (0.100 g, 0.23 mmol) was methylated (procedure A) in THF (1 mL) using *n*-butyllithium (0.15 mL, 0.25 mmol) and methyl iodide (0.02 mL, 0.25 mmol) in DMF (0.18 mL). The mixture of monoethers **44** and **45** (0.042 g) was separated by column chromatography and their proportion (**44/45**=61:39) estimated by ^1H NMR spectroscopy. Use of sodium hydride (0.010 g, 0.25 mmol) instead of butyllithium in the above experiment provided a mixture of the two ethers (0.053 g) in the ratio **44/45**=11:89 and the dimethyl ether **46** (0.030 g, 28%).

3.2.16. Racemic 2-*O*-methyl-4-*O*-trityl-*myo*-inositol 1,3,5-orthoformate (45). To a solution of the ditosylate **25** (0.300 g, 0.60 mmol) in DMF, sodium hydride (0.036 g, 0.90 mmol) was added followed by methyl iodide (0.06 mL, 0.90 mmol). The reaction mixture was stirred for 15 min and worked up with ethyl acetate as usual to get 2-*O*-methyl-4,6-di-*O*-(*p*-toluenesulfonyl)-*myo*-inositol 1,3,5-orthoformate (0.287 g, 93%). Mp 141–143 °C. ^1H NMR ($CDCl_3$): δ 7.75–7.95 (d, 4H, $J=8.2$ Hz), 7.30–7.50 (d, 4H, $J=8.2$ Hz), 5.40–5.48 (d, 1H, $J=1.6$ Hz), 5.05–5.19 (t, 2H, $J=4$ Hz), 4.26–4.37 (m, 2H), 4.13–4.22 (m, 1H), 3.59–3.68 (m, 1H), 3.42 (s, 3H), 2.48 (s, 6H). The methyl ether (0.450 g, 0.90 mmol) and sodium methoxide (0.486 g,

9 mmol) were refluxed in dry methanol/THF (4:1) for 6 h. The solvents were evaporated and the solid obtained was chromatographed over silica gel using 1:1 ethyl acetate–light petroleum as eluent to obtain 2-*O*-methyl-*myo*-inositol 1,3,5-orthoformate (0.124 g, 69%). Mp 179–181 °C. ^{1}H NMR ($(CD_3)_2CO$): δ 5.36–5.41 (d, 1H, $J=1.2$ Hz), 4.98–5.10 (br s, 2H, D_2O exchangeable), 4.39–4.52 (m, 2H), 4.24–4.31 (m, 2H), 4.15–4.23 (m, 1H), 3.75–3.82 (m, 1H), 3.46 (s, 3H). To a solution of the diol obtained above (0.080 g, 0.40 mmol) in DMF was added sodium hydride (0.024 g, 0.60 mmol) and trityl chloride (0.167 g, 0.60 mmol) and the reaction mixture stirred at ambient temperature for 1 h and worked up as usual with ethyl acetate. Column chromatography over silica gel gave the trityl ether **45** (0.054 g, 31%). Mp 191–193 °C.

Acknowledgements

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Supplementary data

^{1}H NMR spectra of the mixture of monomethyl ethers (**44** and **45**) obtained by the methylation of **42** using butyllithium/methyl iodide and sodium hydride/methyl iodide can be found, in the online version, at doi:10.1016/j.tet.2004.11.025

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Efficient synthesis of various acycloalkenyl derivatives of pyrimidine using cross-metathesis and Pd(0) methodologies

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Abstract—Novel acyclonucleosides (**9a–d**, **10a–d**, **18a**,**b** and **19a**,**b**) have been prepared using Pd(0) and cross-metathesis methodologies. The allylic *N*-alkylation under Tsuji–Trost conditions was used to introduce the nucleobase, while the Suzuki–Miyaura reaction afforded C-5 substituted uracil analogues. The cross-metathesis performed with a ruthenium catalyst was used to provide new acycloalkenyl nucleosides. The antiviral activities of all final compounds have been evaluated.

1. Introduction

Interest in acyclic nucleosides began in the mid-1970s when acyclovir was first reported as a potent anti-herpes drug.[1] The unprecedented selectivity of acyclovir as an antiviral drug and the subsequent clarification of its behavior towards virally coded enzymes provided massive impetus for further synthesis of such compounds and for the investigation of their biochemical fate. Many variations, both of the acyclic glycone and of the heterocyclic base, have been described.[2,3] Acyclonucleosides are commonly synthesized by reaction of nucleic bases with α-chloromethyl ethers in the presence of strong bases[4] or by reaction of persilylated nucleic bases with an activated aglycone catalyzed by various Lewis acid[5] (Vorbrüggen conditions).[6] Others' approaches have employed an acid catalyzed transglycosylation,[7] an oxidative cleavage of the pentose moiety of cyclic nucleosides.[8] Acycloalkenyl nucleosides can be produced through the alkylation of 1,4-dichloro-2-butyne with the heterocycle followed by an acetylene–allene isomerization,[9] or from a protected glyceraldehydes using a Wittig–Horner–Emmons reaction; nevertheless, in the later case, only the *Z*-α,β-unsaturated ester was obtained exclusively without any trace of the *E*-isomer.[10]

Efforts aimed at synthesizing and isolating new actives nucleosides now require the development and elaboration of new strategy yielding facile and rapid access to a large variety of compounds. To our knowledge, no attempt has been made to use a combination of olefin cross-metathesis[11] and palladium-assisted routes[12] to make acyclonucleosides; our aim was thus to fill this gap. As part of our drug discovery program, we have previously reported[13] a preliminary account of methodologies leading to acycloalkenyl nucleosides. In this paper, we report an extension of this strategy as a powerful route for the synthesis and the diversification of new acycloalkenyl pyrimidine nucleosides including trisubstituted alkene and allylic phosphonate (Fig. 1).

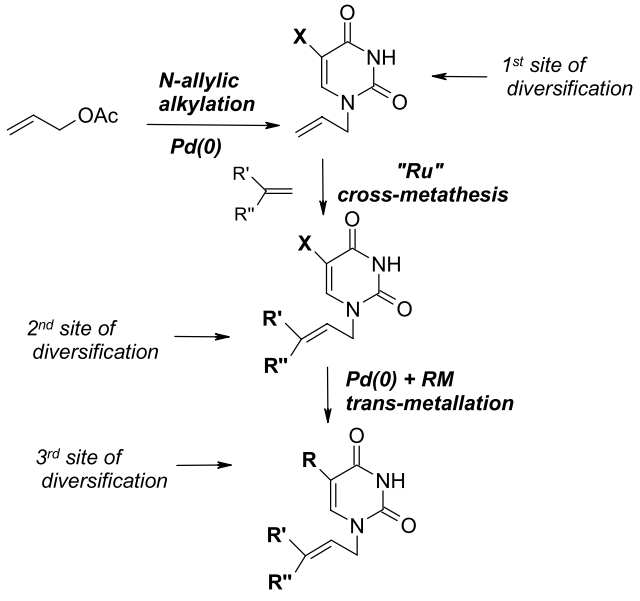

Figure 1.

Keywords: Cross-metathesis; Acyclonucleosides; Suzuki–Miyaura; Pd(0).
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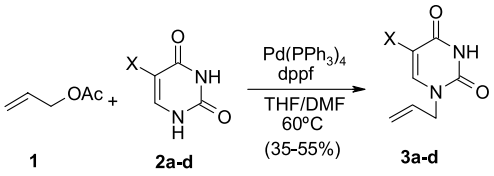
2. Results and discussion

2.1. Allylic *n*-alkylation by Tsuji–Trost reaction

The first step of this synthetic approach consists in the regioselective synthesis of *N*-allyl derivatives of nucleobases using Pd(0)-catalyzed reaction of commercially available allylic acetate with various pyrimidines under Tsuji–Trost conditions (Scheme 1).



Entry	Nucleobase	X	Product	Yield (%)
1	**2a**	H	**3a**	45[a]
2	**2b**	CH_3	**3b**	55
3	**2c**	I	**3c**	35
4	**2d**	F	**3d**	52[b]

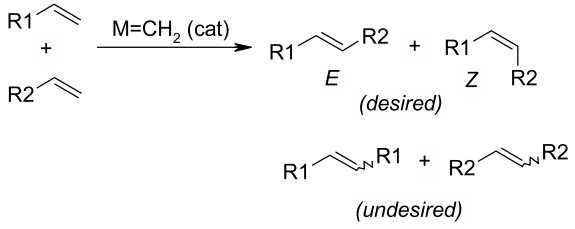
[a]total yield: formation of a 4/1 mixture of monoallylated and diallylated compounds separable by chromatography. [b]total yield: formation of a 5/2 mixture of monoallylated and diallylated compounds separable by chromatography.

Scheme 1.

Thus, treatment of uracil derivatives **2a–d** with allyl acetate **1** in the presence of freshly prepared $Pd(PPh_3)_4$ and dppf [(1,1′-bis(diphenyl-phosphinoferocene)] in a mixture of THF/DMF, led to the desired N-1 allylic pyrimidine derivatives **3a–d** in moderate yield. It is interesting to note that in the case of uracil (entry 1) and 5-fluorouracil (entry 4), the Tsuji–Trost allylic alkylation led to a 4/1 and 5/2 mixture of N-1 monoallylated (**3a** or **3d**, respectively) and N1,N3-diallylated analogues. The formation of bis-alkylated product has been reported[14] previously as has the influence of the solvent on the regioselectivity of the Pd(0)-catalyzed allylation of uracils.[15]

2.2. Cross-metathesis

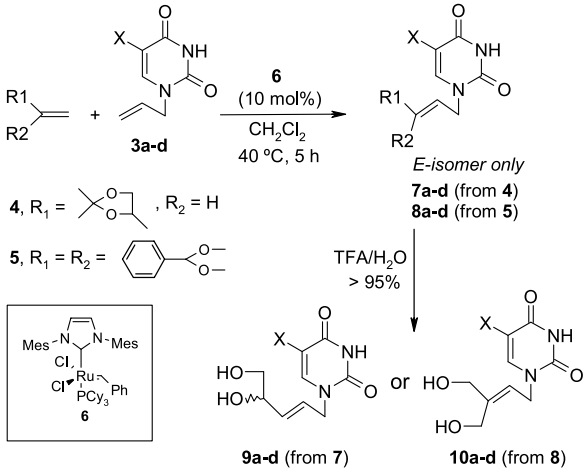
In contrast to the vast number of successful ring-closing metathesis reactions, only a few examples of selective cross-metathesis in the presence of functional groups have been reported.[16] In fact, the metal carbene catalyzed intermolecular coupling between two different olefins potentially yields four new alkenes as depicted in Scheme 2. Thus, the allylthymine cross-metathesis efficiency depends



Scheme 2.

on the selectivity observed in the coupling. Optimization of the desired alkene as well as the stereocontrol of the formed double bond is a crucial issue to access its usefulness for the synthesis of unsaturated acyclonucleosides.

In order to achieve diversification within the acyclic nucleoside family, we have explored and optimized the cross-metathesis reaction of two terminal olefins, 2,2-dimethyl-4-vinyl-[1,3]dioxolane[17] (**4**) and 5-methylene-2-phenyl-[1,3]dioxane[18] (**5**), with allyluracils (**3a–d**). Under optimized conditions moderate to good yields of the desired products were achieved (Scheme 3).



Entry	Olefin	X	Product	Yield (%)
1	**4**	H	**7a**	78
2	//	CH_3	**7b**	50
3	//	I	**7c**	56
4	//	F	**7d**	62
5	**5**	H	**8a**	53
6	//	CH_3	**8b**	64
7	//	I	**8c**	57
8	//	F	**8d**	70

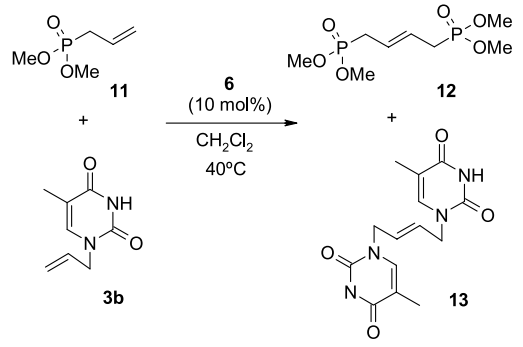
Scheme 3.

It is interesting to note that: (1) no self-metathesis products were observed; (2) those metathetical coupling reactions all proceed with a high or exclusive degree of *trans* selectivity. The ^1H NMR clearly showed that only the *E*-isomer was produced as the major compound with no detectable corresponding *Z*-isomer. Even though its origin is not clear at present, the stereoselectivity of this reaction seems to be substrate dependant; (3) the synthesis of trisubstituted carbon–carbon double bonds such as in **8a–d**, which still remains an ongoing challenge, proceeded smoothly with the ruthenium–carbene species bearing one imidazol-2-ylidene ligand **6**.[19] This catalyst displays a great tolerance towards an array of polar groups.

The acidic deprotection (TFA/H_20, 2/1, v/v) of **7a–d** and **8a–d** afforded in quantitative yields the acycloalkenyl nucleosides **9a–d** and **10a–d**, respectively.

Based on the well-known potent and broad spectrum of

antiviral acyclic phosphonate nucleosides (ANP),[3a,b,20] we then turned our attention to the introduction of a phosphonate moiety using the cross-metathesis methodology. Vinyl or allyl phosphonates have been already reported to be viable cross-metathesis partners in metathesis reaction catalyzed by second generation catalyst.[21] Thus, the allylthymine **3b** was used as substrate in a cross-metathesis reaction with the commercially available allyl phosphonic acid dimethyl ester (**11**) under various conditions (Scheme 4). When a first-generation ruthenium catalyst (up to 1 equiv) was employed (entry 1), no reaction occurred; the starting material was always recovered after allowing the reaction to proceed as long as a few days. When the second generation catalyst **6** was used, the starting material **3b** was rapidly consumed generating a complex mixture of products, which could not be separated by silica gel column chromatography. Any attempt in modifying the solvent or increasing the amount of allylic phosphonate **11** (entries 2–4) always led to the same results. The ^{1}H NMR data suggests that two compounds (**12**,**13**) issuing from the self-metathesis of **11** and **3b**, respectively are present in the complex mixture.



Entry	equiv.	Catalyst (10%)	Solvent	Results
1	5	Grubbs 1	CH_2Cl_2	S.M.
2	5	Nolan (**6**)	CH_2Cl_2	homodimers
3	5	//	Toluene	homodimers
4	10	//	CH_2Cl_2	homodimers

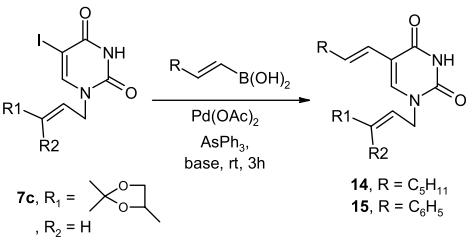
Scheme 4.

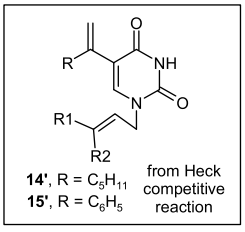
To explain the lack of formation of the desired cross coupling compound, we hypothesized first that the allylic phosphonate **11** may be more reactive than the allylic thymine **3b** in the cross-metathesis reaction; the phosphonate dimer **12** could be initially formed allowing thus the allylic thymine to react only with itself affording the bipyrimidinic derivative **13**. Another hypothesis is based on the reversible nature of the cross-metathesis reaction which ensures the preferential formation of the most thermodynamically stable product, for example, the homodimers in the present case. These results are in agreement with the recently reported general empirical model for olefin reactivity in the cross-metathesis reaction.[22] In fact, categorizing olefins by their relative ability to undergo homodimerization via cross-metathesis, the allyl phosphonate is able to rapidly produce the homodimers.

3. Suzuki–Miyaura coupling

3.1. With alkenyl boronic derivatives

To bring further structural modifications and diversity to the synthesized acycloalkenyl nucleosides, we turned our attention to the coupling of various organoboron compounds with iodinated acycloalkenyl pyrimidine **7c** under Suzuki–Miyaura conditions.[23,24] This reaction is suitable in numerous synthetic pathways to pharmaceutical agents, as boron derivatives are non-toxic, easily prepared and stable. Thus the 5-iodinated derivative **7c** was reacted in THF, at rt, with two boronic acid compounds in the presence of $Pd(OAc)_2$, $AsPh_3$ and K_2CO_3 (Scheme 5).





Entry	Compound	R	Base	Ratio Suzuki : Heck	Yield (%)
1	**14**		K_2CO_3	6 : 3	45
2	//	//	KOH	8 : 2	52
3	**15**		K_2CO_3	5 : 4	55
4	//	//	KOH	7 : 3	60

Scheme 5.

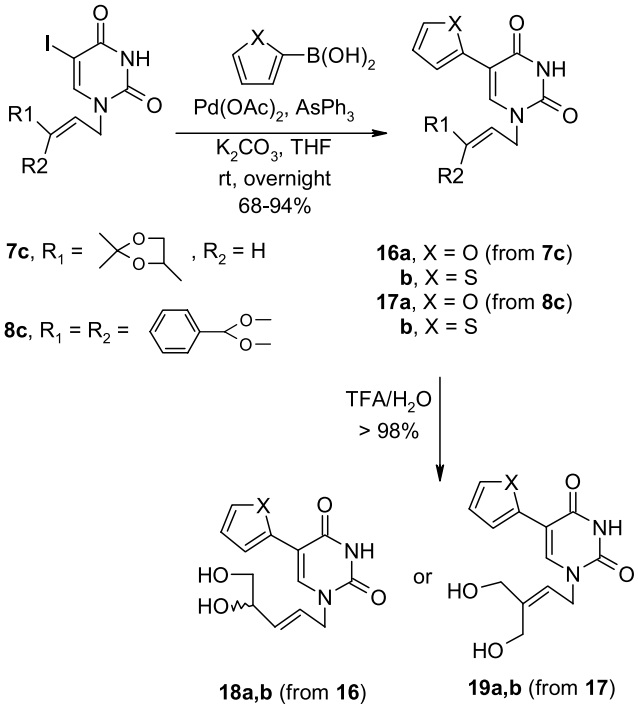
During the Pd(0) transmetallation coupling between **7c** with pentylboronic acid, we observed the formation of two non-separable compounds, one (**14**) resulting from the expected Suzuki–Miyaura reaction and the second (**14′**) from an unexpected Heck reaction. This competition between both reactions has been already reported in the literature[25] for non-aromatic boronic acid. Owing to the low nucleophilicity of an alkenylboronic acid compared with aryl derivatives, the transmetallation step on the Pd(0) catalyst slowly proceeded and a Heck type side reaction took place competitively. In order to accelerate the transmetallation step and suppress the formation of the isomer **14′**, a stronger base such as KOH was used instead of K_2CO_3. This resulted in an increase of the amount of the expected compound **14**; nevertheless, the presence of the byproduct **14′** led us to consider other derivatives. Similar results were obtained with the vinylbenzeneboronic acid affording an inseperable mixture of **15** and **15′**. We thus

turned our attention to the more reactive heterocyclic boronic acids.

3.2. With heterocyclic boronic acid

Herdewijn et al.[26] have described the synthesis and marked antiviral activities of uridine derivatives bearing a thiophene ring at the C-5 position of the nucleobase. Therefore the Suzuki–Miyaura coupling reaction between iodinated derivatives **7c** and **8c**, with the commercially available thiophene (X=S) - or furan (X=O) boronic acids, in the presence of $Pd(OAc)_2$, $AsPh_3$ and K_2CO_3, at rt in THF overnight afforded the desired compounds **16a**,**b** and **17a**,**b**, respectively, in good yields (Scheme 6). These compounds have been obtained by Stille reaction, in similar yields, using appropriate tin derivatives in the presence of $Pd_2(dba)_3$ (20 mol%) and $AsPh_3$ (40 mol%).

The acidic deprotection (TFA/H_20, 2/1, v/v) of nucleosides **16** and **17** afforded in quantitative yields the acycloalkenyl nucleosides **18** and **19**, respectively.



Scheme 6.

4. Biological results

The synthesized compounds **9a–d**, **10a–d**, **18a**,**b** and **19a**,**b**, along with the known antiviral compounds (acyclovir for HSV and AZT for HIV), were tested for their anti-HIV and anti-HSV activity in vitro, and the results are shown in Table 1.

Among these nucleosides analogues, only compounds **10d**, **18a** and **18b** were found to exhibit moderate anti-HIV activity, with an EC_{50} of 72.9, 10.1 and 3.9 μM, respectively. Compounds **18a** and **18b** exhibited also moderate anti-HSV activity with and EC_{50} of 12.2 and 8.8 μM, respectively. Nevertheless, those compounds and especially **18b** showed toxicity against PBM, CEM or VERO cells. The antiviral[27] and cytotoxicity[28] assays were done as previously described.

5. Conclusion

An efficient route to various acycloalkenyl nucleosides (**9a–d**, **10a–d**, **18a**,**b** and **19a**,**b**) has been developed using a combination of Pd(0) and cross-metathesis methodologies. The allylic N-alkylation under Tsuji–Trost conditions was used to introduce the nucleobase, meanwhile the Suzuki–Miyaura reaction afforded C-5 substituted uracil analogues. The cross-metathesis, with a ruthenium catalyst, was used to access new acycloalkenyl nucleosides. The antiviral activities of all final compounds have been determined.

Table 1. Evaluation of synthesized acyclic nucleosides antiviral activity against human immunodeficiency virus (HIV), herpes simplex virus (HSV-1) and cytotoxicity against PBM, CEM and VERO cells in vitro, expressed in μM

Compound	Anti-HIV-1 activity in PBMCs	HSV-1 plaque Reduction assay	Toxicity (IC_{50}) in:		
	EC_{50}	EC_{50}	PBM	CEM	VERO
AZT[a]	0.016	>10	>100	14.0	29.0
Acyclovir[a]	>100	0.11	>100	>100	>100
9a	(100	(100	(100	(100	(100
9b	(100	(100	(100	(100	(100
9c	(100	(100	(100	(100	(100
9d	ND[b]	ND	ND	ND	ND
10a	(100	(100	(100	(100	(100
10b	(100	(100	(100	(100	(100
10c	(100	(100	(100	(100	(100
10d	72.9	(100	64.9	49.3	(100
18a	10.1	12.2	20.5	16.8	27.6
18b	3.9	8.8	13.4	6.6	4.9
19a	(100	(100	(100	(100	(100
19b	(100	(100	70.9	65.1	(100

[a] Reference compounds.
[b] ND: not determined.

6. Experimental

6.1. General methods

Commercially available chemicals were reagent grade and used as received. THF was distilled from sodium/benzophenone and CH_2Cl_2 from CaH_2 immediately prior use. The reactions were monitored by thin-layer chromatography (TLC), analysis using silica gel plates (kieselgel 60 F_{254}, E. Merck). Compounds were visualized by UV irradiation and/or spraying with 20% H_2SO_4 in EtOH, followed by charring at 150 °C. Column chromatography was performed on Silica Gel 60 M (0.040–0.063 mm, E. Merck). NMR spectra were recorded with a Brucker AVANCE DPX 250 Fourier transform 250 spectrometer, with Me_4Si as the internal standard, unless otherwise stated. Chemical shifts are given in ppm (δ). High Resolution Mass spectra were performed by the Centre regional de Mesures Physiques de l'Ouest (University of Rennes, France).

6.2. General procedure for Tsuji–Trost reaction

To a solution of pyrimidine (**2**) (8.40 mmol) in DMF/THF (100 mL, 1/1) was added NaH (202 mg, 8.40 mmol, 60% dispersion in oil). After heating this suspension at 60 °C for 45 min, allyl acetate **1** (0.45 mL, 4.20 mmol), dppf (232 mg, 0.42 mmol) and freshly prepared $Pd(PPh_3)_4$ (485 mg, 0.42 mmol) were successively added. The reaction was heated to 40 °C until complete conversion was reached. The mixture was allowed to return to room temperature, diluted with EtOAc (25 mL) and washed with an aqueous saturated solution of NH_4Cl. The organic layer was dried over anhydrous $MgSO_4$, filtered then concentrated in vacuo and the residue was finally purified by column flash chromatography to afford (**3**).

6.2.1. 1-Allyl-2,4(1*H*,3*H*)-pyrimidinedione (3a).[15] Eluant PE/EtOAc 5/5; white solid; mp 102 °C; ^{1}H NMR ($CDCl_3$) δ 4.30 (d, 2H, J=5.7 Hz), 5.22 (dd, 2H, J=9.4, 16.3 Hz), 5.68 (d, 1H, J=7.8 Hz), 5.72–5.93 (m, 1H), 7.10 (d, 1H, J=7.8 Hz), 9.84 (br s, NH); ^{13}C NMR ($CDCl_3$) δ 50.1 (CH_2), 102.5 (CH), 119.5 (CH_2), 131.5 (CH), 143.9 (CH), 151.0, 164.2; MS: m/z 153 $[M+H]^+$; 175 $[M+Na]^+$; UV (MeOH) λ_{max} 265 nm.

6.2.2. 1-Allyl-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (3b).[29] Eluant PE/EtOAc 3/7; yield 55%; white solid; mp 122 °C; ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3H), 4.31 (d, 2H, J=5.8 Hz), 5.18–5.33 (m, 2H), 5.77–5.92 (m, 1H), 6.96 (s, 1H), 9.74 (br s, NH); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 51.6 (CH_2), 112.8, 120.9 (CH_2), 133.6 (CH), 141.5 (CH), 152.8, 166.3; MS: m/z 167 $[M+H]^+$; UV (MeOH) λ_{max} 269 nm.

6.2.3. 1-Allyl-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (3c). Eluant PE/EtOAc 4/6; yield 35%; white solid; mp 204 °C; ^{1}H NMR (DMSO-d_6) δ 4.26–4.30 (m, 2H), 5.10–5.5.21 (m, 2H), 5.79–5.94 (m, 1H), 8.12 (s, 1H), 11.64 (br s, NH); ^{13}C NMR (DMSO-d_6) δ 49.4 (CH_2), 68.3, 117.7 (CH_2), 132.9 (CH), 149.6 (CH), 150.4, 161.1; HRMS ESI Obsd, m/z 300.9451; calcd for $C_7H_7N_2O_4INa$, m/z 300.9450 $[M+Na]^+$; UV (MeOH) λ_{max} 290 nm.

6.2.4. 1-Allyl-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (3d).[30] Eluant PE/EtOAc 3/7; white solid; mp 101 °C; ^{1}H NMR ($CDCl_3$) δ 4.35 (d, 2H, J=5.9 Hz), 5.35 (dd, 2H, J=10.9, 16.1 Hz), 5.78–5.96 (m, 1H), 7.27 (d, 1H, J=5.4 Hz), 9.65 (sl, NH); ^{13}C NMR (DMSO) δ 50.9 (CH_2), 120.9 (CH_2), 128.5 (CH), 131.5 (CH), 141.1 (C–F), 150.3, 158.1; MS: m/z 171 $[M+H]^+$; UV (MeOH) λ_{max} 270 nm.

6.3. General procedure for cross-metathesis reaction

To a solution of allyl derivative (0.66 mmol) in freshly distilled CH_2Cl_2 (12.5 mL) were successively added the protected diol **4** or **5** (3.32 mmol) and ruthenium catalyst **6** (56 mg, 0.06 mmol). The reaction mixture was stirred at 40 °C during 5 h. After evaporation of volatiles the crude residue was purified by flash chromatography.

6.3.1. 1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-2,4(1*H*,3*H*)-pyrimidinedione (7a). Eluant PE/EtOAc 2/8; yield 78%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.41 (s, 3H), 3.58 (dd, 1H, J=8.0 Hz), 4.10 (dd, 1H, J=6.4, 8.0 Hz), 4.25–4.47 (m, 2H), 4.48–4.57 (m, 1 H), 5.63–5.78 (m, 2H), 5.83 (dt, 1H, J=5.3, 15.7 Hz), 7.13 (d, 1H, J=7.8 Hz), 9.45 (s, NH); ^{13}C NMR ($CDCl_3$) δ 25.9 (CH_3), 26.8 (CH_3), 49.0 (CH_2), 69.3 (CH_2), 76.8 (CH), 102.8 (CH), 109.8, 126.9 (CH), 133.2 (CH), 143.8 (CH), 150.8 (CO), 163.8 (CO); HRMS EI Obsd, m/z 237.0892; calcd for $C_{11}H_{13}N_2O_4$, m/z 237.08753 $[M-CH_3]^+$; UV (MeOH) λ_{max} 265 nm.

6.3.2. 1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (7b). Eluant PE/EtOAc 2/8; yield 50%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.42 (s, 3H), 1.90 (s, 3H), 3.58 (dd, 1H, J=8.0 Hz), 4.10 (dd, 1H, J=6.4, 8.0 Hz), 4.22–4.41 (m, 2H), 4.47–4.57 (m, 1H), 5.69 (dd, 1H, J=6.6, 15.2 Hz), 5.82 (dt, 1H, J=7.0, 15.2 Hz) 6.94 (s, 1H), 9.32 (s, NH); ^{13}C NMR ($CDCl_3$) δ 12.4 (CH_3), 25.9 (CH_3), 26.7 (CH_3), 48.8 (CH_2), 69.4 (CH_2), 76.0 (CH), 109.8, 111.3, 127.3 (CH), 132.7 (CH), 139.7 (CH), 150.9, 164.4; HRMS EI Obsd, m/z 266.1269; calcd for $C_{13}H_{18}N_2O_4$, m/z 266.12666 $[M]^{+\cdot}$; UV (MeOH) λ_{max} 270 nm.

6.3.3. 1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (7c). Eluant PE/EtOAc 5/5; yield 56%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.43 (s, 3H), 3.61 (dd, 1H, J=7.3, 8.1 Hz), 4.12 (dd; 1H, J=6.3, 8.1 Hz), 4.31–4.44 (m, 2H), 4.51–4.59 (m, 1H), 5.71–5.90 (m; 2H), 7.57 (s, 1H), 9.03 (bs, NH); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.8, 49.5, 68.4, 69.3, 75.8, 109.9, 126.3, 133.9, 148.2, 150.4, 160.4; HRMS EI Obsd, m/z 378.087; calcd for $C_{12}H_{15}N_2O_4I$, m/z 300.9450 $[M]^{+\cdot}$; UV (MeOH) λ_{max} 288 nm.

6.3.4. 1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (7d). Eluant PE/EtOAc 4/6; yield 62%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.43 (s, 3H), 3.60 (dd, 1H, J=7.3, 8.1 Hz), 4.12 (dd; 1H, J=6.3, 8.1 Hz), 4.33–4.42 (m, 2H), 4.51–4.61 (m, 1H), 5.72–5.90 (m, 2H), 7.23 (d, 1H, J=5.4 Hz,), 9.60 (s, NH); ^{13}C NMR ($CDCl_3$) δ 25.8 (CH_3), 26.7 (CH_3), 49.3 (CH_2), 69.3 (CH_2), 75.8 (CH), 109.9, 126.0 (CH), 127.8 (CH), 134.1 (CH), 140.1 (C–F), 149.5, 157.3;

HRMS ESI Obsd, *m/z* 293.1604; calcd for $C_{12}H_{15}FN_2O_4Na$, *m/z* 293.1608 $[M+Na]^+$; UV (MeOH) λ_{max} 270 nm.

6.3.5. 1-[2-(2-Phenyl-1,3-dioxan-5-yliden)ethyl]-2,4(1*H*, 3*H*)-pyrimidinedione (8a). Eluant PE/EtOAc 2/8; yield 53%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 4.28–4.55 (m, 5H), 4.96–5.05 (m, 1H), 5.43–5.51 (m, 1H), 5.58 (d, 1H, $J=7.3$ Hz), 5.69 (s, 1H), 7.28–7.49 (m, 5H), 7.63 (d, 1H, $J=7.3$ Hz), 11.29 (s, NH); ^{13}C NMR (DMSO-d_6) δ 43.6 (CH_2), 65.3 (CH_2), 70.6 (CH_2), 100.5 (CH), 101.2 (CH), 119.6 (CH), 126.1 (CH $\times$2), 128.1 (CH $\times$2), 128.7 (CH), 133.9, 138.3, 145.2 (CH), 150.8, 163.7; HRMS ESI Obsd, *m/z* 323.1007; calcd for $C_{16}H_{16}N_2O_4Na$, *m/z* 323.1008 $[M+Na]^+$; UV (MeOH) λ_{max} 265 nm.

6.3.6. 5-Methyl-1-[2-(2-phenyl-1,3-dioxan-5-yliden)-ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (8b). Eluant PE/EtOAc 2/8; yield 64%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 1.76 (s, 3H), 4.26–4.60 (m, 5H), 4.92–5.05 (m, 1H), 5.41–5.52 (m, 1H), 5.69 (s, 1H), 7.29–7.61 (m, 6H), 11.28 (s, NH); ^{13}C NMR (DMSO-d_6) δ 11.9 (CH_3), 43.4 (CH_2), 65.3 (CH_2), 70.7 (CH_2), 100.4 (CH), 108.8, 119.7 (CH), 126.1 (CH $\times$2), 128.0 (CH $\times$2), 128.7 (CH), 133.7, 138.3, 140.9 (CH), 150.7, 164.2; HRMS ESI Obsd, *m/z* 337.3415; calcd for $C_{17}H_{18}N_2O_4Na$, *m/z* 337.3417 $[M+Na]^+$; UV (MeOH) λ_{max} 270 nm.

6.3.7. 5-Iodo-1-[2-(2-phenyl-1,3-dioxan-5-yliden) ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (8c). Eluant PE/EtOAc 4/6; yield 57%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 4.17–4.26 (m, 1H), 4.42–4.55 (m, 4H), 4.93–4.99 (m, 1H), 5.45 (t, 1H, $J=6.7$ Hz), 5.68 (s, 1H), 7.36–7.40 (m, 3H), 7.47–7.51 (m, 2H), 7.61 (s, 1H), 8.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 44.8 (CH_2), 66.1 (CH_2), 68.8, 71.9 (CH_2), 102.0 (CH), 118.6 (CH), 126.4 (CH $\times$2), 128.7 (CH $\times$2), 129.5 (CH), 136.7, 137.9, 148.3 (CH), 150.6, 160.5; HRMS ESI Obsd, *m/z* 448.9980; calcd for $C_{16}H_{15}N_2O_4INa$, *m/z* 448.9974 $[M+Na]^+$; UV (MeOH) λ_{max} 290 nm.

6.3.8. 5-Fluoro-1-[2-(2-phenyl-1,3-dioxan-5-yliden)-ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (8d). Eluant PE/EtOAc 5/5; yield 70%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 4.23–4.55 (m, 5H), 4.95–5.00 (m, 1H), 5.48 (t, 1H, $J=6.6$ Hz), 5.69 (s, 1H), 7.34–7.41 (m, 5H), 8.08 (d, 1H, $J=6.6$ Hz), 11.81 (s, NH); ^{13}C NMR (DMSO-d_6) δ 43.9 (CH_2), 65.3 (CH_2), 70.6 (CH_2), 100.5 (CH), 119.2 (CH), 126.1 (CH $\times$2), 128.1 (CH $\times$2), 129.4 (CH), 129.7 (CH, $J=132.3$ Hz), 134.1, 138.3, 139.7 (C–F), 149.4, 157.5; HRMS ESI Obsd, *m/z* 341.3052; calcd for $C_{16}H_{15}FN_2O_4Na$, *m/z* 341.3048 $[M+Na]^+$; UV (MeOH) λ_{max} 269 nm.

6.4. General procedure for Suzuki reaction

Under dry nitrogen, to a solution of iodo derivatives (0.132 mmol) in THF (1 mL), boronic acid derivatives (0.529 mmol), $Pd(OAc)_2$ (0.053 mmol), Ph_3As (0.026 mmol) and K_2CO_3 (1.188 mmol) were added. The reaction was stirred at room temperature until complete conversion was reached. After evaporation of volatiles the crude residue was purified by column flash chromatography.

6.4.1. 1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-(2-furyl)-2,4(1*H*,3*H*)-pyrimidinedione (16a). Eluant PE/EtOAc 5/5; yield 94%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.42 (s, 3H), 3.60 (dd, 1H, $J=$ 8.1 Hz), 4.11 (dd, 1H, $J=6.3$, 8.1 Hz), 4.42 (d, 2H, $J=$ 5.3 Hz), 4.49–4.57 (m, 1H), 5.76 (dd, 1H, $J=6.6$, 15.7 Hz), 5.89 (dt, 1H, $J=5.65$ Hz, $J=15.7$ Hz), 6.43 (dd, 1H, $J=$ 1.8, 3.5 Hz), 7.04 (d, 1H, $J=3.5$ Hz), 7.33 (d, 1H, $J=$ 1.8 Hz), 7.61 (s, 1H), 10.01 (s, NH); ^{13}C NMR ($CDCl_3$) δ 25.9 (CH_3), 26.7 (CH_3), 49.5 (CH_2), 69.3 (CH_2), 75.9 (CH), 107.4, 109.5, 109.8 (CH), 111.9 (CH), 126.8 (CH), 133.1 (CH), 137.5 (CH), 141.2 (CH), 145.6, 150.0, 160.7; HRMS ESI Obsd, *m/z* 341.1106; calcd for $C_{16}H_{18}N_2O_5Na$, *m/z* 341.1113 $[M+Na]^+$; UV (MeOH) λ_{max} 284 nm.

6.4.2. 1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-(2-thienyl)-2,4(1*H*,3*H*)-pyrimidinedione (16b). Eluant PE/EtOAc 5/5; yield 68%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.43 (s, 3H), 3.61 (dd, 1H, $J=$ 8.0 Hz), 4.12 (dd, 1H, $J=6.3$, 8.0 Hz), 4.38–4.48 (m, 2H), 4.53–4.60 (m, 1H), 5.78 (dd, 1H, $J=6.6$, 15.7 Hz), 5.90 (dt, 1H, $J=5.6$ Hz, $J=15.7$ Hz), 7.00–7.05 (m, 1H), 7.25–7.29 (m, 1H), 7.37–7.40 (m, 1H), 7.48 (s, 1H), 9.98 (s, NH); ^{13}C NMR ($CDCl_3$) δ 25.8 (CH_3), 26.7 (CH_3), 49.4 (CH_2), 69.3 (CH_2), 75.8 (CH), 109.8, 110.4, 124.5 (CH), 125.6 (CH), 126.7, 127.1, 133.2 (CH), 138.7 (CH), 150.1, 161.7; HRMS ESI Obsd, *m/z* 357.0889; calcd for $C_{16}H_{18}N_2O_4NaS$, *m/z* 357.0885 $[M+Na]^+$; UV (MeOH) λ_{max} 260, 324 nm.

6.4.3. 5-(2-Furyl)-1-[2-(2-phenyl-1,3-dioxan-5-yliden)-ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (17a). Eluant PE/EtOAc 5/5; yield 75%; pale yellow gum; ^{1}H NMR ($CDCl_3$) δ 4.18–4.33 (m, 1H), 4.42–4.68 (m, 4H), 4.93–5.07 (m, 1H), 5.51 (t, 1H, $J=6.4$ Hz), 5.68 (s, 1H), 6.45–6.47 (m, 1H), 7.08–7.10 (m, 1H), 7.28–7.42 (m, 4H), 7.47–7.55 (m, 2H), 7.65 (s, 1H), 10.05 (s, NH); ^{13}C NMR ($CDCl_3$) δ 44.6 (CH_2), 65.8 (CH_2), 71.6 (CH_2), 101.5 (CH), 107.5, 109.6 (CH), 111.9 (CH), 118.7 (CH), 126.2 (CH $\times$ 2), 128.4 (CH $\times$2), 129.1 (CH), 135.7, 137.3 (CH), 137.8, 141.3 (CH), 145.6, 150.1, 160.7; HRMS ESI Obsd, *m/z* 389.3741; calcd for $C_{20}H_{18}N_2O_5Na$, *m/z* 389.3748 $[M+Na]^+$; UV (MeOH) λ_{max} 284 nm.

6.4.4. 1-[2-(2-Phenyl-1,3-dioxan-5-yliden)ethyl]-5-(2-thienyl)-2,4(1*H*,3*H*)-pyrimidinedione (17b). Eluant PE/EtOAc 5/5; yield 76%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 4.35–4.56 (m, 5H), 5.00–5.09 (m, 1H), 5.48–5.61 (m, 1H), 5.71 (s, 1H), 6.99–7.12 (m, 1H), 7.28–7.52 (m, 8H), 8.30 (s, 1H), 11.69 (s, NH); ^{13}C NMR (DMSO-d_6) δ 44.2 (CH_2), 65.3 (CH_2), 70.6 (CH_2), 100.4 (CH), 107.9, 119.6 (CH), 122.6 (CH), 125.6 (CH), 126.1 (CH $\times$2), 126.4 (CH), 128.1 (CH $\times$2), 128.7 (CH), 133.8, 133.9, 138.3, 140.7 (CH), 149.8, 161.7; HRMS ESI Obsd, *m/z* 405.0880; calcd for $C_{20}H_{18}N_2O_4NaS$, *m/z* 405.0885 $[M+Na]^+$; UV (MeOH) λ_{max} 260, 324 nm.

6.5. General procedure for deprotection

Acetal derivatives (0.22 mmol) were stirred at room temperature during 3 h in mixture of TFA/H_2O (10 mL/5 mL). After evaporation of volatiles, crude residue are purified by flash chromatography.

6.5.1. 1-[(*E*)-4,5-dihydroxy-2-pentenyl]-2,4 (1*H*,3*H*)-pyrimidinedione (9a). Eluant CH_2Cl_2/MeOH 8/2; yield

98%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.20–3.26 (m, 2H), 3.82–3.97 (m, 1H), 4.27–4.31 (m, 2H), 4.57 (t, OH, J=5.6 Hz), 4.79 (d, OH, J=4.8 Hz), 5.51–5.65 (m, 3H), 7.43 (d, 1H, J=7.6 Hz), 11.17 (s, NH); ^{13}C NMR (DMSO-d_6) δ 38.8 (CH_2), 65.9 (CH_2), 71.4 (CH), 99.8 (CH), 123.8 (CH), 134.1 (CH), 140.8 (CH), 151.2, 162.8; HRMS ESI Obsd, *m/z* 235.0697; calcd for $C_9H_{12}N_2O_4Na$, *m/z* 235.0695 $[M+Na]^+$; UV (MeOH) λ_{max} 265 nm.

6.5.2. 1-[(*E*)-4,5-dihydroxy-2-pentenyl]-5-methyl-2,4-(1*H*,3*H*)-pyrimidinedione (9b). Eluant CH_2Cl_2/MeOH 8/2; yield 96%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 1.74 (s, 3H), 3.22–3.32 (m, 2H), 3.89–4.01 (m, 1H), 4.18–4.25 (m, 2H), 4.60 (t, OH, J=5.8 Hz), 4.85 (d, OH, J=5.0 Hz), 5.57–5.65 (m, 2H), 7.44 (s, 1H), 11.23 (s, NH); ^{13}C NMR (DMSO-d_6) δ 12.0 (CH_3), 48.1 (CH_2), 65.8 (CH_2), 71.3 (CH), 108.7, 124.2 (CH), 135.2 (CH), 141.0 (CH), 150.7, 164.3; HRMS ESI Obsd, *m/z* 249.0851; calcd for $C_{10}H_{14}N_2O_4Na$, *m/z* 249.0851 $[M+Na]^+$; UV (MeOH) λ_{max} 270 nm.

6.5.3. 1-[(*E*)-4,5-dihydroxy-2-pentenyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (9c). Eluant CH_2Cl_2/MeOH 8/2; yield 97%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.21–3.35 (m, 2H), 3.91–4.03 (m, 1H), 4.22–4.36 (m, 2H), 5.61–5.79 (m, 2H), 8.12 (s, 1H), 11.64 (s, NH); ^{13}C NMR (DMSO-d_6) δ 48.9 (CH_2), 65.7 (CH_2), 68.4, 71.4 (CH), 124.2 (CH), 135.8 (CH), 149.8 (CH), 150.6, 161.3; HRMS ESI Obsd, *m/z* 361.1015; calcd for $C_9H_{11}IN_2O_4Na$, *m/z* 361.1011 $[M+Na]^+$; UV (MeOH) λ_{max} 290 nm.

6.5.4. 1-[(*E*)-4,5-dihydroxy-2-pentenyl]-5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione (9d). Eluant CH_2Cl_2/MeOH 8/2; yield 97%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.14–3.32 (m, 2H), 3.94–3.99 (m, 1H), 4.18–4.35 (m, 2H), 4.61 (t, OH, J=5.6 Hz), 4.85 (d, OH, J=4.8 Hz), 5.62–5.78 (m, 2H), 7.99 (d, 1H, J=6.6 Hz), 11.77 (brs, NH); ^{13}C NMR (DMSO-d_6) δ 48.6 (CH_2), 65.7 (CH_2), 71.3 (CH), 123.6 (CH), 129.5 (CH), 135.7 (CH), 139.6 (C–F), 149.4, 157.2; HRMS ESI Obsd, *m/z* 253.1957; calcd for $C_9H_{11}FN_2O_4Na$, *m/z* 253.1953 $[M+Na]^+$; UV (MeOH) λ_{max} 270 nm.

6.5.5. 1-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-2,4(1*H*,3*H*)-pyrimidinedione (10a). Eluant CH_2Cl_2/MeOH 9/1; yield 98%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.94 (d, 2H, J=5.0 Hz), 4.03 (d, 2H,, J=5.3 Hz), 4.38 (d, 2H,, J=7.0 Hz), 4.75 (t, OH, J=5.0 Hz), 4.82 (t, OH, J=5.3 Hz), 5.44 (t, 1H, J=7.0 Hz), 5.55 (d, 1H, J=7.2 Hz), 7.59 (d, 1H, J=7.2 Hz), 11.24 (s, NH); ^{13}C NMR (DMSO-d_6) δ 44.2 (CH_2), 56.9 (CH_2), 62.4 (CH_2), 101.1 (CH), 118.7 (CH), 144.7, 145.3 (CH), 150.9, 163.7; HRMS ESI Obsd, *m/z* 235.0690; calcd for $C_9H_{12}N_2O_4Na$, *m/z* 235.0695 $[M+Na]^+$; UV (MeOH) λ_{max} 265 nm.

6.5.6. 1-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione (10b). Eluant CH_2Cl_2/MeOH 9/1; yield 97%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 1.74 (s, 3H), 3.94 (d, 2H, J=5.0 Hz), 4.03 (d, 2H,, J=5.3 Hz), 4.35 (d, 2H,, J=7.0 Hz), 4.72 (t, OH, J=5.0 Hz), 4.80 (t, OH, J=5.3 Hz), 5.43 (t, 1H, J=7.0 Hz), 7.47 (s, 1H), 11.22 (s, NH); ^{13}C NMR (DMSO-d_6) δ 11.9 (CH_3), 43.9 (CH_2), 56.9 (CH_2), 62.4 (CH_2), 108.7, 118.9 (CH), 141.0, 144.4 (CH), 150.9, 164.3; HRMS ESI Obsd, *m/z* 249.0850; calcd for $C_{10}H_{14}N_2O_4Na$, *m/z* 249.0851 $[M+Na]^+$; UV (MeOH) λ_{max} 270 nm.

6.5.7. 1-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione (10c). Eluant CH_2Cl_2/MeOH 9/1; yield 92%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.94 (d, 2H, J=5.0 Hz), 4.02 (d, 2H, J=5.0 Hz), 4.40 (d, 2H, J=6.9 Hz), 4.76 (t, OH, J=5.0 Hz), 4.83 (t, OH, J=5.0 Hz), 5.44 (t, 1H, J=6.9 Hz), 8.13 (s, 1H), 11.60 (s, NH); ^{13}C NMR (DMSO-d_6) δ 44.6 (CH_2), 56.9 (CH_2), 62.4 (CH_2), 68.3, 118.7 (CH), 144.9, 149.6 (CH), 150.7, 161.1; HRMS ESI Obsd, *m/z* 360.9666; calcd for $C_9H_{11}N_2O_4INa$, *m/z* 360.9661 $[M+Na]^+$; UV (MeOH) λ_{max} 290 nm.

6.5.8. 5-Fluoro-1-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]-2,4(1*H*,3*H*)-pyrimidinedione (10d). Eluant CH_2Cl_2/MeOH 9/1; yield 95%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.94 (d, 2H, J=5.0 Hz), 4.02 (d, 2H, J=5.0 Hz), 4.34 (d, 2H, J=7.2 Hz), 4.75–4.85 (m, OH ×2), 5.45 (t, 1H, J=7.2 Hz), 8.01 (d, 1H, J=6.9 Hz), 11.78 (s, NH); ^{13}C NMR (DMSO-d_6) δ 44.5 (CH_2), 56.9 (CH_2), 62.4 (CH_2), 118.4 (CH), 129.7 (CH), 139.2 (C–F), 145.1, 149.6, 157.4; HRMS ESI Obsd, *m/z* 253.1952; calcd for $C_9H_{11}FN_2O_4Na$, *m/z* 253.1955 $[M+Na]^+$; UV (MeOH) λ_{max} 270 nm.

6.5.9. 1-[(*E*)-4,5-dihydroxy-2-pentenyl]-5-(2-furyl)-2,4(1*H*,3*H*)-pyrimidinedione (18a). Eluant CH_2Cl_2/MeOH 9/1; yield 93%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.18–3.32 (m, 2H), 3.88–4.03 (m, 1H), 4.37–4.41 (m, 2H), 4.60 (t, OH, J=5.6 Hz), 4.87 (d, OH, J=5.0 Hz), 5.66–5.81 (m, 2H), 6.52 (dd, 1H, J=1.0, 3.4 Hz), 6.85 (d, 1H, J=3.4 Hz), 7.65 (d, 1H, J=1.0 Hz), 8.00 (s, 1H), 11.62 (s, NH); ^{13}C NMR (DMSO-d_6) δ 48.7 (CH_2), 65.8 (CH_2), 71.3 (CH), 105.1, 107.8 (CH), 111.7 (CH), 124.0 (CH), 135.5 (CH), 139.4 (CH), 141.4 (CH), 146.4, 149.7, 160.6; HRMS ESI Obsd, *m/z* 301.0806; calcd for $C_{13}H_{14}N_2O_5Na$, *m/z* 301.0800 $[M+Na]^+$; UV (MeOH) λ_{max} 284 nm.

6.5.10. 1-[(*E*)-4,5-dihydroxy-2-pentenyl]-5-(2-thienyl)-2,4(1*H*,3*H*)-pyrimidinedione (18b). Eluant CH_2Cl_2/MeOH 9/1; yield 90%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.19–3.32 (m, 2H), 3.88–4.02 (m, 1H), 4.31–4.48 (m, 2H), 4.60 (t, OH, J=5.7 Hz), 4.86 (d, OH, J=5.0 Hz), 5.68–5.85 (m, 2H), 7.06 (dd, 1H, J=4.2 Hz), 7.44 (d, 2H, J=4.2 Hz), 8.21 (s, 1H), 11.65 (s, NH); ^{13}C NMR (DMSO-d_6) δ 48.8 (CH_2), 65.7 (CH_2), 71.3 (CH), 107.9, 122.6 (CH), 124.0 (CH), 125.5 (CH), 126.4 (CH), 133.9, 135.6 (CH), 140.7 (CH), 149.7, 161.8; HRMS ESI Obsd, *m/z* 317.0572; calcd for $C_{13}H_{14}N_2O_4NaS$, *m/z* 317.0572 $[M+Na]^+$; UV (MeOH) λ_{max} 260, 324 nm.

6.5.11. 5-(2-Furyl)-1-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]-2,4(1*H*,3*H*)-pyrimidinedione (19a). Eluant CH_2Cl_2/MeOH 9/1; yield 96%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.95 (d, 2H,, J=4.4 Hz), 4.05 (d, 2H, J=5.1 Hz), 4.51 (d, 2H, J=6.6 Hz), 4.78–4.84 (m, OH × 2), 5.47 (t, 1H, J=6.6 Hz), 6.21–6.22 (m, 1H), 6.79–6.81 (m, 1H), 7.34–7.36 (m, 1H), 7.90 (s, 1H), 11.59 (s, NH); ^{13}C NMR (DMSO-d_6) δ 44.7 (CH_2), 57.0 (CH_2), 62.4 (CH_2), 105.0, 108.8 (CH), 109.5 (CH), 118.9 (CH), 139.2 (CH), 144.7 (CH), 145.9, 149.8, 152.4, 160.5; HRMS ESI Obsd, *m/z* 301.2647; calcd for $C_{13}H_{14}N_2O_5Na$, *m/z* 301.2642 $[M+Na]^+$; UV (MeOH) λ_{max} 284 nm.

6.5.12. 1-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-5-(2-thienyl)-2,4(1*H*,3*H*)-pyrimidinedione (19b). Eluant CH_2Cl_2/MeOH 9/1; yield 93%; pale yellow gum; ^{1}H NMR (DMSO-d_6) δ 3.96 (d, 2H, $J=5.0$ Hz), 4.07 (d, 2H, $J=5.3$ Hz), 4.50 (d, 2H, $J=7.0$ Hz), 4.77–4.83 (m, OH $\times$ 2), 5.53 (t, 1H, $J=7.0$ Hz), 7.05 (dd, 1H, $J=3.8$, 5.0 Hz), 7.43 (t, 2H, $J=5.0$ Hz), 8.25 (s, 1H), 11.65 (s, NH); ^{13}C NMR (DMSO-d_6) δ 44.8 (CH_2), 56.9 (CH_2), 62.4 (CH_2), 107.8, 118.9 (CH), 122.5 (CH), 125.5 (CH), 126.4 (CH), 133.9, 140.8 (CH), 144.8, 149.8, 161.7; HRMS ESI Obsd, *m/z* 317.0574; calcd for $C_{13}H_{14}N_2O_4NaS$, *m/z* 317.0572 $[M+Na]^+$; UV (MeOH) λ_{max} 260, 324 nm.

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Facile synthesis of regio-isomeric naphthofurans and benzodifurans

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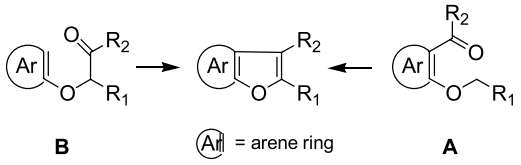
Abstract—Naphtho[1,2-*b*]furans **1a–f**, naphtho[2,1-*b*]furans **2a–f**, benzo[1,2-*b*:5,4-*b*′]difurans **3a–b**, benzo[1,2-*b*:4,5-*b*′]difurans **4a–b**, and benzo[1,2-*b*:4,3-*b*′]difurans **5a–b** were synthesized by base-catalyzed cyclization reaction of the corresponding *o*-alkoxybenzoylarene derivatives. The *o*-alkoxybenzoylarenes were obtained from the etherification reaction of the *o*-hydroxybenzoylarenes, which were prepared either by the reaction of methoxyarenes with benzoyl chloride in the presence of aluminum chloride or by photo-Fries rearrangement of aryl benzoates.

1. Introduction

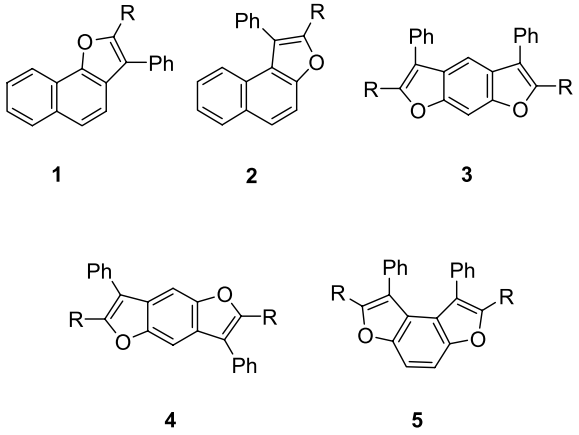
Arene ring-fused furans have attracted widespread interest in view of their presence in natural products, and their biological and pharmacological activities.[1–4] Among arenofurans, benzofurans have been the subject of the most extensive studies and numerous synthetic methods have been developed for them.[1,2,5–7] Compared to benzofurans, the reports on the synthesis of naphthofurans[3,5,8] and benzodifurans[4,9–11] are rather limited, though many of the extended arenofurans exhibit interesting biological properties[3,4] and have potential applications as fluorescent dyes and probes, and as photosensitizers.[9,12]

A major route for the synthesis of various arene ring-fused furan derivatives is the intramolecular formation of a furan moiety starting from properly substituted arene compounds via dehydrative cyclization of either *o*-alkoxycarbonyl compounds of type **A**[2,4b–d,6,7a,8b–e,9–11] or α-aryloxycarbonyl compounds of type **B** (Scheme 1).[5b–d] For the efficient synthesis of variously substituted benzodifurans and naphthofurans, availability of the corresponding starting materials **A** or **B** and facile methods of dehydrative cyclization reaction of the precursors are the key factors.



Scheme 1. A major route for the synthesis of arene ring-fused furan derivatives.

We have been interested in the preparation of various alkoxybenzoylarene derivatives **A** and their photocyclization reaction leading to benzo[*b*]furan[6] and benzodifuran ring systems.[10,11] However, we could not obtain naphthofurans and benzodifurans other than benzo[1,2-*b*:5,4-*b*′]difuran from the photocyclization reactions of the corresponding alkoxybenzoylarenes.[11] In this paper, we describe facile syntheses of regioisomeric naphthofurans **1–2** and benzodifurans **3–5** by base-catalyzed dehydrative cyclization reaction of appropriate *o*-alkoxybenzoylarene derivatives.



Keywords: Naphtho[1,2-*b*]furan; Naphtho[2,1-*b*]furan; Benzo[1,2-*b*:4,5-*b*′]difuran; Benzo[1,2-*b*:5,4-*b*′]difuran; Benzo[1,2-*b*:4,3-*b*′]difuran.
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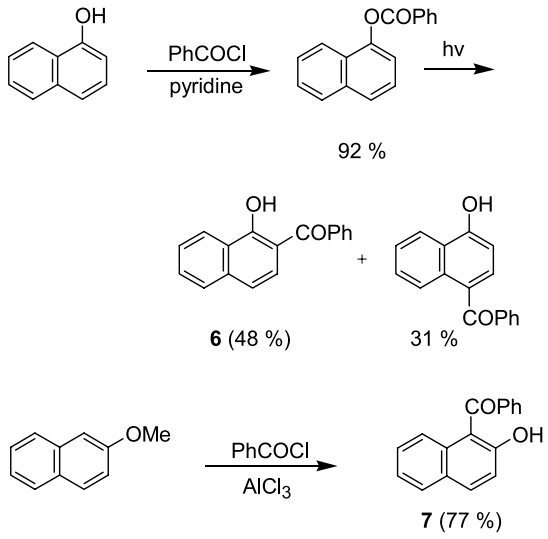
2. Results and discussion

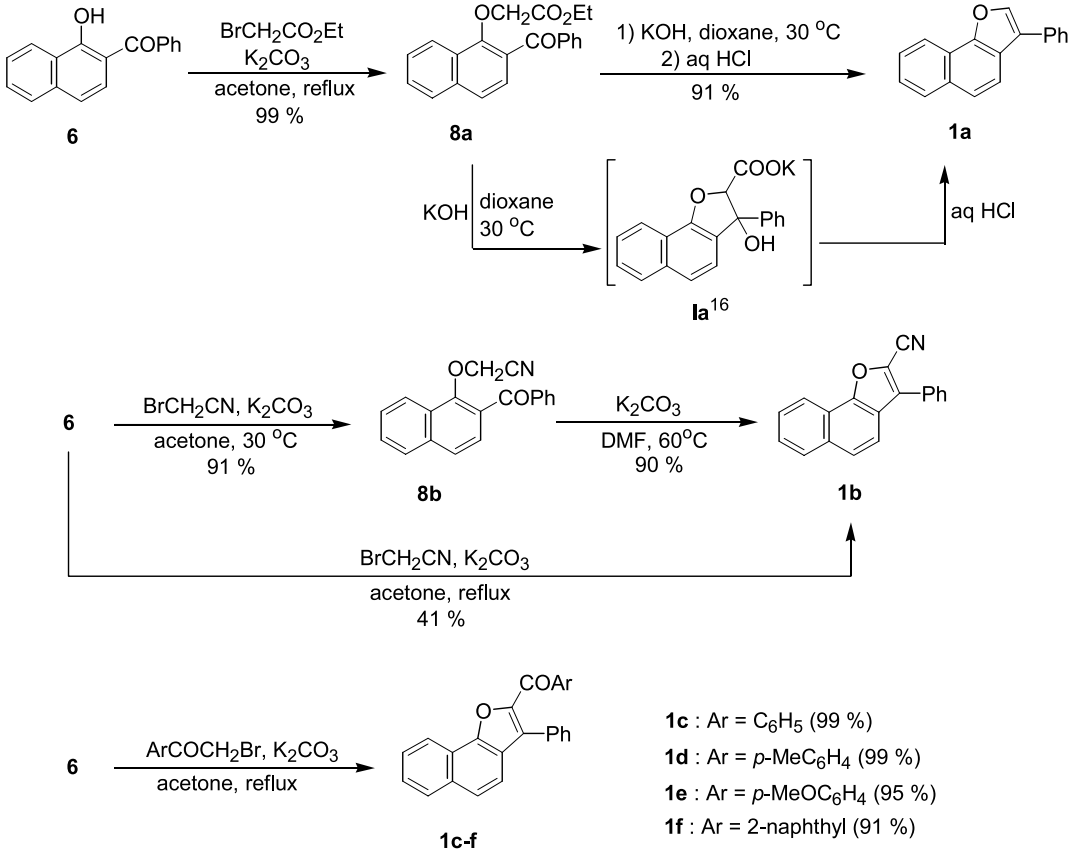
2.1. Synthesis of naphthofurans 1 and 2

Regioisomeric *o*-hydroxybenzoylnaphthalenes **6** and **7**, the starting materials for the naphthofurans **1** and **2**, were prepared as shown in Scheme 2. 2-Benzoyl-1-naphthol **6** was prepared in 48% yield from photo-Fries rearrangement of 1-naphthyl benzoate in methanol, which also gave the *p*-isomer, 4-benzoyl-1-naphthol as a co-product in 31% yield: Crouse et al. reported that photoirradiation of 1-naphthyl benzoate gave the *o*-isomer **6** with 47% yield without the *para* isomer,[13] while Gu et al. reported that both isomers were obtained with 1:1 ratio.[14] 1-Benzoyl-2-naphthol **7** was obtained in 77% yield from the reaction of 2-methoxynaphthalene with benzoyl chloride in the presence of $AlCl_3$. The corresponding reaction of 1-methoxynaphthalene gave 4-benzoyl-1-methoxynaphthalene in 94% yield without formation of any 2-benzoylated products. It is noteworthy that the $AlCl_3$-catalyzed benzoylation reaction of 2-methoxynaphthalene gives demethylated product **7**, while the same reaction of 1-methoxynaphthalene gives non-demethylated product, 4-benzoyl-1-methoxynaphthalene. Such selective demethylation of methoxy group *ortho* to carbonyl group had previously been reported in the reaction of aryl methyl ether with $AlCl_3$.[15]

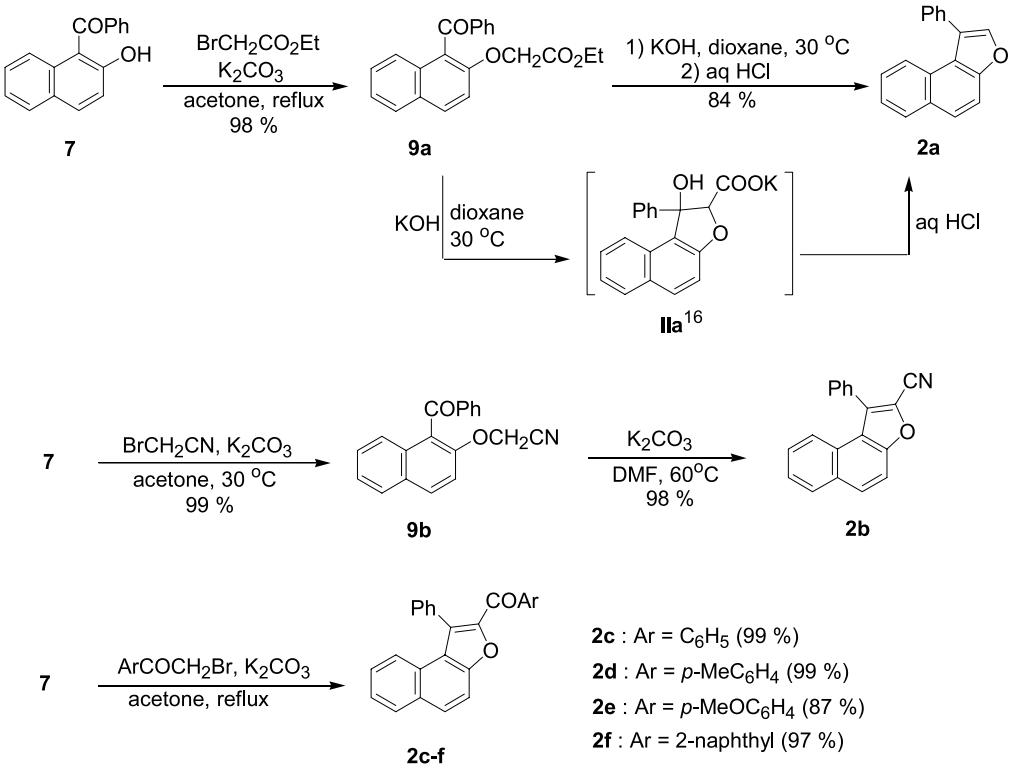


Scheme 2. Preparation of *o*-benzoylhydroxynaphthalenes **6** and **7**.

o-Alkoxybenzoylnaphthalenes **8** and **9** were prepared with 91–99% yields by reacting *o*-benzoylnaphthols **6** and **7** with alkyl halide in the presence of potassium carbonate in acetone. It is known that *o*-alkoxy-substituted benzophenones photocyclize readily to benzo[*b*]furans via intramolecular δ-hydrogen abstraction.[6,9–11] Thus, we attempted photocyclization reaction of **8a** and **9a** to obtain the corresponding naphthofurans. However, irradiation of a solution of **8a** or **9a** in various solvents (benzene, methanol, *t*-butanol, or cyclohexane) with either 350 or 254 nm lamps did not produce any significant amounts of cyclized products and most of the starting materials were recovered. The failure of the photocyclization reaction made us to try base-catalyzed cyclization reaction and the reaction



Scheme 3. Synthesis of naphtho[1,2-*b*]furan derivatives **1a–f**.

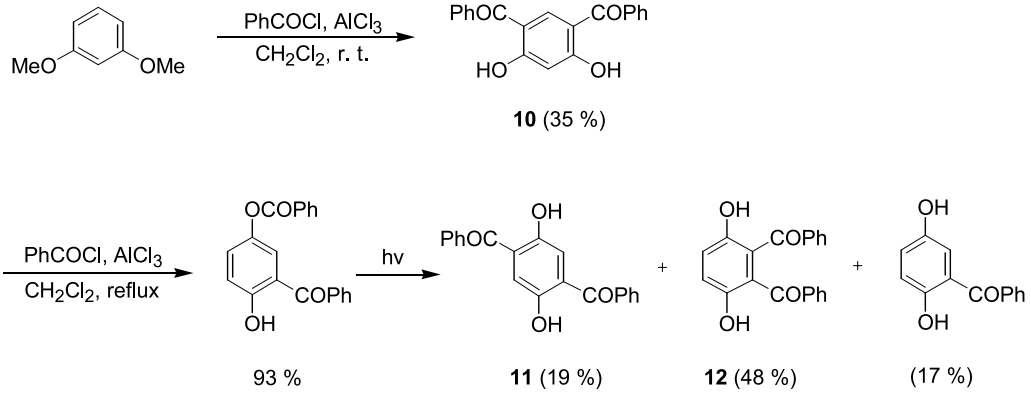


Scheme 4. Synthesis of naphtho[2,1-*b*]furan derivatives **2a–f**.

provided naphthofurans **1** and **2** in excellent yields (84–99%). The synthetic routes are summarized in Schemes 3 and 4.

Depending on the α-substituent in the alkyl halide, the reactions of **6** and **7** with alkyl halides in the presence of K_2CO_3 in acetone either stop at the alkylation stage or further proceed to the cyclization/dehydration step. When the α-substituent is ethoxycarbonyl, *o*-alkoxybenzoylnaphthalene **8a** and **9a** were obtained at reflux temperature of acetone. Treatment of **8a** and **9a** with KOH in dioxane at 30 °C produced **Ia** and **IIa**, respectively.[16] Acidification of the salts **Ia** and **IIa** with aq HCl resulted in decarboxylative dehydroxylation to provide 3-phenylnaphtho[1,2-*b*]furan **1a** and 1-phenylnaphtho[2,1-*b*]furan **2a**, respectively: **1a** and/or **2a** had been previously prepared either by cyclodehydration of the corresponding 2-naphthyloxy-1-phenylethanone, type **B** starting material,[5b–d] or by cyclofragmentation of epoxysulfone.[5a] Chatterjea et al. reported that **9a** is cyclized to 2-ethoxycarbonyl-1-phenylnaphtho[2,1-*b*]furan by sodium/ethanol.[8d] However, repetition of the reaction by us gave not only the reported product, but also its hydrolyzed product, 1-phenylnaphtho[2,1-*b*]furan-2-carboxylate and decarboxylated product **2a** with poorly reproducible products ratios.

The naphthofurans **1b** and **2b** were obtained in overall yields of 82 and 97% yields, respectively, from the two-step reactions of **6** and **7** with bromoacetonitrile involving isolated **8b** and **9b** intermediates. The one-step reaction of **6** to produce **1b** in refluxing acetone solution without isolating the intermediate **8b** gave much low yield, 41%. When the α-substituents in the alkyl halide are benzoyl and napthoyl groups, alkylation and then cyclization/dehydration



Scheme 5. Preparation of dibenzoyldihydroxybenzenes **10–12**.[9,10,15]

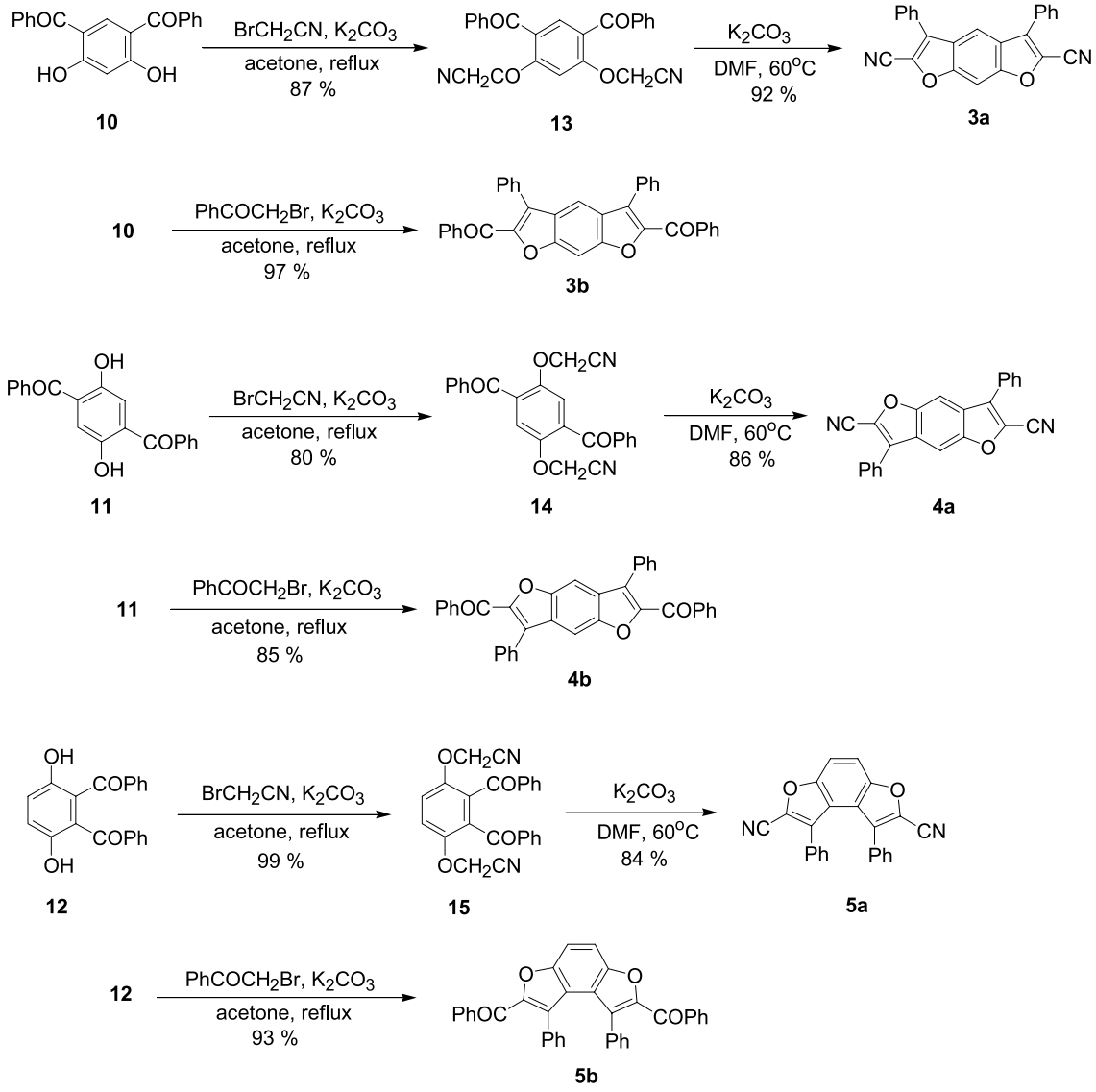
reactions proceeded in one pot at refluxing temperature of acetone to give the corresponding naphthofurans **1c–f** and **2c–f** in 87–99% yields.[17]

2.2. Synthesis of regioisomeric benzodifuran derivatives 3–5

Regioisomeric dihydroxydibenzoylbenzenes **10–12**, starting materials for the synthesis of the benzodifurans **3–5**, were prepared by the reported procedures (Scheme 5).[9,10,15] The reaction of 1,3-dimethoxybenzene with benzoyl chloride in the presence of aluminum chloride provided 1,5-dibenzoyl-2,4-dihydroxybenzene **10** in 35% yield.[9,10] 2,5-Dibenzoyl-1,4-dihydroxybenzene **11** and 2,3-dibenzoyl-1,4-dihydroxybenzene **12** were obtained in two steps from 1,4-dimethoxybenzene and separated.[15]

Alkylation of **10–12** to dialkoxydibenzoylbenzenes **13–15** and subsequent dehydrative cyclization reactions of **13–15** to produce **3–5** were carried out in the same manner described for the synthesis of naphthofurans **1** and **2**, which are shown in Scheme 6. For cyano-derivatives **3a–5a**, alkylated intermediates **13–15** were isolated and cyclization/dehydration of the intermediates gave the desired products with the overall yields of 69–83%. For **3b–5b**, alkylation and dehydrative cyclization reactions proceeded in one pot at refluxing temperature of acetone to give the corresponding benzodifurans in 85–97% yields: the synthesis of **3b** from the same starting materials, but by phase transfer catalytic method or microwave irradiation had been reported.[4d]

The symmetrical nature of the compounds **3–5** is manifested in their NMR spectra. Based on the symmetry of the compounds, the expected number of ^{13}C NMR peaks is 11 for **3a**, 10 for **4a** and **5a**, 15 for **3b**, and 14 for **4b** and **5b**. The actual carbon numbers present in the compounds are 24 for the **a** series and 36 for the **b** series. The observed number of peaks in the ^{13}C NMR spectra exactly matches the expected number or one less number due to overlapping.



Scheme 6. Synthesis of various regioisomeric benzodifurans **3–5**.

3. Conclusions

Facile synthetic methods for various regioisomeric naphthofurans **1** and **2** and benzodifurans **3–5** have been developed. The starting materials for the syntheses, regioisomeric *o*-hydroxybenzoylarenes, were prepared either by the reaction of methoxyarenes with benzoyl chloride in the presence of aluminum chloride or by photo-Fries rearrangement of aryl benzoates, depending on the positions of the substituents. The allkylation of *o*-hydroxybenzoylarenes followed by cyclization/dehydration reactions afforded the desired arenofurans in excellent yields.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, using tetramethylsilane (in $CDCl_3$) or residual undeuterated solvent (in DMSO-d_6 and D_2O) as an internal standard.

4.2. Preparation of 2-benzoyl-1-naphthol 6

Benzoyl chloride (3.51 g, 25.0 mmol) in dichloromethane (50 mL) was added slowly to a solution of 1-naphthol (3.00 g, 20.8 mmol) and pyridine (6.58 g, 83.2 mmol) in dichloromethane (250 mL) and refluxed for 3 h under nitrogen atmosphere. The reaction mixture was washed with 10% aqueous HCl and then dried with anhydrous sodium sulfate. The concentrated reaction mixture was purified by silica gel column chromatography (eluent: 9:1 hexane–ethyl acetate) to give 1-naphthyl benzoate (4.75 g, 92%): mp 58–59 °C (lit.[13] 47–48 °C). A methanol solution (870 mL) of 1-naphthyl benzoate (4.75 g, 19.1 mmol) in a quartz vessel was purged with nitrogen for 1 h and then irradiated under nitrogen with 254 nm mercury lamps using RPR-100 photochemical reactor (Southern New England Ultraviolet Company) for 17 h. The reaction mixture was concentrated and purified by silica gel column chromatography eluting with 9:1 hexane–ethyl acetate to provide 2.28 g (48%) of 2-benzoyl-1-naphthol **6** and 1.47 g (31%) of 4-benzoyl-1-napththol.

2-Benzoyl-1-naphthol **6**: mp 70–72 °C (lit. 63–64 °C;[13] 70.85 °C[18]); ^{1}H NMR ($CDCl_3$) δ 13.95 (s, 1H), 8.52 (d, 1H, J=8 Hz), 7.75 (d, 1H, J=8 Hz), 7.71 (d, 2H, J=8 Hz), 7.64 (t, 1H, J=8 Hz), 7.61–7.49 (m, 5H), 7.21 (d, 1H, J=9 Hz).

4-Benzoyl-1-napththol: mp 164–165 °C (lit. 166–167 °C[19]); ^{1}H NMR (DMSO-d_6) δ 11.10 (br s, 1H), 8.33 (d, 1H, J=8 Hz), 8.26 (dd, 1H, J=8, 2 Hz), 7.71 (d, 2H, J=8 Hz), 7.63 (t, 1H, J=8 Hz), 7.60–7.49 (m, 5H), 6.92 (d, 1H, J=8 Hz).

4.3. Reaction of 2-methoxynaphthalene with benzoyl chloride: preparation of 7

A solution of 2-methoxynaphthalene (1.00 g, 6.32 mmol) and benzoyl chloride (1.06 g, 7.58 mmol) in dichloromethane (30 mL) was added slowly to the suspension of $AlCl_3$ (1.80 g, 13.9 mmol) in dichloromethane (30 mL), and stirred for 20 h at room temperature under nitrogen atmosphere. Then the reaction mixture was poured to a beaker containing ice water (45 mL) and conc HCl (15 mL) and stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane three times. The organic layers were combined, dried with anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluent: 5:1 hexane–ethyl acetate) and then recrystallization from dichloromethane to afford 1-benzoyl-2-naphthol **7** (1.22 g, 77%): mp 139–141 °C (lit. 141.05 °C;[18] 135–137 °C[8d]); ^{1}H NMR ($CDCl_3$) δ 11.20 (s, 1H), 7.93 (d, 1H, J=9 Hz), 7.74 (d, 1H, J=8 Hz), 7.62 (d, 2H, J=8 Hz), 7.55 (t, 1H, J=7 Hz), 7.40 (t, 2H, J=8 Hz), 7.31–7.22 (m, 3H), 7.15 (t, 1H, J=8 Hz).

The same reaction using 1-methoxynaphthalene (0.200 g, 1.26 mmol) instead of 2-methoxynapthalene gave 94% yield (0.309 g) of 4-benzoyl-1-methoxynaphthalene:[20] ^{1}H NMR ($CDCl_3$) δ 8.39–8.33 (m, 2H), 7.83 (d, 2H, J=8 Hz), 7.61–7.42 (m, 6H), 6.78 (d, 1H, J=8 Hz), 4.05 (s, 3H).

4.4. Preparation of 1a and 2a

A solution of ethyl bromoacetate (1.21 g, 7.25 mmol) in acetone (50 mL) was added to the reaction mixture of benzoylnaphthol (**6** or **7**, 1.50 g, 6.04 mmol) and potassium carbonate (3.34 g, 24.2 mmol) in acetone (100 mL) and heated at reflux for 2 h under nitrogen atmosphere. After removing potassium carbonate by filtration, the reaction mixture was concentrated. To the residue, water was added and extracted with dichloromethane. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (eluent: 5:1 hexane–ethyl acetate) to give the alkylated compound, **8a** or **9a**.

4.4.1. Compound 8a. Yield, 99%; mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 8.43 (dd, 1H, J=6, 3 Hz), 7.90–7.85 (m, 3H), 7.68 (d, 1H, J=8 Hz), 7.61–7.56 (m, 3H), 7.47–7.42 (m, 3H), 4.59 (s, 2H), 4.18 (q, 2H, J=7 Hz), 1.23 (t, 3H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 196.16, 168.41, 153.47, 137.17, 135.77, 133.26, 130.08, 128.33, 127.90, 127.76, 127.64, 127.01, 126.79, 125.72, 123.99, 123.30, 72.36, 61.15, 14.11. IR (KBr): 1758, 1662, 1281, 1196, 1100 cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43%. Found: C, 75.46; H, 5.41%.

4.4.2. Compound 9a. Yield, 98%; mp 78–80 °C (lit.[8d] oil); ^{1}H NMR ($CDCl_3$) δ 7.93–7.88 (m, 3H), 7.85–7.81 (m, 1H), 7.57–7.52 (m, 2H), 7.44–7.35 (m, 4H), 7.18 (d, 1H, J=9 Hz), 4.63 (s, 2H), 4.16 (q, 2H, J=7 Hz), 1.20 (t, 3H, J=7 Hz); ^{13}C NMR ($CDCl_3$) δ 197.08, 168.46, 152.22, 137.69, 133.42, 131.60, 131.04, 129.67, 129.22, 128.43, 128.02, 127.43, 124.49, 124.20, 123.87, 113.63, 66.47, 61.30, 14.11.

To the reaction flask containing potassium hydroxide (0.280 g, 5.00 mmol) in dioxane (20 mL), **8a–9a** (0.500 g, 1.50 mmol) was added and stirred at 30 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a solid residue. The solid residue was dissolved in water (10 mL), acidified with aq HCl, stirred for 1 h at 80 °C, and then extracted with ether. The ether layers were

dried, concentrated, and then purified by silica gel column chromatography (eluent: 5:1 hexane–ethyl acetate) to give **1a**–**2a**.

4.4.3. Compound 1a. Yield, 91%; mp 111–113 °C; ^{1}H NMR ($CDCl_3$) δ 8.33 (d, 1H, J=8 Hz), 7.93 (d, 1H, J=8 Hz), 7.90 (s, 1H), 7.86 (d, 1H, J=9 Hz), 7.71–7.66 (m, 3H), 7.59 (t, 1H, J=8 Hz), 7.52–7.45 (m, 3H), 7.37 (t, 1H, J=8 Hz); ^{13}C NMR ($CDCl_3$) δ 151.31, 140.38, 132.11, 131.40, 128.91, 128.18, 127.58, 127.39, 126.35, 125.27, 123.57, 123.42, 121.83, 121.53, 120.03, 118.66. IR (KBr): 1558, 1521, 1445, 1387, 1128 cm^{-1}. Anal. Calcd for $C_{18}H_{12}O$: C, 88.50; H, 4.95%. Found: C, 88.52; H, 4.92%.

4.4.4. Compound 2a. Yield, 84%; oil; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1H, J=8 Hz), 7.93 (d, 1H, J=8 Hz), 7.76 (d, 1H, J=9 Hz), 7.69 (d, 1H, J=9 Hz), 7.68 (s, 1H), 7.62–7.58 (m, 2H), 7.53–7.46 (m, 3H), 7.42 (t, 1H, J=8 Hz), 7.34 (t, 1H, J=8 Hz); ^{13}C NMR ($CDCl_3$) δ 153.04, 141.59, 133.02, 130.72, 129.79, 128.82, 128.51, 128.24, 127.78, 125.89, 125.86, 124.37, 124.27, 123.30, 120.65, 112.58. IR (KBr): 1525, 1489, 1386, 1225, 1109 cm^{-1}. Anal. Calcd for $C_{18}H_{12}O$: C, 88.50; H, 4.95%. Found: C, 88.64; H, 4.84%.

When the solid residues obtained from the reaction of **8a** and **9a** with KOH were washed with abs. ethanol several times to remove potassium hydroxide, the potassium salts of 3-hydroxy-3-phenyl-2,3-dihydronaphtho[1,2-*b*]furan-2-carboxylic acid **Ia** and 1-hydroxy-1-phenyl-1,2-dihydronaphtho[2,1-*b*]furan-2-carboxylic acid **IIa** were obtained, respectively.[16]

4.4.5. Compound Ia. Mp 303 °C (dec); ^{1}H NMR (D_2O) δ 8.13 (d, 1H, J=8 Hz), 7.79 (d, 1H, J=8 Hz), 7.58 (t, 1H, J=8 Hz), 7.52 (t, 1H, J=8 Hz), 7.35–7.27 (m, 6H), 6.94 (d, 1H, J=9 Hz), 4.95 (s, 1H); ^{13}C NMR (D_2O) δ 174.98, 167.37, 156.55, 144.97, 136.51, 129.92, 129.69, 129.25, 128.94, 127.89, 126.09, 123.47, 123.35, 123.23, 121.94, 95.67, 85.23. IR (KBr): 3500–2500 (broad), 1607, 1399, 1064 cm^{-1}. Anal. Calcd for $C_{19}H_{13}KO_4$: C, 66.26; H, 3.80%. Found: C, 66.05; H, 3.95%.

4.4.6. Compound IIa. Mp 280–281 °C (dec); ^{1}H NMR (D_2O) δ 7.80 (d, 1H, J=9 Hz), 7.67 (d, 1H, J=8 Hz), 7.30–7.25 (m, 3H), 7.16–7.08 (m, 4H), 7.03 (t, 1H, J=7 Hz), 6.94 (t, 1H, J=7 Hz), 4.98 (s, 1H); ^{13}C NMR (D_2O) δ 175.07, 159.07, 145.75, 134.11, 131.75, 130.83, 130.67, 130.01, 128.95, 128.76, 127.46, 125.03, 123.74, 122.46, 114.26, 96.13, 85.49. IR (KBr): 3500–2500 (broad), 1601, 1408, 1239 cm^{-1}. Anal. Calcd for $C_{19}H_{13}KO_4$: C, 66.26; H, 3.80%. Found: C, 66.28; H, 3.79%.

4.5. Preparation of 1b and 2b

A solution of bromoacetonitrile (0.116 g, 0.967 mmol) in acetone (5 mL) was added dropwise to the reaction mixture of benzoylnaphthol, **6**–**7** (0.200 g, 0.806 mmol) and potassium carbonate (0.446 g, 3.22 mmol) in acetone (10 mL) and stirred at 30 °C for 3–6 h under nitrogen atmosphere. After removing potassium carbonate by filtration, the reaction mixture was concentrated. To the residue, water was added and extracted with dichloromethane. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (eluent: 5:1 hexane–ethyl acetate) to give **8b**–**9b**.

4.5.1. Compound 8b. Yield, 91%; oil; ^{1}H NMR ($CDCl_3$) δ 8.29–8.26 (m, 1H), 7.94–7.91 (m, 1H), 7.84–7.81 (m, 2H), 7.76 (d, 1H, J=8 Hz), 7.68–7.58 (m, 3H), 7.49–7.43 (m, 3H), 4.84 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 195.68, 152.25, 136.97, 135.81, 133.59, 130.15, 128.47, 128.26, 128.08, 127.55, 127.48, 125.59, 125.22, 122.61,115.11, 60.57 (one sp^2 carbon is missing due to overlap). IR (neat): 1662, 1597, 1447, 1338, 1281, 1246, 1090 cm^{-1}. Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88%. Found: C, 79.50; H, 4.63; N, 4.85%.

4.5.2. Compound 9b. Yield, 99%; mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1H, J=9 Hz), 7.90–7.87 (m, 1H), 7.84–7.81 (m, 2H), 7.59 (t, 1H, J=7 Hz), 7.55–7.52 (m, 1H), 7.47–7.39 (m, 5H), 4.75 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 196.31, 150.69, 137.35, 133.90, 131.55, 131.46, 130.04, 129.56, 128.72, 128.19, 127.81, 125.61, 125.43, 124.52, 114.85, 114.31, 55.35. IR (KBr): 1665, 1592, 1579, 1509, 1281, 1242, 1219 cm^{-1}. Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88%. Found: C, 79.46; H, 4.63; N, 4.89%.

The reaction mixture of potassium carbonate (0.385 g, 2.78 mmol) and **8b**–**9b** (0.200 g, 0.696 mmol) in DMF (8 mL) was stirred at 60 °C for 3.5 h. After removing potassium carbonate by filtration, the filtrate was concentrated. To the residue, water was added and extracted with dichloromethane. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (eluent: 2:1 hexane–dichloromethane for **1b**; 2:1 hexane–ethyl acetate for **2b**) to give **1b**–**2b**.

4.5.3. Compound 1b. Yield, 90%; mp 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 8.36 (d, 1H, J=8 Hz), 7.96 (d, 1H, J=8 Hz), 7.80–7.76 (m, 4H), 7.70–7.56 (m, 4H), 7.55–7.50 (m, 1H); ^{13}H NMR ($CDCl_3$) δ 152.47, 134.18, 133.16, 129.45, 129.31, 128.66, 128.41, 128.30, 127.40, 127.27, 125.54, 122.80, 120.88, 120.81, 120.71, 118.31, 112.72. IR (KBr): 2217, 1459, 1444, 1378, 1197, 1077 cm^{-1}. Anal. Calcd for $C_{19}H_{11}NO$: C, 84.74; H, 4.12; N, 5.20%. Found: C, 84.76; H, 4.12; N, 5.04%.

4.5.4. Compound 2b. Yield, 98%; mp 99–102 °C; ^{1}H NMR ($CDCl_3$) δ 7.96–7.90 (m, 3H), 7.68–7.56 (m, 6H), 7.51 (t, 1H, J=8 Hz), 7.41 (t, 1H, J=8 Hz); ^{13}C NMR ($CDCl_3$) δ 154.19, 135.37, 130.99, 130.53, 129.54, 129.48, 129.39, 129.17, 129.05, 127.82, 127.26, 125.57, 124.51, 122.95, 119.58, 112.20, 112.07. IR (KBr): 2229, 1584, 1530, 1444, 1262, 1218 cm^{-1}. Anal. Calcd for $C_{19}H_{11}NO$: C, 84.74; H, 4.12; N, 5.20%. Found: C, 84.71; H, 4.12; N, 5.18%.

4.6. Preparation of 1c–f and 2c–f

A solution of the corresponding bromoacetophenone or bromoacetonaphthone (0.484 mmol) in acetone (4 mL) was added dropwise to the reaction mixture of benzoylnaphthol, **6**–**7** (0.100 g, 0.403 mmol) and potassium carbonate (0.223 g, 1.61 mmol) in acetone (4 mL) and heated at reflux for 2–6 h under nitrogen atmosphere until the benzoylnaphthol disappeared. After removing potassium carbonate

by filtration, the reaction mixture was concentrated. To the residue, water was added and extracted with dichloromethane. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (eluent: dichloromethane for **1c** and **1e**; 1:1 hexane–dichloromethane for **1d**, **1f**, **2d**, and **2e**; 2:1 hexane–ethyl acetate for **2c** and **2f**) to give the corresponding naphthofurans.

4.6.1. Compound 1c. Yield, 99%; mp 119–120 °C; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, 1H, J=8 Hz), 7.98–7.94 (m, 3H), 7.72 (d, 1H, J=9 Hz), 7.67–7.55 (m, 5H), 7.51 (t, 1H, J=7 Hz), 7.44–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 184.75, 151.09, 146.91, 137.51, 133.35, 132.39, 130.97, 130.85, 130.00, 129.82, 128.40, 128.26, 127.99, 126.98, 126.87, 124.86, 123.73, 121.23, 120.99, 119.17 (one carbon is missing due to overlap). IR (KBr): 1643, 1539, 1490, 1339, 1288, 1213 cm^{-1}. Anal. Calcd for $C_{25}H_{16}O_2$: C, 86.19; H, 4.63%. Found: C, 86.13; H, 4.72%.

4.6.2. Compound 1d. Yield, 99%; mp 157–160 °C; ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 1H, J=8 Hz), 7.95 (d, 1H, J=8 Hz), 7.92 (d, 2H, J=8 Hz), 7.71 (d, 1H, J=8 Hz), 7.67–7.56 (m, 5H), 7.45–7.35 (m, 3H), 7.21 (d, 2H, J=8 Hz), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 184.36, 150.91, 147.13, 143.25, 134.88, 133.27, 131.08, 130.42, 130.06, 129.99, 128.76, 128.39, 128.25, 128.16, 126.87, 126.82, 124.77, 123.76, 121.27, 120.94, 119.19, 21.73. IR (KBr): 1637, 1605, 1545, 1385, 1340, 1165 cm^{-1}. Anal. Calcd for $C_{26}H_{18}O_2$: C, 86.16; H, 5.01%. Found: C, 86.16; H, 5.08%.

4.6.3. Compound 1e. Yield, 95%; mp 180–181 °C; ^{1}H NMR ($CDCl_3$) δ 8.42 (d, 1H, J=8 Hz), 8.04 (d, 2H, J=9 Hz), 7.96 (d, 1H, J=8 Hz), 7.72 (d, 1H, J=8 Hz), 7.68–7.57 (m, 5H), 7.45–7.35 (m, 3H), 6.90 (d, 2H, J=9 Hz), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 183.24, 163,14, 150.78, 147.24, 133.20, 132.13, 131.17, 130.18, 130.01, 129.97, 128.40, 128.29, 128.14, 126.79, 124.72, 123.74, 121.27, 120.89, 119.17, 113.40, 55.46 (one sp^2 carbon is missing due to overlap). IR (KBr): 1626, 1596, 1543, 1508, 1488, 1165 cm^{-1}. Anal. Calcd for $C_{26}H_{18}O_3$: C, 82.52; H, 4.79%. Found: C, 82.58; H, 4.67%.

4.6.4. Compound 1f. Yield, 91%; mp 162–164 °C; ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.42 (d, 1H, J=8 Hz), 8.04 (dd, 1H, J=8, 2 Hz), 7.97 (d, 1H, J=7 Hz), 7.88–7.84 (m, 3H), 7.75–7.55 (m, 7H), 7.51 (t, 1H, J=7 Hz), 7.38 (t, 2H, J=7 Hz), 7.32–7.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 184.59, 151.14, 147.15, 135.18, 134.71, 133.38, 132.23, 132.01, 131.04, 130.85, 129.99, 129.46, 128.44, 128.30, 128.24, 127.87, 127.63, 127.00, 126.93, 126.46, 125.42, 124.91, 123.82, 121.31, 120.98, 119.23 (one carbon is missing due to overlap). IR (KBr): 1739, 1635, 1545, 1361, 1292, 1191 cm^{-1}. Anal. Calcd for $C_{29}H_{18}O_2$: C, 87.42; H, 4.55%. Found: C, 87.44; H, 4.63%.

4.6.5. Compound 2c. Yield, 99%; mp 140–143 °C (lit.[8e] 137 °C); ^{1}H NMR ($CDCl_3$) δ 7.95–7.90 (m, 4H), 7.73 (d, 1H, J=9 Hz), 7.68 (d, 1H, J=8 Hz), 7.51–7.42 (m, 7H), 7.39–7.30 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 184.59, 152.85, 147.67, 137.35, 132.73, 132.28, 131.39, 130.99, 130.25, 129.77, 129.62, 129.15, 128.69, 128.47, 128.25, 127.97, 126.92, 125.14, 123.19, 121.91, 112.65. IR (KBr): 1653, 1646, 1545, 1342, 1333, 1014 cm^{-1}. Anal. Calcd for $C_{25}H_{16}O_2$: C, 86.19; H, 4.63%. Found: C, 86.21; H, 4.71%.

4.6.6. Compound 2d. Yield, 99%; mp 122–124 °C (lit.[8e] 105 °C); ^{1}H NMR ($CDCl_3$) δ 7.92 (t, 2H, J=8 Hz), 7.87 (d, 2H, J=8 Hz), 7.73 (d, 1H, J=9 Hz), 7.68 (d, 1H, J=8 Hz), 7.52–7.43 (m, 6H), 7.33 (t, 1H, J=8 Hz), 7.19 (d, 2H, J=8 Hz), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 184.14, 152.66, 147.87, 143.14, 134.73, 132.87, 130.99, 130.98, 130.00, 129.85, 129.75, 129.11, 128.72, 128.68, 128.46, 128.14, 126.85, 125.09, 123.21, 121.94, 112.64, 21.72. IR (KBr): 1635, 1606, 1545, 1343, 1182, 1013 cm^{-1}. Anal. Calcd for $C_{26}H_{18}O_2$: C, 86.16; H, 5.01%. Found: C, 86.14; H, 5.03%.

4.6.7. Compound 2e. Yield, 87%; mp 144–145 °C (lit.[8e] 180 °C); ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 2H, J=9 Hz), 7.92 (t, 2H, J=9 Hz), 7.73 (d, 1H, J=9 Hz), 7.68 (d, 1H, J=8 Hz), 7.53–7.42 (m, 6H), 7.32 (t, 1H, J=8 Hz), 6.88 (d, 2H, J=9 Hz), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 182.91, 163.03, 152.52, 147.98, 132.96, 132.14, 130.95, 130.64, 130.04, 129.81, 129.76, 129.09, 128.64, 128.46, 128.14, 126.80, 125.04, 123.19, 121.90, 113.36, 112.58, 55.43. IR (KBr): 1643, 1600, 1550, 1489, 1255, 1180 cm^{-1}. Anal. Calcd for $C_{26}H_{18}O_3$: C, 82.52; H, 4.79%. Found: C, 82.47; H, 4.96%.

4.6.8. Compound 2f. Yield, 97%; mp 139–142 °C; ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 7.96 (dd, 1H, J=9, 2 Hz), 7.92 (d, 1H, J=8 Hz), 7.91 (d, 1H, J=9 Hz), 7.86 (d, 1H, J=8 Hz), 7.81 (d, 1H, J=8 Hz), 7.80 (d, 1H, J=8 Hz), 7.74 (d, 1H, J=9 Hz), 7.70 (d, 1H, J=8 Hz), 7.57–7.30 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 184.41, 152.85, 147.86, 135.05, 134.54, 132.75, 132.05, 131.60, 131.33, 130.97, 130.19, 129.71, 129.40, 129.14, 128.68, 128.44, 128.14, 128.12, 127.82, 127.59, 126.89, 126.37, 125.18, 125.12, 123.17, 121.92, 112.64. IR (KBr): 1647, 1623, 1559, 1491, 1361, 1336 cm^{-1}. Anal. Calcd for $C_{29}H_{18}O_2$: C, 87.42; H, 4.55%. Found: C, 87.38; H, 4.69%.

4.7. Preparation of 3a, 4a and 5a

Dibenzoyldihydroxybenzenes **10–12** are available from our earlier studies.[10,15] A solution of bromoacetonitrile (0.166 g, 1.38 mmol) in acetone (5 mL) was added dropwise to the reaction mixture of dibenzoyldihydroxybenzene **10–12** (0.200 g, 0.628 mmol) and potassium carbonate (0.694 g, 5.02 mmol) in acetone (10 mL) and heated at reflux for 2–12 h under nitrogen atmosphere until the dibenzoyldihydroxybenzene disappeared. After removing potassium carbonate by filtration, the reaction mixture was concentrated. To the residue, water was added and extracted with dichloromethane. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (eluent: 1:1 hexane–dichloromethane for **13**; 1:9 hexane–ethyl acetate for **15**) to give **13** and **15** with 87 and 99% yields, respectively. In case of **14**, the reaction mixture was concentrated and the residue was washed with water to remove potassium carbonate. Further washing of the residue with cold methanol provided **14** with 80% yield.

4.7.1. Compound 13. Mp 179–180 °C; ^{1}H NMR (DMSO-d_6) δ 7.75 (d, 4H, J=7 Hz), 7.66 (t, 2H, J=7 Hz), 7.53 (t, 4H, J=7 Hz), 7.52 (s, 1H), 7.31 (s, 1H), 4.09 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 193.05, 156.88, 136.84, 133.45, 131.38,

129.19, 128.58, 122.76, 115.45, 99.38, 54.29. IR (KBr): 1661, 1600, 1447, 1262, 1196, 1040 cm^{-1}. Anal. Calcd for $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07%. Found: C, 72.74; H, 4.03; N, 7.04%.

4.7.2. Compound 14. Mp 245–247 °C; ^1H NMR (DMSO-d_6) δ 7.82 (d, 4H, $J=8$ Hz), 7.72 (t, 2H, $J=7$ Hz), 7.57 (t, 4H, $J=7$ Hz), 7.47 (s, 2H), 5.13 (s, 4H); ^{13}C NMR (DMSO-d_6) δ 193.42, 148.14, 135.95, 134.03, 131.37, 129.39, 128.82, 115.82, 114.20, 54.37. IR (KBr): 1664, 1596, 1448, 1411, 1217, 1049 cm^{-1}. Anal. Calcd for $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07%. Found: C, 72.89; H, 4.11; N, 6.92%.

4.7.3. Compound 15. Mp 147–150 °C; ^1H NMR ($CDCl_3$) δ 7.70 (d, 4H, $J=8$ Hz), 7.53 (t, 2H, $J=8$ Hz), 7.39 (t, 4H, $J=8$ Hz), 7.25 (s, 2H), 4.63 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 193.44, 149.29, 136.73, 133.80, 131.78, 129.41, 128.44, 115.74, 114.30, 54.77. IR (KBr): 1739, 1669, 1597, 1470, 1450, 1292 cm^{-1}. Anal. Calcd for $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07%. Found: C, 72.74; H, 4.05; N, 7.05%.

The reaction mixture of potassium carbonate (0.558 g, 4.04 mmol) and **13–15** (0.200 g, 0.504 mmol) in DMF (8 mL) was stirred at 60 °C for 2–20 h until the starting material disappeared. After concentrating the reaction mixture, the residue was washed with water and then cold methanol to give **3a** and **4a** with 92 and 86% yields, respectively. In case of **5a**, the reaction mixture was filtered to remove potassium carbonate and then concentrated. To the residue, water was added and extracted with dichloromethane. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (eluent: 2:1 hexane–dichloromethane) to give **5a** with 84% yield.

4.7.4. Compound 3a. Mp 295–297 °C; ^1H NMR ($CDCl_3$) δ 8.15 (s, 1H), 7.81 (s, 1H), 7.73 (d, 4H, $J=8$ Hz), 7.63–7.52 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 155.78, 133.16, 129.94, 129.59, 128.39, 127.86, 125.01, 123.93, 114.21, 111.86, 96.15. IR (KBr): 2221, 1626, 1568, 1448, 1342, 1200 cm^{-1}. Anal. Calcd for $C_{24}H_{12}N_2O_2$: C, 79.99; H, 3.36; N, 7.77%. Found: C, 79.96; H, 3.28; N, 7.65%.

4.7.5. Compound 4a. Mp 290–291 °C; ^1H NMR ($CDCl_3$) δ 7.96 (s, 2H), 7.75 (d, 4H, $J=8$ Hz), 7.63–7.53 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 152.91, 133.14, 129.99, 129.59, 128.26, 127.79, 126.83, 125.53, 111.93, 104.14. IR (KBr): 2227, 1571, 1483, 1445, 1419, 1221 cm^{-1}. Anal. Calcd for $C_{24}H_{12}N_2O_2$: C, 79.99; H, 3.36; N, 7.77%. Found: C, 79.95; H, 3.34; N, 7.67%.

4.7.6. Compound 5a. Mp 211–214 °C; ^1H NMR ($CDCl_3$) δ 7.80 (s, 2H), 7.12–7.06 (m, 6H), 6.94 (t, 4H, $J=8$ Hz); ^{13}C NMR ($CDCl_3$) δ 153.65, 134.18, 129.17, 128.55, 128.25, 128.05, 126.16, 118.95, 113.23, 111.71. IR (KBr): 2226, 1559, 1462, 1447, 1412, 1050 cm^{-1}. Anal. Calcd for $C_{24}H_{12}N_2O_2$: C, 79.99; H, 3.36; N, 7.77%. Found: C, 79.91; H, 3.34; N, 7.64%.

4.8. Preparation of 3b, 4b and 5b

A solution of bromoacetophenone (0.413 g, 2.07 mmol) in acetone (5 mL) was added dropwise to the reaction mixture of dibenzoyldihydroxybenzene **10–12** (0.300 g, 0.942 mmol) and potassium carbonate (1.04 g, 7.54 mmol) in acetone (10 mL) and heated at reflux for 15–24 h under nitrogen atmosphere until the starting material disappeared. After concentrating the reaction mixture, the residue was washed with water and then recrystallized from 2:1 acetone–CH_2Cl_2 to give **3b** and **4b** with 97 and 85% yields, respectively. In case of **5b**, the reaction mixture was filtered to remove potassium carbonate and then concentrated. To the residue, water was added and extracted with dichloromethane. The organic layer was dried, concentrated, and then purified by silica gel column chromatography (eluent: 1:1 hexane–dichloromethane) to give **5b** with 93% yield.

4.8.1. Compound 3b. Mp 228–230 °C (lit.[4d] 208–209 °C); ^1H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.86 (s, 1H), 7.85 (d, 4H, $J=7$ Hz), 7.49–7.43 (m, 6H), 7.36–7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 185.29, 154.83, 148.04, 136.84, 132.67, 130.37, 129.85, 129.67, 129.09, 128.41, 128.00, 126.38, 115.01, 95.61 (one carbon is missing due to overlap). IR (KBr): 1653, 1542, 1445, 1331, 1236 cm^{-1}. Anal. Calcd for $C_{36}H_{22}O_4$: C, 83.38; H, 4.28%. Found: C, 83.39; H, 4.30%.

4.8.2. Compound 4b. Mp 259–260 °C; ^1H NMR ($CDCl_3$) δ 7.91 (d, 4H, $J=8$ Hz), 7.88 (s, 2H), 7.54 (dd, 4H, $J=8$, 2 Hz), 7.49 (t, 2H, $J=7$ Hz), 7.45–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 185.26, 151.71, 148.59, 136.87, 132.81, 130.42, 129.80, 129.69, 129.08, 128.52, 128.46, 128.06, 104.17 (one carbon is missing due to overlap). IR (KBr): 1640, 1554, 1445, 1333, 1235 cm^{-1}. Anal. Calcd for $C_{36}H_{22}O_4$: C, 83.38; H, 4.28%. Found: C, 83.34; H, 4.25%.

4.8.3. Compound 5b. Mp 185–187 °C; ^1H NMR ($CDCl_3$) δ 7.82 (s, 2H), 7.70 (d, 4H, $J=7$ Hz), 7.40 (t, 2H, $J=8$ Hz), 7.25 (t, 4H, $J=8$ Hz), 6.90 (d, 4H, $J=7$ Hz), 6.85 (t, 2H, $J=8$ Hz), 6.69 (t, 4H, $J=8$ Hz); ^{13}C NMR ($CDCl_3$) δ 185.60, 152.16, 148.67, 136.90, 132.41, 131.21, 129.57, 129.48, 127.93, 127.85, 127.26, 121.66, 112.94 (one carbon is missing due to overlap). IR (KBr): 1653, 1545, 1377, 1268, 1243 cm^{-1}. Anal. Calcd for $C_{36}H_{22}O_4$: C, 83.38; H, 4.28%. Found: C, 83.44; H, 4.32%.

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16. The stereochemistry of the intermediates **Ia** and **IIa** is not clear. However, based on the reports that the corresponding *cis* isomer is preferentially formed from the base-catalyzed cyclization of ethyl 2-acylphenoxyacetates[21,22] and the fact that only one singlet peak at δ 5.0 (C*H*COOK) is observed in their ^{1}H NMR spectra (see Section 4), it can be safely assumed that the structures of **Ia** and **IIa** are *cis* (2-carboxy group and 3-hydroxyl group of the furan ring are *cis*).
17. The synthesis of **2c–e** by the same method, but using ethanol instead of acetone as a solvent had been reported (the reported yield of **2e** was 57% and the yields of **2c** and **2d** were not mentioned).[8e]
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Base- and light-assisted synthesis of anthracenes from 3-allylnaphthalene-2-carbaldehydes

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Abstract—The synthesis of substituted anthracenes from naphthalene precursors is described. The key step involved heating *ortho*-allyl substituted naphthalene-2-carbaldehydes and potassium *t*-butoxide in DMF with concomitant irradiation from a high pressure mercury lamp to afford anthracenes in yields of 76–98%.

1. Introduction

Anthraquinone derivatives[1–3] such as **1a**,[1] carminic acid **1b**,[3] bisdeoxydothistromin **1c**[3] and daunorubicin **1d** (Fig. 1) are widespread in nature. Often these compounds display significant biological activity. For example, the anthracyclinone daunorubicin **1d** and its derivatives are important antineoplastic agents.[4]

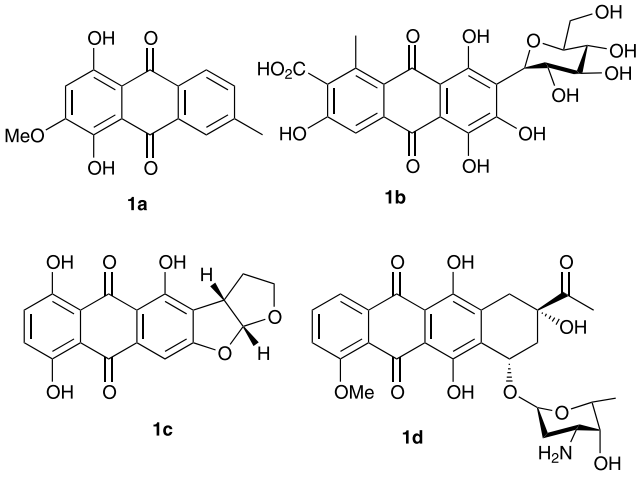

Figure 1.

A common method for synthesis of anthraquinones is from suitably substituted anthracenes. In turn many methods have been developed for the synthesis of anthracenes.[5] A major portion of this synthetic methodology was developed specifically for the synthesis of anthracyclinones.[6] Methods developed more than 10 years ago include the use of Friedel–Crafts methodology,[7] the phthalide annulation reaction[8] and the Diels–Alder reaction.[9] However, these approaches can require the use of harsh reaction conditions and may suffer from lack of regiocontrol. More recently, the development of sophisticated transition metal-mediated reactions has led to new methods for the construction of the anthracene nucleus. For example, amongst others, a domino Tsuji–Trost–Heck process has been used for the synthesis of tetrahydroanthracenes.[10] The metathesis reaction has now also been successfully applied to the synthesis of anthracenes.[11,12]

In this paper, we report on a regioselective aromatic ring-forming reaction for the synthesis of anthracenes from 3-allylnaphthalene-2-carbaldehydes by treatment with base under photochemical conditions. We have previously used this methodology for the synthesis of naphthalenes, phenanthrenes and ring-fused carbazoles.[13–17] Although the mechanism of the reaction is unclear, a possible pathway has been proposed in a previous publication.[14]

2. Results and discussion

In order to utilise our previously described aromatic ring-forming reaction for the synthesis of anthracenes such as **2**, we needed to assemble a suitably substituted naphthalene

Keywords: Anthracenes; Aromatic ring; Potassium *t*-butoxide.
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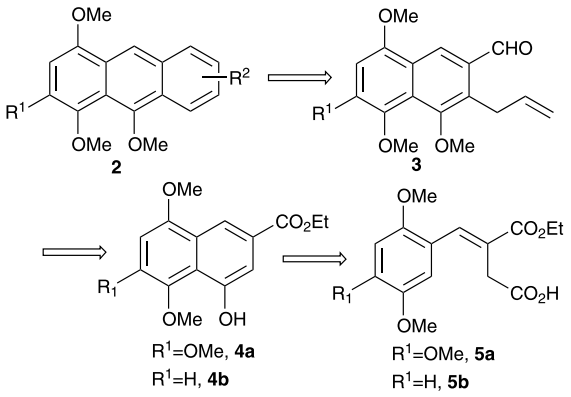
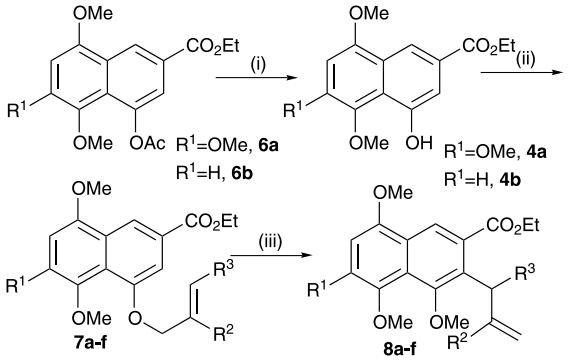


Figure 2. Retrosynthesis of anthracenes.

precursor. As shown in Figure 2, a naphthalene such as **3** containing a *C*-allyl substituent *ortho* to a carbonyl substituent was required. It was envisaged that the synthesis of **3** could be achieved from precursors **4a** or **4b**, both of which are readily available using Stobbe condensation methodology.[18]

As described in the literature,[19–21] treatment of commercially available 2,4,5-trimethoxybenzaldehyde or 2,5-dimethoxybenzaldehyde with diethyl succinate and potassium *t*-butoxide in *t*-butyl alcohol afforded the intermediate half esters **5a** and **5b**, which were treated with sodium acetate in acetic anhydride to give naphthalenes **6a** and **6b**, respectively.



Scheme 1. Reagents and conditions: (i) NaOH, EtOH; (ii) substituted allyl halide, K_2CO_3, Me_2CO, 16 h (yields, see Table 1); (iii) (a) heat, 160 °C, (b) Me_2SO_4, Me_2CO, 16 h (yields, see Table 1).

Table 1. Yields of O-allylation and Claisen reactions

Entry	Substituent	Yield (%)	
		4→7	**7→8**
a	R^1=OMe, R^2=R^3=H	93	72
b	R^1=OMe, R^3=H; R^2=Me	77	60
c	R^1=OMe, R^2=H; R^3=Me	83	67
d	R^1=R^2=R^3=H	94	74
e	R^1=R^3=H; R^2=Me	78	67
f	R^1=R^2=H; R^3=Me	83	66

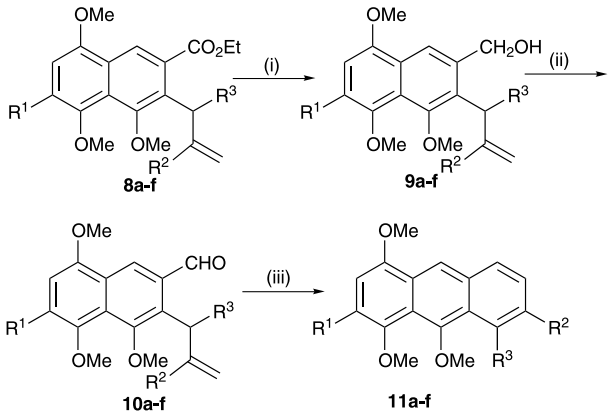
As shown in Scheme 1, both **6a** and **6b** were converted into the desired naphthols **4a** and **4b** upon exposure to sodium hydroxide. The stage was now set for the introduction of the allyl substituents *ortho* to the esters of **4a** and **4b**. This was easily achieved with the use of the Claisen rearrangement.[22] Formation of a number of substituted allyl ethers **7a–f** of both **4a** and **4b** proceeded in high yield as shown in Table 1. Heating **7a–f** in the absence of solvent afforded high yields of the Claisen rearranged intermediates, and these were immediately protected as their methyl ethers **8a–f**. It was clear from the ^{1}H NMR spectra of these compounds that the desired products had been formed. For example, **8a** showed, inter alia, only two aromatic singlets at δ 6.68 and 8.54. It was also clear that the *C*-allyl substituent was present, as complex signals at δ 3.88–4.14, 4.90–5.04 and 6.02–6.12 were evident.

The next step entailed the conversion of the ethyl ester of compounds **8a–f** into the required aldehyde necessary to attempt the aromatic ring forming reaction. The best way to do this was achieved by reducing the ester of **8a–f** with lithium aluminium hydride to the intermediate alcohols **9a–f** in high yields. Oxidation of these alcohols[23] with trifluoroacetic anhydride in DMSO afforded good yields of the desired aldehydes **10a–f**. Spectral evidence for the presence of an aromatic aldehyde was obtained from both the ^{1}H and ^{13}C NMR spectra. Aldehyde **10a** showed a signal at δ 10.16 in the ^{1}H NMR spectrum, while a signal for the corresponding carbonyl was evident at δ 192.3 in the ^{13}C NMR spectrum. We were now in a position to attempt our aromatic ring forming reaction on the *o*-allyl substituted aromatic aldehydes **10a–f** in order to produce the desired anthracenes **11a–f**. Exposure of **10a–f** to potassium *t*-butoxide in DMF with concomitant irradiation from a high-pressure mercury lamp afforded the substituted anthracenes **11a–f** in generally good to excellent yields as shown in Table 2. The ^{1}H NMR spectrum of anthracene **11b** indicated that both the allyl and aldehyde substituents of the starting material **10b** were absent, but that additional aromatic signals were present. In the ^{1}H NMR spectrum there were five distinct signals. A singlet was present at δ 6.60 (3-H), a doublet of doublet at δ 7.24 (6-H), a doublet at δ 7.86 (5-H), a multiplet at δ 8.07–8.08 (8-H) and a singlet at δ 8.54 (10-H) (Scheme 2).

In summary, we have developed a new method for the

Table 2. Yields for aldehyde formation and aromatic ring forming reaction

Entry	Substituent	Yields		
		8→9	**9→10**	**10→11**
a	R^1=OMe, R^2=R^3=H	87	66	81
b	R^1=OMe, R^3=H; R^2=Me	92	70	98
c	R^1=OMe, R^2=H; R^3=Me	85	66	76
d	R^1=R^2=R^3=H	93	74	87
e	R^1=R^3=H; R^2=Me	89	78	91
f	R^1=R^2=H; R^3=Me	86	74	78



Scheme 2. Reagents and conditions: (i) $LiAlH_4$, Et_2O, (yields, see Table 2); (ii) TFAA, DMSO, Et_3N, CH_2Cl_2 (yields, see Table 2); (iii) Bu^{t}OK, DMF, 70–80 °C, hν (yields, see Table 2).

synthesis of anthracenes by making use of our previously developed potassium *t*-butoxide mediated reaction with concomitant irradiation from a high-pressure mercury lamp. This method may have use for the synthesis of the anthracyclinones and more highly functionalised anthracenes or anthraquinones.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker AC-200 or Bruker DRX 400 spectrometer at the frequency indicated. DEPT, CH-correlated and HMBC spectra were run on some samples to enable assignments of some of the signals. NMR spectroscopic assignments with the same superscript may be interchanged. Infra-red spectra were recorded either on a Bruker IFS 25 Fourier Transform spectrometer or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a VG 70E MS or a VG 70 SEQ mass spectrometer. Macherey-Nagel kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography and Macherey-Nagel kieselgel 60 (particle size 0.040–0.063 mm) was used for preparative flash chromatography. All solvents used for reactions and chromatography were distilled prior to use.

3.1.1. (*E*)-3-Ethoxycarbonyl-4-(2,4,5-trimethoxyphenyl)-but-3-enoic acid 5a. 2,4,5-Trimethoxybenzaldehyde (3.23 g, 16.5 mmol) was added to a solution of diethyl succinate (7.12 g, 6.80 cm^3, 41.0 mmol) in *t*-BuOH (15 cm^3). *t*-BuOK (3.68 g, 32.8 mmol) was added and the resulting reaction mixture heated under reflux for 40 min under N_2. H_2O (50 cm^3) was added to the cooled mixture, which was acidified by dropwise addition of aqueous HCl (33%). The organic layer was extracted with CH_2Cl_2 (3×40 cm^3), dried with $MgSO_4$, filtered and concentrated in vacuo. The organic residue was purified by column chromatography (30% EtOAc/hexane) with silica gel to afford the product **5a** (4.92 g, 92%) as a low melting semi-solid with similar spectroscopic data to those reported by Charlton.[20] Found (M^+ 324.1213. $C_{16}H_{20}O_7$ requires 324.1209); IR ν_{max}/cm^{-1} (film) 3467 (br, OH stretch), 1690 (s, C=O stretch), 1607 (m, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.35 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 3.55 (2H, s, 2-H), 3.82, 3.84, 3.93 (each 3H, s, OCH_3), 4.29 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 6.54 (1H, s, 4-H), 6.95 (1H, s, Ar3′-H), 8.00 (1H, s, Ar6′-H), 10.78 (1H, br s, CO_2H); δ_C (50 MHz, $CDCl_3$) 14.0 ($CO_2CH_2CH_3$), 34.2 (2-C), 55.9 (OCH_3), 56.1 (OCH_3), 56.2 (OCH_3), 61.1 (OCH_2CH_3), 96.7 (Ar3′-C), 112.9 (Ar6′-C), 114.9 (Ar1′-C), 123.6 (3-C), 138.2 (4-C), 142.6 (ArC), 151.8 (ArC), 152.5 (ArC), 167.7 ($CO_2CH_2CH_3$), 177.0 (CO_2H); *m*/*z* 324 (M^+, 100%), 296 (6), 280 (14), 265 (9), 251 (6), 235 (8), 219 (9), 206 (12), 205 (18), 191 (20), 175 (7), 147 (5).

3.1.2. Ethyl 4-acetoxy-5,6,8-trimethoxy-2-naphthoate 6a. (*E*)-3-Ethoxycarbonyl-4-(2,4,5-trimethoxyphenyl)but-3-enoic acid **5a** (2.71 g, 8.36 mmol) was treated with NaOAc (0.82 g, 10.0 mmol) in Ac_2O (70 cm^3) and heated under reflux under N_2 for 45 min. The reaction mixture was cooled and the solvent removed under reduced pressure. The residue was then taken up in a mixture of EtOAc (20 cm^3) and H_2O (70 cm^3) after which Na_2CO_3 was added until no further effervescence was evident. The organic layer was then extracted with EtOAc (4×30 cm^3), dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc as eluant to afford pale yellow crystals (2.37 g, 81%) of the product **6a**. Found (M^+ 348.1228. $C_{18}H_{20}O_7$ requires 348.1209); mp 179.5–181 °C (EtOH/hexane); lit.[20] 180–181 °C ($CHCl_3$/hexane); IR ν_{max}/cm^{-1} 3346 (br, OH stretch), 1712 (s, C=O stretch), 1612 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.42 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 2.38 (3H, s, $OCOCH_3$), 3.82, 3.98 and 3.99 (each 3H, s, OCH_3), 4.40 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 6.68 (1H, s, 7-H), 7.68 (1H, d, J=1.7 Hz, 3-H), 8.84 (1H, d, J=1.7 Hz, 1-H); δ_C (50 MHz, $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 20.6 (CO_2CH_3), 55.9 (OCH_3), 56.6 (OCH_3), 61.0 (OCH_3)[a], 61.7 ($CO_2CH_2CH_3$)[a], 95.4 (7-C), 120.2 (3-C), 121.9 (ArC), 123.9 (1-C), 124.6 (ArC), 124.6 (ArC), 135.4 (ArC), 145.0 (ArC), 152.3 (ArC), 154.1 (ArC), 166.0 ($CO_2CH_2CH_3$)[b], 169.7 (CO_2CH_3)[b]; *m*/*z* 348 (M^+, 62%), 306 (66), 291 (100), 263 (8), 235 (8).

3.1.3. Ethyl 4-hydroxy-5,6,8-trimethoxy-2-naphthoate 4a. Ethyl-4-acetoxy-5,6,8-trimethoxy-2-naphthoate **6a** (2.37 g, 6.80 mmol) was dissolved in a mixture of EtOH (30 cm^3) and H_2O (10 cm^3). NaOH (0.74 g, 19 mmol) in H_2O (3 cm^3) was added and the reaction mixture allowed to stir for 10 min at rt. The reaction mixture was added to H_2O (20 cm^3) and then acidified by the dropwise addition of aqueous HCl (33%). The organic layer was then extracted with CH_2Cl_2 (4×30 cm^3), dried with $MgSO_4$ and concentrated in vacuo. The residue was then purified by silica gel column chromatography using EtOAc–hexane mixtures (10–50%) to yield the product **4a** (1.75 g, 84%) as white crystals. Mp 153–155 °C (EtOH/hexane). Found (M^+ 306.1103. $C_{16}H_{18}O_6$ requires 306.1103); IR ν_{max}/cm^{-1} 3346 (br, OH stretch), 1711 (s, C=O stretch), 1612 (s, ArC=C stretch); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 3.99, 4.00 and 4.01 (each 3H, s, OCH_3), 4.40 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 6.61 (1H, s, 7-H), 7.42 (1H, d, J=1.6 Hz, 3-H), 8.38 (1H, d, J=1.6 Hz, 1-H), 9.69 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 55.8 (OCH_3), 56.9 (OCH_3), 60.8 (OCH_3)[a],

62.1 ($CO_2CH_2CH_3$)[a], 95.2 (7-C), 110.3 (3-C), 116.4 (1-C), 120.4 (ArC), 121.7 (ArC), 126.5 (ArC), 136.2 (ArC), 149.3 (ArC), 153.1 (ArC), 154.2 (ArC), 166.7 ($CO_2CH_2CH_3$); *m/z* 306 (M^+, 72%), 292, (17), 291 (100), 263 (18), 261 (11), 235 (16), 203 (8), 123 (7).

3.1.4. (*E*)-3-Ethoxycarbonyl-4-(2,5-dimethoxyphenyl)-but-3-enoic acid 5b. 2,5-Dimethoxybenzaldehyde (5.09 g, 30.7 mmol) was dissolved in dry *t*-BuOH (90 cm^3). Diethyl succinate (10.60 g, 10.12 cm^3, 61.02 mmol) and *t*-BuOK (5.21 g, 45.8 mmol) were successively added to the reaction mixture which was then stirred at reflux under N_2 for 45 min. Upon cooling, the solution was quenched with H_2O (15 cm^3) and acidified with aqueous HCl (33%) at which point it turned yellow. The organic material was extracted with Et_2O (3×50 cm^3). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to yield a reddish brown oil that was purified by silica gel column chromatography (10–50% EtOAc/hexane) to afford the product **5b** as pale yellow crystals (6.31 g, 70%) with similar spectroscopic data to those described by Bloomer.[21] Found (M^+ 294.1109. $C_{15}H_{18}O_6$ requires 294.1103); mp 80–82 °C (EtOAc/hexane); lit.[21] 110 °C; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 3.52 (2H, s, 2-H), 3.80 (3H, s, OCH_3) 3.91 (3H, s, OCH_3), 4.29 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 6.83–6.93 (3H, m, 4-H, Ar3′-H, Ar4′-H), 7.99 (1H, br s, Ar6′-H), 10.78 (1H, s, CO_2H); *m/z* 294 (M^+, 100%), 276 (26), 264 (17), 248 (60), 233 (61), 205 (19), 195 (32), 175 (38), 161 (53), 101 (21), 77 (10), 55 (11).

3.1.5. Ethyl 4-acetoxy-5,8-dimethoxy-2-naphthoate 6b. (*E*)-3-Ethoxycarbonyl-4-(2,5-dimethoxyphenyl)but-3-enoic acid **5b** (1.16 g, 3.94 mmol) was treated with Ac_2O (20 cm^3) and anhydrous NaOAc (0.32 g, 3.9 mmol) and stirred at 140 °C under N_2 for 40 min. The solution was cooled and the solvent removed under reduced pressure. The residue was taken up in H_2O and the organic material extracted with CH_2Cl_2 (3×30 cm^3). The combined organic layers were treated with Na_2CO_3 until no noticeable effervescence occurred. The organic layer was washed with H_2O (3× 50 cm^3), dried with $MgSO_4$ and concentrated in vacuo. The yellow residue that resulted was then purified by silica gel column chromatography using EtOAc/hexane mixtures (10–80%) as eluting solvent to afforded the product **6b** (0.71 g, 57%). Mp 155–156 °C (EtOAc/hexane), lit.[21] 155 °C. Found (M^+ 318.1110. $C_{17}H_{18}O_6$ requires 318.1103); IR ν_{max}/cm^{-1} 1753 (m, C=O stretch), 1713 (s, C=O stretch), 1607 (m, ArC=C stretch); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 2.38 (3H, s, $OCOCH_3$), 3.89 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.42 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 6.77 (1H, d, J=8.6 Hz, 6-H)[a], 6.86 (1H, d, J=8.6 Hz, 7-H)[a], 7.69 (1H, d, J= 1.6 Hz, 3-H), 8.89 (1H, J=1.6 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 20.9 (CH_3CO_2Ar), 55.8 (OCH_3), 56.53 (OCH_3), 61.19 ($CO_2CH_2CH_3$), 104.8 (7-C)[a], 108.7 (6-C)[a], 119.5 (3-C)[b], 123.4 (1-C)[b], 127.5 (2×ArC), 127.7 (ArC), 146.4 (ArC), 148.7 (ArC), 150.5 (ArC), 165.9 ($CO_2CH_2CH_3$)[c], 170.1 (CH_3CO_2Ar)[c]; *m/z* 318 (M^+, 31%), 277 (16), 276 (100), 273 (7), 262 (9), 261 (55), 233 (10), 165 (8), 115 (5), 43 (11).

3.1.6. Ethyl 4-hydroxy-5,8-dimethoxy-2-naphthoate 4b. Ethyl 4-acetoxy-5,8-dimethoxy-2-naphthoate, **5b** (0.51 g, 1.6 mmol) was dissolved in a mixture of EtOH (3 cm^3) and H_2O (6 cm^3). NaOH (0.13 g, 3.2 mmol) in H_2O (1.5 cm^3) was added dropwise to the stirred mixture and allowed to stir for a further 10 min. The mixture was poured into H_2O (30 cm^3) and acidified with aqueous HCl (33%). The organic layer was then extracted with CH_2Cl_2 (3×40 cm^3). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo, yielding a yellow residue, which was then purified by column chromatography (10–50% EtOAc/hexane) to afford white needles of the product **4b** (0.34 g, 77%). Found (M^+ 276.1000. $C_{15}H_{16}O_5$ requires 276.0998). Mp 119–120 °C, (EtOAc/hexane); IR ν_{max}/cm^{-1} 3391 (br, OH stretch), 1712 (m, C=O stretch), 1615 (s, ArC=C stretch); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 3.93 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.41 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 6.63 (1H, d, J=8.5 Hz, 6-H)[a], 6.72 (1H, d, J=8.5 Hz, 7-H)[a], 7.48 (1H, d, J= 1.2 Hz, 3-H), 8.44 (1H, d, J=1.2 Hz, 1-H), 9.45 (1H, s, OH); δ_C (50 MHz, $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 55.7 (OCH_3), 56.3 (OCH_3), 61.0 ($CO_2CH_2CH_3$), 103.7 (7-C)[a], 105.8 (6-C)[a], 110.5 (3-C), 115.8 (1-C), 117.6 (ArC), 127.5 (ArC), 128.9 (ArC), 149.6 (ArC), 151.1 (ArC), 154.5 (ArC), 166.6 ($CO_2CH_2CH_3$); *m/z* 276 (M^+, 100%), 261 (63), 248 (6), 233 (17), 231 (10), 210 (5), 151 (8).

3.2. General procedure for preparing substituted 4-allyloxy-2-naphthoates

Typically, naphthol **4b** (2.00 g, 7.24 mmol) and the appropriate allylic bromide or chloride (1.96 g, 16.3 mmol, for allyl bromide) were dissolved in acetone (150 cm^3) containing K_2CO_3 (2.26 g, 16.3 mmol). When allylic chlorides were used as reagents, KI (0.1 mol equiv) was also added to effect halogen exchange. The resulting reaction mixture was then heated at reflux for 12–24 h (longer times for the chlorides). The reaction mixture was cooled and the solvent removed under reduced pressure. H_2O (50 cm^3) was then added to the residue and the organic material, extracted using CH_2Cl_2 (4×40 cm^3). The organic layer was then separated and dried using $MgSO_4$ and then concentrated in vacuo. The organic residue obtained was then purified by column chromatography (10–30% EtOAc/hexane) to afford, for example, **7d** (2.15 g, 94%). The following compounds were prepared using this procedure.

3.2.1. Ethyl 5,6,8-trimethoxy-4-(prop-2-enyloxy)-2-naphthoate 7a. The product **7a** (2.10 g, 93%) was isolated as pale yellow crystals from **4a** and allyl bromide. Found (M^+ 346.1422. $C_{19}H_{22}O_6$ requires 346.1416); mp 82–83 °C (EtOAc/hexane); IR ν_{max}/cm^{-1} 1710 (s, C=O stretch), 1600 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.43 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 3.83 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.42 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.72 (2H, dt, J=5.2, 1.6 Hz, CH_2CHCH_2), 5.34 (1H, dm, J=10.5 Hz, CH_2CHCH_2), 5.60 (1H, dm, J= 17.2 Hz, CH_2CHCH_2), 6.21 (1H, ddt, J=17.2, 10.5, 5.2 Hz, CH_2CHCH_2), 6.70 (1H, s, 7-H), 7.43 (1H, d, J=1.6 Hz, 3-H), 8.56 (1H, d, J=1.6 Hz, 1-H); δ_C (50 MHz, $CDCl_3$) 14.4 ($CO_2CH_2CH_3$), 55.8 (OCH_3), 57.1 (OCH_3), 60.8 ($CO_2CH_2CH_3$)[a], 61.9 (OCH_3)[a], 70.3 (OCH_2CHCH_2), 95.9 (7-C), 107.7 (3-C), 117.4 (OCH_2CHCH_2)[b], 118.4 (1-C)[b], 122.1 (ArC), 124.0 (ArC), 124.9 (ArC), 133.1 (CH_2CHCH_2),

137.7 (ArC), 152.1 (ArC), 153.4 (ArC),154.4 (ArC), 166.8 ($CO_2CH_2CH_3$); *m/z* 346 (M^+, 100%), 305 (98), 290 (10), 277 (17), 259 (15), 232 (19), 217 (19), 204 (29), 189 (15), 173 (11), 159 (8), 145 (4), 115 (15), 71 (8), 49 (7).

3.2.2. Ethyl 5,6,8-trimethoxy-4-(2-methylprop-2-enyloxy)-2-naphthoate 7b. The product **7b** (1.81 g, 77%) was isolated as a pale yellow semisolid from **4a** and 3-chloro-2-methylpropene. Found (M^+ 360.1571. $C_{20}H_{24}O_6$ requires 360.1573); IR ν_{max}/cm^{-1} (film) 1703 (s, C=O stretch), 1617 and 1599 (s, ArC=C stretch), 1508; δ_H (200 MHz, $CDCl_3$) 1.43 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.64 (3H, br s, $CH_2CCH_3CH_2$) 3.81 (3H, s, OCH_3), 4.00 (6H, s, 2× OCH_3), 4.18 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.61 (2H, br s, $CH_2CCH_3CH_2$), 5.04 (1H, br s, $CH_2CCH_3CH_2$), 5.30 (1H, br s, $CH_2CCH_3CH_2$), 6.70 (1H, s, 7-H), 7.43 (1H, d, $J=$ 1.6 Hz, 3-H), 8.56 (1H, d, $J=1.6$ Hz, 1-H); δ_C (50 MHz, $CDCl_3$) 14.4 ($CO_2CH_2CH_3$), 19.6 ($OCH_2CCH_3CH_2$), 55.8 (OCH_3), 56.9 (OCH_3), 60.9 ($CO_2CH_2CH_3$)[a], 61.9 (OCH_3)[a], 73.1 ($OCH_2CCH_3CH_2$), 95.6 (7-C), 107.1 (3-C), 112.6 ($OCH_2CCH_3CH_2$), 118.2 (1-C), 122.9 (ArC), 124.0 (ArC), 124.9 (ArC), 137.7 ($CH_2CCH_3CH_2$), 140.9 (ArC), 152.0 (ArC), 153.4 (ArC), 154.6 (ArC),166.9 ($CO_2CH_2CH_3$); *m/z* 360 (M^+, 90%), 305 (100), 277 (38), 259 (8), 232 (6), 204 (7), 115 (6), 55 (19).

3.2.3. Ethyl 5,6,8-trimethoxy-4-(but-2-enyloxy)-2-naphthoate 7c. The product **7c** (1.95 g, 83%) was isolated as a pale yellow oil from **4a** and crotyl bromide. Found (M^+ 360.1567. $C_{20}H_{24}O_6$ requires 360.1573); IR ν_{max}/cm^{-1} (film) 1701 (s, C=O stretch), 1600 (s, C=C stretch); δ_H (200 MHz, $CDCl_3$) 1.43 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.63 (3H, dd, $J=6.1$, 1.2 Hz, $CH_2CHCHCH_3$), 3.84 (3H, s, OCH_3), 4.00 (6H, s, 2×OCH_3), 4.42 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.62 (2H, dd, $J=6.1$, 1.2 Hz, $CH_2CHCHCH_3$), 5.80–6.05 (2H, m, $CH_2CHCHCH_3$), 6.70 (1H, s, 7-H), 7.43 (1H, d, $J=1.6$ Hz, 3-H), 8.55 (1H, d, $J=1.6$ Hz, 1-H); δ_C (50 MHz, $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 19.6 ($OCH_2CHCHCH_3$), 55.7 (OCH_3), 56.9 (OCH_3), 60.8 ($CO_2CH_2CH_3$)[a], 62.0 (OCH_3)[a], 81.5 ($OCH_2CHCHCH_3$), 94.9 (7-C), 103.1 (3-C), 113.2 ($OCH_2CHCHCH_3$), 120.5 (1-C), 121.6 (ArC), 124.7 (ArC), 125.4 (ArC), 143.1 ($OCH_2CHCHCH_3$), 143.4 (ArC), 151.5 (ArC), 153.2 (ArC),153.2 (ArC),169.4 ($CO_2CH_2CH_3$); *m/z* 360 (M^+, 78%), 305 (100), 291 (48), 277 (38), 263 (24), 204 (7), 168 (4), 115 (4), 55 (10).

3.2.4. Ethyl 5,8-dimethoxy-4-(prop-2-enyloxy)-2-naphthoate 7d. Compound **7d** (2.15 g, 94%) was obtained from **4b** and allyl bromide as pale yellow crystals. Found (M^+ 316.1308. $C_{18}H_{20}O_5$ requires 316.1311); mp 70–71 °C (EtOAc/hexane); IR ν_{max}/cm^{-1} 1711 (s, C=O stretch), 1610 and 1600 (s, C=C stretch); δ_H (200 MHz, $CDCl_3$) 1.44 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.47 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.72 (2H, dt, $J=4.7$, 1.6 Hz, CH_2CHCH_2), 5.34 (2H, dm, $J=10.6$ Hz, CH_2CHCH_2), 5.66 (2H, dm, $J=17.2$ Hz, CH_2CHCH_2), 6.18 (1H, ddt, $J=17.2$, 10.6, 4.6 Hz, CH_2CHCH_2), 6.76 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.88 (1H, d, $J=8.5$ Hz, 7-H)[a], 7.47 (1H, d, $J=1.6$ Hz, 3-H), 8.61 (1H, d, $J=1.6$ Hz, 1-H); δ_C (50 MHz, $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 55.6 (OCH_3), 57.2 (OCH_3), 61.0 ($CO_2CH_2CH_3$), 70.4 (OCH_2CHCH_2) 104.8 (7-C), 107.3 (6-C), 109.4 (3-C), 116.7 (OCH_2CHCH_2), 117.8 (1-C), 120.6 (ArC), 127.4 (ArC), 127.8 (ArC), 133.0 (OCH_2CHCH_2), 150.3 (ArC), 150.6 (ArC), 155.7 (ArC), 166.7 ($CO_2CH_2CH_3$); *m/z* (M^+, 100%), 288 (23), 275 (50), 247 (28), 202 (7), 173 (11), 115 (7).

3.2.5. Ethyl 5,8-dimethoxy-4-(2-methylprop-2-enyloxy)-2-naphthoate 7e. The product **7e** (1.86 g, 78%) was isolated as a pale yellow oil from **4b** and 3-chloro-2-methylpropene. Found (M^+ 330.1468. $C_{19}H_{22}O_5$ requires 330.1467); IR ν_{max}/cm^{-1} (film) 1700 (s, C=O stretch), 1610 (s, C=C stretch); δ_H (200 MHz, $CDCl_3$) 1.44 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.94 (3H, br s, $OCH_2C(CH_3)CH_2$), 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.45 (2H, q $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.60 (2H, br s, $OCH_2C(CH_3)CH_2$), 5.06 (1H, br s, $OCH_2C(CH_3)CH_2$), 5.37 (1H, br s, $OCH_2C(CH_3)CH_2$), 6.77 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.87 (1H, d, $J=8.5$ Hz, 7-H)[a], 7.46 (1H, d, $J=1.6$ Hz, 3-H), 8.60 (1H, d, $J=1.6$ Hz, 1-H); δ_C (50 MHz, $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 19.5 ($CH_2C(CH_3)CH_2$), 55.8 (OCH_3), 57.0 (OCH_3), 61.1 ($CO_2CH_2CH_3$), 72.7 ($OCH_2C(CH_3)CH_2$), 104.9 (7-C), 106.8 (6-C)[a], 108.9 (3-C)[a], 112.1 ($CH_2C(CH_3)CH_2$)[b], 117.7 (1-C)[b], 120.5 (ArC), 127.5 (ArC), 127.9 (ArC), 140.8 ($CH_2C(CH_3)CH_2$), 150.3 (ArC), 150.9 (ArC), 160.0 (ArC), 166.9 ($CO_2CH_2CH_3$); *m/z* 330 (M^+, 100%), 315 (5), 285 (8), 275 (69), 257 (9), 247 (8), 229 (7), 202 (6), 187 (7), 174 (12), 160 (6), 115 (7), 55 (7).

3.2.6. Ethyl 5,8-dimethoxy-4-(but-2-enyloxy)-2-naphthoate 7f. The product **7f** was isolated as the *E* isomer from **4b** and crotyl bromide as a pale yellow oil (1.98 g, 83%). Found (M^+ 330.1467. $C_{19}H_{22}O_5$ requires 330.1467); IR ν_{max}/cm^{-1} (film) 1713 (s, C=O stretch), 1615 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.44 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.73–1.82 (3H, m, $CH_2CHCHCH_3$), 3.91 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.43 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.64 (2H, dm, $J=5.4$ Hz, $CH_2CHCHCH_3$), 5.78–6.09 (2H, m, $CH_2CHCHCH_3$), 6.76 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.88 (1H, d, $J=8.5$ Hz, 7-H)[a], 7.48 (1H, d, $J=1.6$ Hz, 3-H), 8.61 (1H, d, $J=1.6$ Hz, 1-H); δ_C (50 MHz, $CDCl_3$) 14.4 ($CO_2CH_2CH_3$), 17.9 ($OCH_2CHCHCH_3$), 55.8 (OCH_3), 57.6 (OCH_3), 61.0 ($CO_2CH_2CH_3$), 70.3 ($OCH_2CHCHCH_3$), 105.0 (7-C)[a], 107.9 (6-C)[a], 110.1 (3-C), 117.9 ($OCH_2CHCHCH_3$), 126.0 (ArC), 126.1 (1-C), 127.6 (ArC), 128.0 (ArC), 129.5 ($OCH_2CHCHCH_3$), 150.6 (ArC), 150.8 (ArC), 156.0 (ArC), 166.6 ($CO_2CH_2CH_3$); *m/z* 330 (M^+, 91%), 276 (100), 261 (49), 247 (9), 233 (8), 229 (6), 187 (7), 173 (10), 159 (6), 115 (9), 55 (20).

3.3. General procedure for preparing substituted 6-methoxy-3-allyl-2-naphthoates

Usually, the naphthoate **7a** (1.00 g, 2.89 mmol) was heated overnight at 160 °C under N_2 for 12 h (up to 18 h for some reactions). The reaction progress was monitored by TLC. When no trace amount of the starting material was present, the residue was allowed to cool and then dissolved in acetone (40 cm^3). Dimethyl sulfate (0.68 cm^3, 7.2 mmol) and K_2CO_3 (0.99 g, 7.2 mmol) were added to the mixture while stirring. The reaction mixture was then heated at reflux under N_2 for 12–24 h. The solvent was removed under reduced pressure and the residue taken up in H_2O (50 cm^3). An aqueous 25% NH_3 solution was added

dropwise to the mixture until no further effervescence took place. The organic layer was extracted using CH_2Cl_2 (4× 30 cm^3) to which H_2O (20 cm^3) was added and the mixture was made acidic by dropwise addition of aqueous HCl (33%). The organic layer was separated and the H_2O layer back-extracted with CH_2Cl_2 (2×30 cm^3). The combined organic layers were washed repeatedly with H_2O (5× 50 cm^3), dried with $MgSO_4$ and concentrated in vacuo. The organic residue was purified by column chromatography on silica gel (using 10–50% EtOAc/hexane as eluant) to afford **8a** (0.74 g, 72%). The following compounds were prepared using the above-mentioned procedure.

3.3.1. Ethyl 4,5,6,8-tetramethoxy-3-(prop-2-enyl)-2-naphthoate 8a. The product **8a** (0.74 g, 72%) was isolated as a yellow oil from **7a**. Found (M^+ 360.1572. $C_{20}H_{24}O_6$ requires 360.1573); IR ν_{max}/cm^{-1} (film) 1713 (s, C=O stretch), 1615 and 1592 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.41 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 3.82 (6H, s, 2×OCH_3), 3.88–4.14 (2H, m (obscured), CH_2CHCH_2), 4.00 and 4.02 (each 3H, s, 2×OCH_3), 4.37 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.90–5.04 (2H, m, CH_2CHCH_2), 6.02–6.12 (1H, m, CH_2CHCH_2), 6.68 (1-H, s, 7-H), 8.54 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 30.1 (CH_2CHCH_2), 55.7 (OCH_3), 56.8 (OCH_3), 60.8 ($CO_2CH_2CH_3$)[a], 62.0 (OCH_3)[a], 62.7 (OCH_3)[a], 94.6 (7-C), 114.6 (CH_2CHCH_2), 120.7 (ArC), 121.6 (1-C), 125.2 (ArC), 126.6 (ArC), 130.3 (ArC), 135.7 (ArC), 138.2 (CH_2CHCH_2), 151.9 (ArC), 153.1 (ArC), 153.5 (ArC), 167.8 ($CO_2CH_2CH_3$); *m/z* 360 (M^+, 100%), 345 (15), 299 (6), 285 (4), 272 (4).

3.3.2. Ethyl 4,5,6,8-tetramethoxy-3-(2-methylprop-2-enyl)-2-naphthoate 8b. The product **8b** (0.71 g, 60%) was obtained from **7b** as a yellow oil. Found (M^+ 374.1722. $C_{21}H_{26}O_6$ requires 374.1729); IR ν_{max}/cm^{-1} (film) 1705 (s, C=O stretch), 1614 (m, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.38 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.87 (3H, br s, $CH_2C(CH_3)CH_2$), 3.80 (OCH_3), 3.82 (OCH_3), 3.91 (2H, br s, $CH_2C(CH_3)CH_2$), 4.01 (OCH_3), 4.03 (OCH_3), 4.19 (1H, br s, $CH_2C(CH_3)CH_2$), 4.34 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.70 (1H, br s, $CH_2C(CH_3)CH_2$), 6.68 (1H, s, 7-H), 8.53 (1H, s, 1-H); *m/z* 374 (M^+, 100%), 360 (11), 359 (13), 346 (21), 313 (9), 271 (6).

3.3.3. Ethyl 4,5,6,8-tetramethoxy-3-(1-methylprop-2-enyl)-2-naphthoate 8c. The compound **8c** (0.79 g, 67%) was isolated as a light yellow oil from **7c**. Found (M^+ 374.1732. $C_{21}H_{26}O_6$ requires 374.1729); IR ν_{max}/cm^{-1} (film) 1712 (s, C=O stretch), 1615 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.42 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.56 (3H, d, $J=7.1$ Hz, $CHCH_3CHCH_2$), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.30–4.40 (3H, m, $CO_2CH_2CH_3$ and $CHCH_3CHCH_2$), 5.02–5.09 (2H, m, $CHCH_3CHCH_2$), 6.26 (1H, ddd, $J=17.2$, 10.4, 5.2 Hz, $CHCH_3CHCH_2$), 6.66 (1H, s, 7-H), 8.23 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 19.7 ($CH(CH_3)CHCH_2$), 28.2 ($CH(CH_3)CHCH_2$), 55.8 (OCH_3), 57.0 (OCH_3), 61.1 (OCH_3)[a], 62.1 (OCH_3)[a], 63.1 ($CO_2CH_2CH_3$)[a], 95.0 (7-C), 113.1 ($CH(CH_3)CHCH_2$), 120.4 (1-C), 121.0 (ArC), 128.7 (ArC), 134.7 (ArC), 135.8 (ArC), 143.1 ($CH(CH_3)CHCH_2$), 143.4 (ArC), 151.5 (ArC), 153.2 (2×ArC), 169.4 ($CO_2CH_2CH_3$); *m/z* 374 (M^+, 100%), 359 (13), 313 (9), 299 (6).

3.3.4. Ethyl 4,5,8-trimethoxy-3-(prop-2-enyl)-2-naphthoate 8d. The compound **8d** (0.77 g, 74%) was isolated as a light yellow oil from **7d**. Found (M^+ 330.1472. $C_{19}H_{22}O_5$ requires 330.1467); IR ν_{max}/cm^{-1} (film) 1717 (s, C=O stretch), 1621 and 1596 (m, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.41 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 3.80 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.94–3.98 (2H, m, CH_2CHCH_2), 4.38 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.92–4.99 (2H, m, CH_2CHCH_2), 6.02–6.09 (1H, m, CH_2CHCH_2), 6.70 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.84 (1H, d, $J=8.5$ Hz, 7-H)[a], 8.54 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 30.2 (CH_2CHCH_2), 55.7 (OCH_3), 56.8 (OCH_3), 61.0 (OCH_3), 62.8 ($CO_2CH_2CH_3$), 104.0 (6-C)[a], 108.4 (7-C)[a], 114.8 (CH_2CHCH_2), 121.1 (1-C), 122.4 (ArC), 126.4 (ArC), 129.7 (ArC), 129.9 (ArC), 138.1 (CH_2CHCH_2), 149.2 (ArC), 150.3 (ArC), 154.6 (ArC), 168.0 ($CO_2CH_2CH_3$); *m/z* 330 (M^+, 100%), 316 (22), 315 (13), 302 (8), 285 (7), 270 (8), 269 (9), 255 (5), 242 (8), 227 (5), 211 (3), 115 (3).

3.3.5. Ethyl 4,5,8-trimethoxy-3-(2-methylprop-2-enyl)-2-naphthoate 8e. The compound **8e** (0.70 g, 67%) was isolated as a light yellow oil from **7e**. Found (M^+ 344.1624. $C_{20}H_{24}O_5$ requires 344.1624); IR ν_{max}/cm^{-1} (film) 1718 (s, C=O stretch), 1620 and 1592 (m, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.39 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.84 (3H, br s, $CH_2C(CH_3)CH_2$), 3.79 (3H, s, OCH_3), 3.91 (2H, br s, $CH_2C(CH_3)CH_2$), 3.95 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.21 (1H, br s, $CHC(CH_3)CH_2$), 4.35 (2H, q, $J=7.1$ Hz, $CO_2CH_2CH_3$), 4.69 (1H, br s, $CHC(CH_3)CH_2$), 6.73 (1H, d, $J=8.5$ Hz, 7-H), 6.87 (1H, d, $J=8.5$ Hz, 6-H), 8.54 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 23.6 ($CH_2C(CH_3)CH_2$), 33.4 ($CH_2C(CH_3)CH_2$), 55.7 (OCH_3), 56.8 (OCH_3), 58.5 (OCH_3), 60.9 ($CO_2CH_2CH_3$), 104.0 (6-C)[a], 108.5 (7-C)[a], 110.0 ($CH_2C(CH_3)CH_2$), 122.3 (ArC), 126.5 (ArC), 129.6 (ArC), 130.3 (ArC), 146.2 (1-C), 149.3 (ArC), 150.3 (ArC), 154.7 (ArC), 168.0 ($CO_2CH_2CH_3$), (one carbon missing); *m/z* 344 (M^+, 100%), 330 (9), 329 (9), 300 (6), 299 (7), 285 (6), 284 (8), 283 (10), 269 (7), 256 (6), 255 (7), 241 (8), 225 (5), 165 (7).

3.3.6. Ethyl 4,5,8-trimethoxy-3-(1-methylprop-2-enyl)-2-naphthoate 8f. The compound **8f** (0.69 g, 66%) was isolated as a light yellow oil from **7f**. Found (M^+ 344.1613. $C_{20}H_{24}O_5$ requires 344.1624); IR ν_{max}/cm^{-1} (film) 1712 (s, C=O stretch), 1604 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.40 (3H, t, $J=7.1$ Hz, $CO_2CH_2CH_3$), 1.58 (3H, d, $J=7.1$ Hz, $CH(CH_3)CHCH_2$), 3.79 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.29–4.41 (3H, m, $CO_2CH_2CH_3$ and $CH(CH_3)CHCH_2$), 5.02–5.13 (2H, $CH(CH_3)CHCH_2$), 6.24 (1H, ddd, $J=17.1$, 10.2, 5.2 Hz, $CH(CH_3)CHCH_2$), 6.71 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.83 (1H, d, $J=8.5$ Hz, 7-H)[a], 8.25 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 19.7 ($CH(CH_3)CHCH_2$), 36.2 ($CH(CH_3)CHCH_2$), 55.8 (OCH_3), 56.6 (OCH_3), 61.2 (OCH_3), 63.2 ($CO_2CH_2CH_3$), 104.0 (6-C)[a], 107.9 (7-C)[a], 113.2 ($CH(CH_3)CHCH_2$), 119.8 (1-C), 121.9 (ArC), 126.7 (ArC), 131.7 (ArC), 134.1 (ArC), 143.1 ($CH(CH_3)CHCH_2$), 149.2 (ArC), 150.1 (ArC), 154.7 (ArC), 169.5 ($CO_2CH_2CH_3$); *m/z* 344 (M^+, 100%), 329 (12), 316

(3), 299 (6), 287 (5), 283 (12), 269 (3), 256 (5), 241 (5), 115 (3).

3.4. General procedure for preparing substituted (6-methoxy-3-allyl-2-naphthyl)methanols

Typically, ester **8a** (0.50 g, 1.4 mmol) was dissolved in THF (20 cm^3). $LiAlH_4$ (0.15 g, 4.0 mmol) was added and the reaction mixture was allowed to stir overnight at rt under N_2. H_2O (0.15 cm^3), aqueous NaOH (3.75 M, 0.15 cm^3) and finally H_2O (0.46 cm^3) were added sequentially, while stirring, to the reaction mixture. The resulting mixture was passed through Celite® to filter off the inorganic solids. The organic phase was then separated and dried ($MgSO_4$) to afford the dry organic phase. The solvent was then removed under reduced pressure to obtain an organic residue which was purified using silica gel column chromatography (10–30% EtOAc/hexane) to afford the pure alcohol **9a** (0.38 g, 85%) in good yield. Similarly, the other naphthylmethanols **9b–9f** were synthesised by this method.

3.4.1. [4,5,6,8-Tetramethoxy-3-(prop-2-enyl)-2-naphthyl]methanol 9a. Compound **9a** (0.39 g, 87%) was isolated as a light yellow oil from **8a**. Found (M^+ 318.1468. $C_{18}H_{22}O_5$ requires 318.1467); IR ν_{max}/cm^{-1} (film) 3400 (br, OH stretch), 1601 and 1522 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.86 (1H, br s, CH_2OH), 3.70 (2H, dt, $J=5.2$, 1.7 Hz, CH_2CHCH_2), 3.81 (6H, s, 2× OCH_3), 3.98 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.78 (2H, s, CH_2OH), 4.90 (1H, dm, $J=17.1$ Hz, CH_2CHCH_2), 5.03 (1H, dm, $J=10.2$ Hz, CH_2CHCH_2), 6.05–6.14 (1H, m, CH_2CHCH_2), 6.66 (1H, s, 7-H), 8.02 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 29.8 (CH_2CHCH_2), 55.8 (CH_2OH), 57.0 (OCH_3), 62.0 (OCH_3), 62.8 (OCH_3), 63.8 (OCH_3), 94.9 (7-C), 112.0 (ArC), 115.1 (CH_2CHCH_2)[a], 117.6 (1-C)[a], 122.0 (ArC), 123.2 (ArC), 129.2 (ArC), 135.7 (ArC), 138.0 (CH_2CHCH_2), 150.0 (ArC), 152.6 (ArC), 153.0 (ArC); *m/z* 318 (M^+, 100%), 303 (19), 285 (3), 257 (5), 135 (6), 115 (3).

3.4.2. [4,5,6,8-Tetramethoxy-3-(2-methylprop-2-enyl)-2-naphthyl]methanol 9b. Compound **9b** (0.41 g, 92%) was isolated as a light yellow oil from **8b**. Found (M^+ 332.1628. $C_{19}H_{24}O_5$ requires 332.1624); IR ν_{max}/cm^{-1} (film) 3500 (br, OH stretch), 1601 (s, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.80 (1H, br s, CH_2OH), 1.90 (3H, br s, $CH_2C(CH_3)CH_2$), 3.62 (2H, br s, $CH_2C(CH_3)CH_2$), 3.80 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.28 (1H, br s, $CH_2C(CH_3)CH_2$), 4.72 (2H, s, CH_2OH), 4.77 (1H, br s, $CH_2C(CH_3)CH_2$), 6.67 (1H, s, 7-H), 8.03 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 23.6 ($CH_2C(CH_3)CH_2$), 33.5 ($CH_2C(CH_3)CH_2$), 55.8 (OCH_3), 57.1 (OCH_3), 62.0 (OCH_3)[a], 62.7 (OCH_3)[a], 63.9 (CH_2OH)[a], 95.0 (7-C), 110.4 ($CH_2C(CH_3)CH_2$)[b], 117.6 (1-C)[b], 122.1 (ArC), 123.2 (ArC), 129.4 (ArC), 135.9 (ArC)[c], 136.3 ($CH_2C(CH_3)CH_2$)[c], 146.4 (ArC), 150.1 (ArC), 152.6 (ArC)[c], 153.0 (ArC); *m/z* 332 (M^+, 100%), 317 (22), 299 (6), 289 (7), 259 (10), 227 (3).

3.4.3. [4,5,6,8-Tetramethoxy-3-(1-methylprop-2-enyl)-2-naphthyl]methanol 9c. Compound **9c** (0.38 g, 85%) was isolated as a light yellow oil from **8c**. Found (M^+ 332.1624. $C_{19}H_{24}O_5$ requires 332.1624); IR ν_{max}/cm^{-1} (film) 3624 (br, OH stretch), 1521 (s, C=C stretch); δ_H (200 MHz, $CDCl_3$) 1.52 (3H, d, $J=7.3$ Hz, $CH(CH_3)CHCH_2$), 1.87 (1H, br s, CH_2OH), 3.79 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.34–4.49 (1H, m, $CH(CH_3)CHCH_2$), 4.72 (1H, d, $J=12.5$ Hz, CH_2OH), 4.86 (1H, d, $J=12.5$ Hz, CH_2OH), 5.00–5.11 (2H, m, $CH(CH_3)CHCH_2$), 6.27 (1H, ddd, $J=17.2$, 10.4, 5.3 Hz, $CH(CH_3)CHCH_2$), 6.65 (1H, s, 7-H), 8.05 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 19.5 ($CH(CH_3)CHCH_2$), 34.9 ($CH(CH_3)CHCH_2$), 55.8 (OCH_3), 57.1 (OCH_3), 62.0 (OCH_3), 63.0 (OCH_3), 63.6 (CH_2OH), 94.9 (7-C), 113.0 ($CH(CH_3)CHCH_2$), 117.5 (3-C), 118.8 ($CH(CH_3)CHCH_2$), 122.0 (ArC), 125.7 (ArC), 130.4 (ArC), 134.9 (ArC), 135.8 (ArC), 143.9 (1-C), 150.1 (ArC), 152.5 (ArC); *m/z* 332 (M^+, 100%), 317 (23), 289 (10), 271 (10), 243 (5), 142 (10), 115 (5).

3.4.4. [4,5,8-Trimethoxy-3-(prop-2-enyl)-2-naphthyl]methanol 9d. Compound **9d** (0.41 g, 93%) was isolated as a light yellow oil from **8d**. Found (M^+ 288.1362. $C_{17}H_{20}O_4$ requires 288.1362); IR ν_{max}/cm^{-1} (film) 3310 (OH stretch), 1732 and 1687 (s, olefinic C=C stretch), 1609 (m, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 1.99 (1H, br s, CH_2OH), 3.67 (2H, dt, $J=5.5$, 1.8 Hz, CH_2CHCH_2), 3.79 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.80 (2H, s, CH_2OH), 4.91 (1H, dm, 17.2, CH_2CHCH_2), 5.00 (1H, dm, $J=10.2$ Hz, CH_2CHCH_2), 6.02–6.12 (1H, m, CH_2CHCH_2), 6.68 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.75 (1H, d, $J=8.5$ Hz, 7-H)[a], 8.08 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 29.7 (CH_2CHCH_2), 55.7 (OCH_3), 56.6 (OCH_3), 62.6 (OCH_3), 63.6 (CH_2OH), 103.5 (ArCH), 106.0 (ArCH), 115.0 (CH_2CHCH_2), 117.1 (CH_2CHCH_2), 120.2 (ArC), 127.3 (ArC), 128.5 (ArC), 137.9 (1-C), 138.4 (ArC), 149.4 (ArC), 149.7 (ArC), 154.1 (ArC). *m/z* 288 (M^+, 100%), 273 (20), 255 (7).

3.4.5. [4,5,8-Trimethoxy-3-(2-methylprop-2-enyl)-2-naphthyl]methanol 9e. Compound **9e** (0.40 g, 89%) was isolated as a light yellow oil from **8e**. Found (M^+ 302.1519. $C_{18}H_{22}O_4$ requires 302.1518); IR ν_{max}/cm^{-1} (film) 3367 (br, OH stretch), 1716 (s, olefinic C=C stretch), 1603 ArC=C); δ_H (200 MHz, $CDCl_3$) 1.88 (3H, br s, $CH_2(CH_3)CCH_2$), 3.61 (2H, br s, $CH_2(CH_3)CCH_2$), 3.78 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.26–4.27 (1H, m, $CH_2(CH_3)CCH_2$), 4.74–4.76 (3H, m, CH_2OH and $CH_2(CH_3)CCH_2$), 6.70 (1H, d, $J=8.5$ Hz, 6-H)[b], 6.74 (1H, d, $J=8.5$ Hz, 7-H)[b], 8.10 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 23.5 ($CH_2C(CH_3)CH_2$), 33.4 ($CH_2C(CH_3)CH_2$), 55.8 (OCH_3), 56.8 (OCH_3), 62.6 (OCH_3), 63.8 (CH_2OH), 103.7 ($CH_2C(CH_3)CH_2$), 106.4 (6-C)[a], 110.5 (7-C)[a], 117.2 ($CH_2C(CH_3)CH_2$), 120.4 (ArC), 127.5 (ArC), 128.7 (ArC), 138.7 ($CH_2C(CH_3)CH_2$), 146.3 (ArC), 149.6 (ArC), 149.8 (ArC), 154.3 (8-C)[c]. *m/z* 302 (M^+, 100%), 287 (13), 269 (11), 256 (15), 127 (21), 115 (10), 45 (13).

3.4.6. [4,5,8-Trimethoxy-3-(1-methylprop-2-enyl)-2-naphthyl]methanol 9f. Compound **9f** (0.38 g, 86%) was isolated as a light yellow oil from **8f**. Found (M^+ 302.1521. $C_{18}H_{22}O_4$ requires 302.1518); IR ν_{max}/cm^{-1} (film) 3387 (br, OH stretch), 1716 (s, olefinic C=C stretch), 1615 (m, ArC=C); δ_H (200 MHz, $CDCl_3$) 1.51 (3H, d, $J=7.2$ Hz, $CH(CH_3)CHCH_2$), 2.01 (1H, br s, CH_2OH), 3.77 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.38–4.44 (1H, m, $CH(CH_3)CHCH_2$), 4.79 (1H, d, $J=12.9$ Hz,

CH_2OH), 4.89 (1H, d, $J=12.9$ Hz, CH_2OH), 4.99–5.11 (2H, m, $CH(CH_3)CHCH_2$), 6.26 (1H, ddd, $J=17.2$, 10.4, 4.5 Hz, $CH(CH_3)CHCH_2$), 6.68 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.76 (1H, d, $J=8.5$ Hz, 7-H)[a], 8.13 (1H, s, 1-H); δ_C (50 MHz, $CDCl_3$) 19.5 ($CH(CH_3)CHCH_2$), 34.9 ($CH(CH_3)CHCH_2$), 55.8 (OCH_3), 56.8 (OCH_3), 63.1 (OCH_3), 63.6 (CH_2OH), 103.7 ($CH(CH_3)CHCH_2$), 106.3 (7-C)[a], 113.0 (6-C)[a], 118.5 ($CH(CH_3)CHCH_2$), 127.4 (ArC), 129.5 (ArC), 134.3 (ArC), 138.5 (ArC), 143.9 (1-C), 149.5 (ArC), 149.8 (ArC), 154.3 (ArC); *m/z* 302 (M^+, 100%), 287 (13), 269 (9), 256 (11), 241 (6), 127 (8).

3.5. General procedure for preparing substituted 6-methoxynaphthalene-2-carbaldehydes

Typically, dimethyl sulfoxide (0.16 cm^3, 2.3 mmol) in CH_2Cl_2 (4 cm^3) was cooled to -60 °C in a flame-dried three neck flask and trifluoroacetic anhydride (0.25 cm^3, 1.8 mmol), also in CH_2Cl_2 (2 cm^3), was added dropwise to the solution over 5 min. The starting material, for example, **9a** (0.30 g, 0.94 mmol) dissolved in CH_2Cl_2 (3 cm^3), was then added to the mixture over a period exceeding 5 min. The mixture was allowed to stir at -60 °C for 10 min and a solution of NEt_3 (3 cm^3) in CH_2Cl_2 (2 cm^3) was then added dropwise to the mixture over 10 min. The reaction mixture was then allowed to warm-up to rt H_2O (20 cm^3) was added to the mixture and the organic material extracted with CH_2Cl_2 (3×30 cm^3). The solvent was then evaporated under reduced pressure to leave a brown residue that was purified by column chromatography (10–30% EtOAc/hexane) to afford the desired carbaldehydes, for example, **10a** in satisfactory yield (0.20 g, 66%). The other carbaldehydes, **10b–f** were synthesised in the same way.

3.5.1. 4,5,6,8-Tetramethoxy-3-(prop-2-enyl)naphthalene-2-carbaldehyde 10a. Compound **10a** (0.20 g, 66%) was isolated as a light yellow oil from **9a**; IR ν_{max}/cm^{-1} (film) 1684 (s, C=O stretch), 1611 (s, olefinic C=C stretch). Found (M^+ 316.1318. $C_{18}H_{20}O_5$ requires 316.1311); δ_H (200 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.01–4.05 (2H, m, obscured, CH_2CHCH_2), 4.04 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.91 (1H, dm, $J=17.2$ Hz, CH_2CHCH_2), 5.02 (1H, dm, $J=10.3$ Hz, CH_2CHCH_2), 6.04–6.21 (1H, m, CH_2CHCH_2), 6.71 (1H, s, 7-H), 8.54 (1H, s, 1-H), 10.16 (1H, s, CHO); δ_C (50 MHz, $CDCl_3$) 28.8 (CH_2CHCH_2), 55.9 (OCH_3), 56.7 (OCH_3), 62.1 (OCH_3), 62.9 (OCH_3), 94.6 (7-C), 115.2 (CH_2CHCH_2), 120.7 (1-C), 126.4 (ArC), 127.0 (ArC), 129.9 (ArC), 130.4 (ArC), 135.9 (ArC), 138.0 (CH_2CHCH_2), 153.2 (ArC), 153.4 (ArC), 154.3 (ArC), 192.3 (CHO); *m/z* 316 (M^+, 100%), 301 (27), 273 (7), 243 (7).

3.5.2. 4,5,6,8-Tetramethoxy-3-(2-methylprop-2-enyl)-naphthalene-2-carbaldehyde 10b. Compound **10b** (0.21 g, 70%) was isolated as a light yellow oil from **9b**; IR ν_{max}/cm^{-1} (film) 1689 (s, C=O stretch), 1618 and 1588 (m, Ar C=C stretch); δ_H (200 MHz, $CDCl_3$) 1.94 (3H, br s, $CH_2C(CH_3)CH_2$), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.91 (2H, s, $CH_2C(CH_3)CH_2$), 4.04 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.18 (1H, br s, $CH_2C(CH_3)CH_2$), 4.75 (1H, br s, $CH_2C(CH_3)CH_2$), 6.72 (1H, s, 7-H), 8.57 (1H, s, 1-H), 10.10 (1H, s, CHO); δ_C (50 MHz, $CDCl_3$) 23.7 ($CH_2C(CH_3)CH_2$), 32.3 ($CH_2C(CH_3)CH_2$), 55.8 (OCH_3), 56.7 (OCH_3), 62.1 (OCH_3), 62.8 (OCH_3), 94.6 (7-C), 110.5 ($CH_2C(CH_3)CH_2$), 120.8 (ArC), 125.7 (1-C), 126.3 (ArC), 129.8 (ArC), 130.6 (ArC), 135.9 ($CH_2C(CH_3)CH_2$), 146.5 ($CH_2C(CH)_3CH_2$), 153.1 (ArC), 153.3 (ArC), 154.4 (ArC), 192.0 (CHO).

3.5.3. 4,5,6,8-Tetramethoxy-3-(1-methylprop-2-enyl)-naphthalene-2-carbaldehyde 10c. Compound **10c** (0.20 g, 66%) was isolated as a light yellow oil from **9c**. Found (M^+ 330.1472. $C_{19}H_{22}O_5$ requires 330.1467); IR ν_{max}/cm^{-1} (film) 1706 (s, C=O stretch), 1715 (s, olefinic C=C stretch); δ_H (200 MHz, $CDCl_3$) 1.59 (3H, d, $J=7.4$ Hz, $CHCH_3CHCH_2$), 3.83 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 4.71–4.79 (1H, m, $CHCH_3CHCH_2$), 4.98–5.16 (2H, m, $CHCH_3CHCH_2$), 6.34 (1H, ddd, $J=14.6$, 10.4, 4.0 Hz, $CHCH_3CHCH_2$), 6.70 (1H, s, 7-H), 8.66 (1H, s, 1-H), 10.41 (1H, s, CHO); δ_C (50 MHz, $CDCl_3$) 21.1 ($CH(CH_3)CHCH_2$), 33.2 ($CHC(CH_3)CHCH_2$), 55.8 (OCH_3), 56.6 (OCH_3), 62.0 (OCH_3), 63.0 (OCH_3), 94.6 (7-C), 113.7 ($CH(CH_3)CHCH_2$), 120.7 (ArC), 123.9 (Ar-CH), 125.9 (ArC), 126.2 (ArC), 130.5 (ArC), 135.6 (ArC), 143.9 ($CH(CH_3)CHCH_2$), 152.4 (ArC), 153.2 (ArC), 154.5 (ArC), 192.2 (CHO); *m/z* 330 (M^+, 100%), 315 (29), 300 (8), 285 (6), 257 (6), 115 (4).

3.5.4. 4,5,8-Trimethoxy-3-(prop-2-enyl)naphthalene-2-carbaldehyde 10d. Compound **10d** (0.22 g, 74%) was isolated as a light yellow oil from **9d**. Found (M^+ 286.1208. $C_{17}H_{18}O_4$ requires 286.1205); IR ν_{max}/cm^{-1} (film) 1692 (s, C=O stretch), 1621 and 1586 (s, C=C stretch); δ_H (400 MHz, $CDCl_3$) 3.83 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.02 (2H, dt, $J=5.5$, 1.7 Hz, CH_2CHCH_2), 4.88 (1H, dm, $J=17.1$ Hz, CH_2CHCH2), 5.02 (1H, dm, $J=10.2$ Hz, CH_2CHCH2), 6.12 (1H, ddt, $J=17.2$, 10.2, 5.5 Hz, $CHCHCH_2$), 6.78 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.96 (1H, d, $J=8.5$ Hz, 7-H)[a], 8.62 (1H, s, 1-H), 10.21 (1H, s, CHO); δ_C (50 MHz, $CDCl_3$) 28.7 (CH_2CHCH_2), 55.7 (OCH_3), 56.9 (OCH_3), 62.8 (OCH_3), 104.4 (CH_2CHCH2), 110.0 (ArCH), 115.3 (ArCH), 123.3 (ArC), 125.9 (ArCH), 126.5 (ArC), 129.4 (ArC), 132.6 (ArC), 137.9 ($CHCHCH_2$), 149.2 (ArC) 150.8 (ArC), 154.8 (ArC), 192.6 (CHO); *m/z* 286 (M^+, 100%), 271 (21), 256 (3), 253 (3), 243 (6), 241 (5), 228 (6), 227 (3), 213 (5), 212 (3), 139 (3), 127 (3), 115 (4).

3.5.5. 4,5,8-Trimethoxy-3-(2-methylprop-2-enyl)-naphthalene-2-carbaldehyde 10e. Compound **10e** (0.24 g, 78%) was isolated as a light yellow oil from **9e**. Found (M^+ 300.1374. $C_{18}H_{20}O_4$ requires 300.1362). IR ν_{max}/cm^{-1} (film) 1706 (s, C=O stretch); δ_H (200 MHz, $CDCl_3$) 1.84 (3H, br s, $CH_2C(CH_3)CH_2$), 3.81 (3H, s, OCH_3), 3.92 (2H, br s, $CH_2C(CH_3)CH_2$), 3.96 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.21–4.30 (1H, m, $CH_2C(CH_3)CH_2$), 4.18–4.25 (1H, m, $CH_2C(CH_3)CH_2$), 6.73 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.87 (1H, d, $J=8.5$ Hz, 7-H)[a], 8.54 (1H, s, 1-H), 10.18 (1H, s, CHO); δ_C (50 MHz, $CDCl_3$) 23.6 ($CH_2C(CH_3)CH_2$), 33.4 ($CH_2C(CH_3)CH_2$), 55.7 (OCH_3), 57.0 (OCH_3), 62.7 (OCH_3), 104.0 ($CH_2C(CH_3)CH_2$), 108.5 (6-C)[a], 110.0 (7-C)[a], 120.9 (C-1), 122.3 (ArC), 126.5 (ArC), 129.6 (ArC), 130.3 (ArC), 146.2 ($CH_2C(CH_3)CH_2$), 149.3 (ArC), 150.3 (ArC), 154.7 (ArC), 192.4 (CHO); *m/z* 300 (M^+, 100%), 285 (35), 267 (8), 257 (4), 242 (6), 227 (7), 115 (6).

3.5.6. 4,5,8-Trimethoxy-3-(1-methylprop-2-enyl)naphthalene-2-carbaldehyde 10f. Compound **10f** (0.22 g, 74%) was isolated as a light yellow oil from **9f**. Found (M^+ 300.1373. $C_{18}H_{20}O_4$ requires 300.1362). IR ν_{max}/cm^{-1} (film) 1688 (s, C=O stretch), 1618 and 1582 (m, olefinic C=C stretch); δ_H (200 MHz, $CDCl_3$) 1.58 (3H, d, $J=7.3$ Hz, $CH(CH_3)CHCH_2$), 3.81 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.68–4.81 (1H, m, $CH(CH_3)CHCH_2$), 5.05 (1H, dm, $J=17.3$ Hz, $CH(CH_3)CHCH_2$), 5.12 (1H, dm, $J=10.3$ Hz, $CH(CH_3)CHCH2$), 6.33 (1H, ddd, $J=17.3$, 10.3, 4.0 Hz, $CH(CH_3)CHCH_2$), 6.75 (1H, d, $J=8.5$ Hz, 6-H)[a], 6.93 (1H, d, $J=8.5$ Hz, 7-H)[a], 8.69 (1H, s, 1-H) 10.48 (1H, s, CHO); δ_C (50 MHz, $CDCl_3$) 21.3 ($CH(CH_3)CHCH_2$), 33.3 ($CH(CH_3)CHCH_2$), 55.8 (OCH_3), 56.9 (OCH_3), 63.2 (OCH_3), 104.4 ($CH(CH_3)CHCH_2$), 109.8 (ArCH), 113.9 (ArCH), 123.0 (1-C), 125.4 (ArC), 126.7 (ArC), 133.1 (ArC), 135.3 (ArC), 144.0 ($CH(CH_3)CHCH_2$), 149.3 (ArC), 151.1 (ArC), 154.2 (ArC), 192.5 (CHO); *m/z* 300 (M^+, 100%), 285 (26), 273 (4), 270 (6), 242 (5), 239 (5), 227 (6), 166 (4), 137 (5), 115 (5).

3.6. General procedure for preparing substituted anthracenes

Typically, carbaldehyde **10a** (0.10 g, 0.32 mmol) was dissolved in dry DMF (10 cm^3) and heated at 80 °C under N_2. *t*-BuOK (0.14 g 1.26 mmol) was then added to the reaction mixture, which was immediately irradiated with a high pressure mercury lamp through a quartz filter while stirring under N_2 at the same temperature for 10 min. The reaction mixture was diluted with H_2O (20 cm^3) and acidified with aqueous HCl (33%). The organic material was extracted with CH_2Cl_2 (4×20 cm^3), dried with $MgSO_4$ and concentrated in vacuo. The resulting crude residue was then purified by silica gel column chromatography (5–20% EtOAc/hexane) to afford the desired substituted anthracenes, for example, **11a**, in good yield (0.076 g, 81%). The compounds below were synthesised according to a similar procedure.

3.6.1. 1,2,4,9-Tetramethoxyanthracene 11a. The compound **11a** (0.076 g, 81%) was isolated as a light yellow oil from **10a**. Found (M^+ 298.1203. $C_{18}H_{18}O_4$ requires 298.1205); IR ν_{max}/cm^{-1} (film) 1523 (m, ArC=C stretch); δ_H (200 MHz, $CDCl_3$) 4.04 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.06 (6H, s, 2×OCH_3), 6.64 (1H, s, 3-H), 7.39–7.54 (2H, m, 2×ArH), 7.96 (1H, br dd, $J=8.4$, 1.1 Hz, ArH), 8.33 (1H, br dd, $J=8.4$, 1.1 Hz, ArH), 8.59 (1H, s, 10-H); δ_C (50 MHz, $CDCl_3$) 55.8 (OCH_3), 57.6 (OCH_3), 62.0 (OCH_3), 63.5 (OCH_3), 94.6 (3-C), 117.3 (ArCH), 120.5 (ArC), 122.1 (ArCH), 123.4 (ArC), 124.9 (ArCH), 125.9 (ArCH), 126.7 (ArC), 128.8 (ArCH), 130.6 (ArC), 135.8 (ArC), 148.3 (ArC), 150.7 (ArC), 152.9 (ArC); *m/z* 298 (M^+, 100%), 283 (59), 268 (7), 255 (13), 251 (11), 243 (8), 239 (6), 223 (6), 211 (5), 149 (11), 134 (12), 126 (9).

3.6.2. 1,2,4,9-Tetramethoxy-7-methylanthracene 11b. Compound **11b** (0.089 g, 98%) was isolated as a light yellow oil from **10b**. Found (M^+ 312.1370. $C_{19}H_{20}O_4$ requires 312.1362). IR ν_{max}/cm^{-1} (film) 1671, 1639 and 1584 (m, ArC=C stretch); δ_H (400 MHz, $CDCl_3$) 2.56 (3H, d, $J=0.8$ Hz, 7-CH_3), 3.92 (3H, s, OCH_3), 4.04 (6H, s, 2×OCH_3), 4.05 (3H, s, OCH_3), 6.60 (1H, s, 3-H), 7.24 (1H, dd, $J=8.6$, 1.6 Hz, 6-H), 7.86 (1H, d, $J=8.6$ Hz, 5-H), 8.07–8.08 (1H, m, 8-H), 8.54 (1H, s, 10-H); δ_C (100 MHz, $CDCl_3$) 22.3 ($ArCH_3$), 55.7 (OCH_3), 57.6 (OCH_3), 61.9 (OCH_3), 63.4 (OCH_3), 94.2 (3-C), 117.1 (ArCH), 120.2 (ArCH), 120.6 (ArC), 122.8 (ArC), 126.9 (ArC), 127.7 (ArCH), 128.6 (ArCH), 129.3 (ArC), 135.6 (ArC), 135.7 (ArC), 148.3 (ArC), 149.8 (ArC), 152.9 (ArC); *m/z* 312 (M^+, 100%), 297 (63), 285 (5), 282 (10), 269 (14), 267 (8), 265 (11), 257 (22), 253 (6), 239 (5), 237 (6), 225 (5).

3.6.3. 1,2,4,9-Tetramethoxy-8-methylanthracene 11c. Compound **11c** (0.067 g, 76%) was isolated as a light yellow oil from **10c**. Found (M^+ 312.1311. $C_{19}H_{20}O_4$ requires 312.1362); IR ν_{max}/cm^{-1} (film) 1674, 1623 and 1579 (m, ArC=C stretch); δ_H (400 MHz, $CDCl_3$) 3.00 (3H, s, 8-CH_3), 3.84 and 3.85 (each 3H, s, 2×OCH_3), 4.03 (6H, s, 2×OCH_3), 6.62 (1H, s, 3-H), 7.20–7.25 (2H, m, 2×ArH), 7.78 (1H, d, $J=8.1$ Hz, ArH), 8.54 (1H, s, 10-H); δ_C (100 MHz, $CDCl_3$) 24.6 (8-CH_3), 55.7 (OCH_3), 57.7 (OCH_3), 61.9 (OCH_3), 63.8 (OCH_3), 94.8 (3-C), 118.0 (ArCH), 122.0 (ArC), 123.1 (ArC), 124.4 (ArCH), 126.4 (ArC), 127.0 (ArC), 127.6 (ArCH), 128.8 (ArCH), 132.1 (ArC), 133.9 (ArC), 148.3 (ArC), 152.7 (ArC), 153.0 (ArC); *m/z* 312 (M^+, 100%), 298 (11), 297 (53), 269 (12), 267 (17), 156 (9), 141 (16).

3.6.4. 1,4,9-Trimethoxyanthracene 11d. Compound **11d** (0.12 g, 87%) was isolated as pale yellow crystals from **10d**; Mp 122–123 °C (EtOH), lit.[24] 123–124 °C. Found (M^+ 268.1102. $C_{17}H_{16}O_3$ requires 268.1099); δ_H (200 MHz, $CDCl_3$) 3.98 (3H, s, OCH_3), 3.99 (3H, s, OCH3), 4.03 (3H, s, OCH_3), 6.56 and 6.62 (each 1H, 2×d, $J=8.2$ Hz, 2-H and 3-H), 7.45–7.48 (2H, m, 2×ArH), 7.98–8.00 (1H, m, ArH), 8.36–8.39 (1H, m, ArH), 8.61 (1H, s, 10-H); δ_C (100 MHz, $CDCl_3$) 55.7 (OCH_3), 56.5 (OCH_3), 63.5 (OCH_3), 101.1 (ArCH), 103.3 (ArCH), 116.8 (ArCH), 122.7 (ArCH), 125.5 (ArCH), 125.8 (ArCH), 126.3 (ArC), 127.1 (ArC), 128.5 (ArCH), 132.1 (ArC), 149.5 (ArC), 149.6 (ArC), 149.9 (ArC), (one C missing); *m/z* 268 (M^+, 100%), 253 (45), 238 (3), 225 (5), 224 (4) 210 (8), 209 (8), 194 (5), 181 (5), 165 (7), 152 (6), 134 (10).

3.6.5. 1,4,10-Trimethoxy-6-methylanthracene 11e. Anthracene **11e** (0.088 g, 91%) was isolated as a low melting solid from **10e**. Found (M^+ 282.1265. $C_{18}H_{18}O_3$ requires 282.1256); IR ν_{max}/cm^{-1} (film) 1667, 1623 and 1578 (m, ArC=C stretch); δ_H (400 MHz, $CDCl_3$) 2.56 (3H, s, 6-CH_3), 3.99 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 6.55 and 6.63 (each 1H, d, $J=8.2$ Hz, 2-H and 3-H), 7.27 (1H, dd, $J=8.6$, 1.6 Hz, 7-H), 7.90 (1H, d, $J=8.6$ Hz, 5-H), 8.11 (1H, d, $J=1.6$ Hz, 8-H), 8.57 (1H, s, 9-H); δ_C (100 MHz, $CDCl_3$) 22.3 (6-CH_3), 55.7 (OCH_3), 56.6 (OCH_3), 63.4 (OCH_3), 100.7 (2-C), 103.5 (3-C), 116.6 (ArCH), 118.4 (ArC), 120.9 (ArCH), 126.5 (ArC), 126.5 (ArC), 128.4 (ArC), 128.6 (ArCH), 130.4 (ArC), 135.2 (ArC), 149.7 (ArC), 149.9 (ArC), 151.8 (ArC); *m/z* 282 (M^+, 100%), 267 (49), 252 (6), 239 (5), 224 (9), 223 (7), 208 (5), 195 (4), 181 (7), 165 (4), 76 (3).

3.6.6. 1,4,10-Trimethoxy-5-methylanthracene 11f. Compound **11f** (0.053 g, 78%) was isolated as yellow semi-solid from **10f**. Found (M^+ 282.1260. $C_{18}H_{18}O_3$ requires 282.1256); IR ν_{max}/cm^{-1} (film) 1668, 1626 and 1573

(m, ArC=C stretch); δ_H (400 MHz, $CDCl_3$) 3.02 (3H, s, 5-CH_3), 3.84 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.62 (1H, d, J=8.2 Hz, 2-H)[a], 6.67 (1H, d, J=8.2 Hz, 3-H)[a], 7.22–7.24 (1H, m, ArH), 7.31 (1H, dd, J=8.3, 6.7 Hz, 7-H), 7.82–7.85 (1H, m, ArH), 8.58 (1H, s, 9-H); δ_C (100 MHz, $CDCl_3$) 24.6 (5-CH_3), 55.7 (OCH_3), 56.6 (OCH_3), 63.4 (OCH_3), 101.0 (2-C)[a], 103.0 (3-C)[a], 114.2 (9-C), 119.7 (ArC), 121.2 (ArCH), 124.0 (ArC), 124.9 (ArC), 126.7 (ArC), 126.9 (ArCH), 130.2 (ArCH), 132.6 (ArC), 133.6 (ArC), 148.4 (ArC), 151.6 (ArC); *m/z* 282 (M^+, 100%), 267 (41), 252 (9), 249 (5), 237 (17), 224 (7), 223 (4), 209 (5), 149 (11), 57 (5).

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A new strategy for the stereoselective synthesis of unnatural α-amino acids

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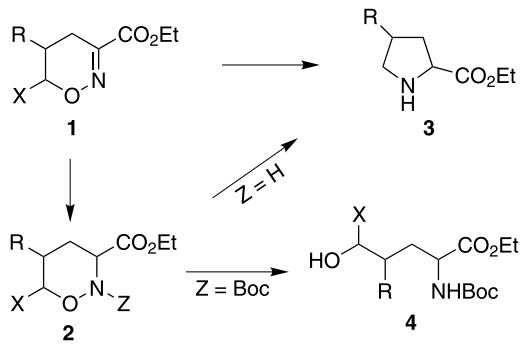
Abstract—A new method for the synthesis of racemic non-proteinogenic α-amino acids has been developed, which involves (i) hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to electron rich alkenes such as enol ethers, enamines and allylsilanes, (ii) $NaCNBH_3$ reduction of the C=N bond in the oxazines thus generated, the stereochemistry of the products being controlled by epimerisation of the thermodynamically less stable isomer to the more stable one, (iii) protection of the N–H group as N-Boc and (iv) finally, N–O bond cleavage of both free and protected products to give proline or bis-homoserine derivatives, respectively. An example with concomitant reduction of the carboxylate group, resulting in the formation of the respective amino alcohol is reported. Applying this methodology to a homochiral enol ether, the protected parent D-proline was prepared in enantiomerically pure form, whereas the asymmetric synthesis of the respective bis-homoserine was unsuccessful.

1. Introduction

The development of new methods for the synthesis of both natural and unnatural α-amino acids has attracted considerable attention over the past decades, since they are important products in chemistry and biology, either as free amino acids or as components of more complex entities.[1,2] Amino acids are used as food additives, pharmaceuticals, agrochemicals and, in organic synthesis, as source chiral materials. The increasing interest in modified peptides in the chemical engineering of proteins has lately refreshed research towards the development of new methodologies for the stereoselective construction of α-amino acids.[3] The rational design of nonproteinogenic α-amino acids, in particular, is of exceptional importance, due to their implementation into nonscissile peptide mimics and peptide isosters.[3] Herein, we report a new approach to α-amino acids, based on the addition of ethyl 2-nitrosoacrylate (in situ generated from the oxime of ethyl bromopyruvate) to alkenes, as the key reaction.[4]

The hetero-Diels–Alder additions of nitrosoalkenes are reverse electron demand reactions[5] and proceed smoothly when electron-rich alkenes, such as enol ethers and enamines, are used as dienophiles. The resulting oxazines are highly versatile intermediates, suitable for a number of further transformations.[6] A potentially useful synthetic application of these oxazines, is their reductive ring contraction to pyrrolidines[7] (Scheme 1), although the reported conversion of ethyl 2-nitrosoacrylate adducts **1** to prolines **3** was of poor stereoselectivity.

It is expected, however, that stereoselective reduction of these adducts to **2** and further hydrogenolytic N–O bond cleavage of **2**, would lead to the formation of proline derivatives **3**, stereoselectively (in case of X=OR or NR_2). Alternatively, protection of the N–H group in **2** as N-Boc and further N–O bond cleavage, could result in the



Scheme 1.

Keywords: α-Amino acids; Amino alcohols; Hetero-Diels–Alder addition; Ethyl 2-nitrosoacrylate; Enol ethers; Enamines; Allylsilanes.
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formation of acyclic amino acids **4**, since the reduced nucleophilicity of nitrogen would not permit a further condensation reaction, when X=OR or NR_2. Depending on the nature of X and the reaction conditions compound **4** would be stable or could be subsequently transformed into a new product. The stereoselective reduction of **1** to **3** is thus the crucial key-step, which would determine the stereoselectivity of the overall process.

2. Results and discussion

Initially, we checked the feasibility of this target, namely the reduction of **1** to **2** and its conversion to **3** and **4** in a stereoselective manner, by using the known cycloadduct **5**[7a] (Scheme 2), lacking any additional substituent. This compound was prepared in quantitative yield by the reaction of the oxime of ethyl bromopyruvate with ethyl vinyl ether in the presence of Na_2CO_3, at room temperature. Reissig et al.[8] reported that the $NaCNBH_3$ reduction of compound **5** proceeds with high diastereoselectivity to give **6** in a 93:7 *cis*/*trans* diastereoisomeric ratio and 87% total yield. In our hands, however, and in repeated experiments, this reaction was much less selective, yielding a varying mixture of *cis*-/*trans*-**6** with an average ratio of ~65:35. These two isomers were easily separated chromatographically, the fast-moving product (*cis*-**6**) being a colorless oil and the slow-moving one (*trans*-**6**), a white solid (mp 103–105 °C), both with ^1H NMR spectra identical to those reported by Reissig et al.[8]

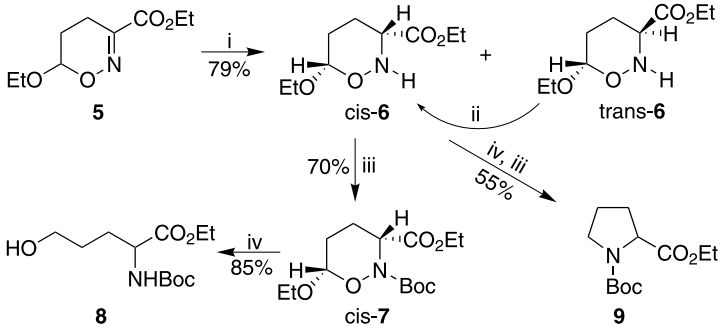
It is most likely that the reported diastereoisomeric ratio does not reflect the exact stereochemical outcome of the reduction, but it is a result of the partial isomerisation of *trans*- to *cis*-**6**. Indeed, refluxing of a solution of *trans*-**6** or the *cis*-/*trans*-**6** mixture in $CHCl_3$ for 3 h in the presence of catalytic amount of Et_3N caused the complete conversion of *trans*- to *cis*-**6**. Apparently, the *cis*-**6** isomer is the thermodynamically more stable product, since the oxazine ring adopting a chair-like conformation has the CO_2Et group equatorial and the EtO group axial, the last being favored by the anomeric effect.

This two-step sequence, involving $NaCNBH_3$ reduction of the hetero-Diels–Alder adducts and then treatment with Et_3N in refluxing $CHCl_3$ composes a highly stereoselective, thermodynamically controlled method for reduction of the oxazine adducts, allowing their conversion exclusively to only one isomer of the respective hydrogenated products. Due to the lack of any further substitution it is apparent that, in this particular case, both *cis*- and *trans*-**6** will give the same product in the next step. As expected, Raney Ni hydrogenolysis of the unprotected oxazine *cis*-**6** afforded directly the respective proline ethyl ester, isolated as the N-Boc protected derivative **9**, in good overall yield. Further protection of the N–H group of *cis*-**6** according to standard procedures, led to *cis*-**7** in high yield. In the last crucial step, the N–O bond cleavage was achieved in high yield by Raney Ni catalytic hydrogenation of *cis*-**7** (Scheme 2) in MeOH at room temperature in the presence of boric acid, a method repeatedly used by us for such purposes.[7e,f,9] It is worthy to note that the N–O bond cleavage was followed by reduction of the aldehyde group formed, the final product being the protected hydroxylated amino acid **8**.

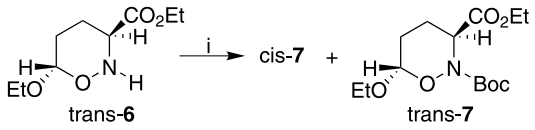
In contrast to *cis*-**6**, repeated attempts for protection of *trans*-**6** always gave mixture of *cis*- and *trans*-**7** (Scheme 3). Separation of this mixture and treatment of *trans*-**7** with a catalytic amount of Et_3N in refluxing $CHCl_3$, caused a rather slow isomerisation of *trans*- to *cis*-**7**, since after 18 h only a ca. 50% conversion was observed. This result clearly shows that the formation of both *cis*- and *trans*-**7**, when protecting *trans*-**6**, results from epimerisation of *trans*- to *cis*-**6**, prior to protection.

Having established reliable procedures for the conversion of the hetero-Diels–Alder adduct **5** to both protected proline and bis-homoserine, we turned our attention to substituted enol ethers. It was apparent that branched amino acids would be prepared stereoselectively, if this methodology could apply in such cases. Thus, the known oxazine **11**,[7a] prepared by adding ethyl 2-nitrosoacrylate to 3,4-dihydro-2*H*-pyran **10** (Scheme 4), was stereoselectively converted to **12** by $NaCNBH_3$ reduction and Et_3N isomerisation of the resulting mixture. Raney Ni hydrogenation of the later, according to the established sequence, gave normally the branched proline derivative **15**.

Compound **12** was protected as its N-Boc derivative **13** and then was subjected to Raney Ni hydrogenation, which caused a partial reduction of the hemiacetal formed, further to N–O bond cleavage. For the shake of simplicity, we decided to reduce completely the intermediate hemiacetal by adding $NaBH_4$, and characterize the product as its diacetate. In the initial experiments,[4] the hemiacetal functionality was selectively reduced to the respective dihydroxyaminocarboxylate, by careful addition of $NaBH_4$.



Scheme 2. Reagents and conditions: (i) $NaCNBH_3$, AcOH, 0 °C→20 °C, 6 h; (ii) Et_3N, $CHCl_3$, reflux, 3 h; (iii) $(Boc)_2O$, Et_3N, CH_2Cl_2, 20 °C, 12 h; (iv) Raney Ni, H_2, H_3BO_3 (20 equiv), $MgSO_4$, MeOH, 85%.



Scheme 3. Reagents and conditions: (i) $(Boc)_2O$, Et_3N, CH_2Cl_2, 20 °C, 12 h.

Any attempt, however, to repeat the selective reduction of hemiacetal, not affecting the carboxylate group was unsuceful. For this reason, we used excess of $NaBH_4$ for the complete reduction of both hemiacetal and ester functionalities, and the amino triol produced was isolated as its tiacetate **14**, as single diastereoisomer. Vicinal amino alcohols[10] are also compounds of immense interest due to their biological activities and synthetic applications.

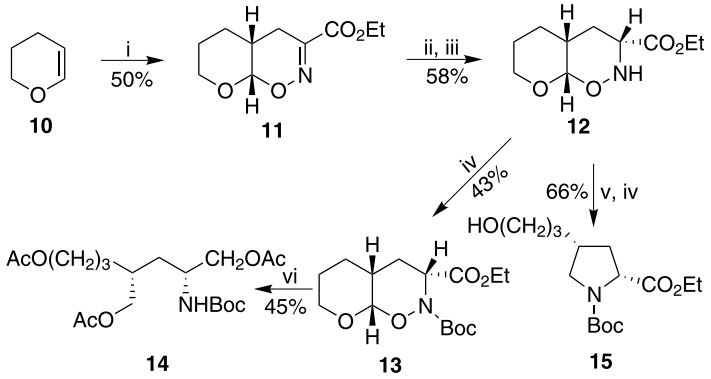
Due to the high electronic density of their double bond, enamines are excellent dienophiles in reverse electron demand Diels–Alder reactions. Such reactions of enamines with ethyl 2-nitrosoacrylate have been reported in the literature[5,6,11] and the adducts have been used inter alia as precursors for the synthesis of substituted prolines and tryptophans. Thus, we easily added ethyl 2-nitrosoacrylate to 4-(1-cyclohexen-1-yl)morpholine **16** (Scheme 5). The adduct, however, was found susceptible to hydrolysis and during the work up it was converted to **17**, isolated in high yield as a mixture of two anomeric hemiacetals in equilibrium via the respective keto form. Recently, Jørgensen et al.[12] reported nitrosoalkene additions to aldehyde-derived enamines, in situ generated using proline as an organocatalyst, to give hydrolised products like **17**.

Treatment of **17** with trimethyl orthoformate in the presence of catalytic TsOH yielded the respective acetal **18**, as an inseparable mixture of two stereoisomers in ~1:1 ratio. As expected, $NaCNBH_3$ reduction of this mixture led to the formation of four diastereoisomers, chromatographically separable as two fractions, each one consisting of a mixture of two isomers. Refluxing of the parent mixture with a catalytic amount of Et_3N in $CHCl_3$ solution caused the complete convertion of the slow moving products to the fast moving ones, their structure assigned as depicted in **19**. Raney Ni catalytic hydrogenation of *cis*-/*trans*-**19** afforded the respective proline derivative **22**, isolated as a mixture of two major diastereoisomers, with unidentified stereochemistry. The difficulty in determining their structure arises from the restricted rotation and the slow equilibrium between the conformers in all N-Boc proline derivatives,[13] resulting in complicated NMR spectra.

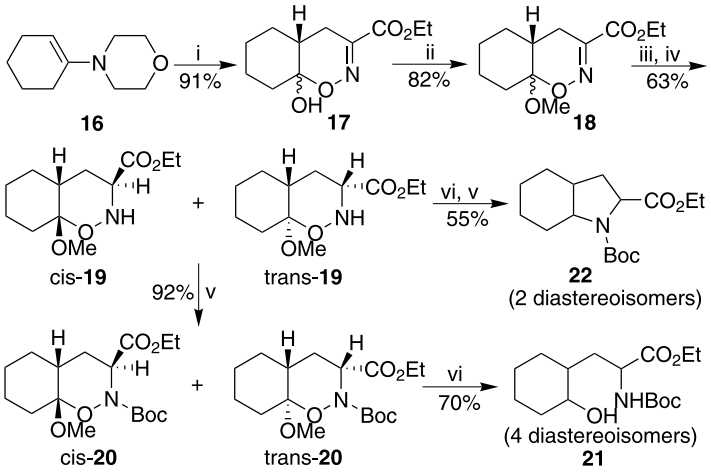
The N–H group of *cis*-/*trans*-**19** was then protected as N-Boc to give *cis*-/*trans*-**20**, which upon Raney Ni catalytic hydrogenation led to **21**, isolated as a mixture of four diastereoisomers in ratio ~3:3:1:1. This fact reveals that the two isomers of **19** and **20** differ not only in the ring junction but also in the amino acid stereocenter. In both diastereoisomers of **19** and **20**, which are the thermodynamically more stable ones, the CO_2Et and MeO groups have a *cis*-disposition, the first one being equatorial and the anomeric MeO group axial. The catalytic hydrogenation of **20** caused not only the N–O bond scission but also reduction of the carbonyl group, thus generating a ~3:1 diastereoisomeric ratio of **21**, as deduced by the ^1H NMR spectrum: the equatorial C*H*OH proton signal of the two *cis*-isomers (regarding the cyclohexane ring) appeared at δ 3.93 and the axial C*H*OH proton signal of the two *trans*-isomers at δ 3.19, both as multiples with a ~3:1 ratio. Furthermore, the N–H proton gave four separate signals (one for every isomer) at δ 5.14, 5.20, 5.30 and 5.51 (all of them as dublets, J ~7.5 Hz) with a ~1:3:3:1 ratio.

Attempted separations of both *cis*-/*trans*-**19** and *cis*-/*trans*-**20** mixtures chromatographically, led only to samples enriched to each compound of the mixture, a fact that allowed the assignment of their NMR spectra. It is also interesting to note, that while the α-H of the aminocarboxylate functionality in both *cis*-/*trans*-**19** isomers lies in axial position (δ 3.90, dd, J=9.8, 3.4 Hz and δ 4.00, dd, J=12.7, 3.5 Hz), the same proton of one isomer of **20** seems to be equatorial (δ 4.04, dd, J=11.3, 4.5 Hz and δ 4.73, dd, J=4.9, 3.1 Hz). It is likely, that the introduction of the bulky Boc group caused a disortion of the oxazine ring, possibly in the *cis*-isomer. Similar conformation seems to be adopted by compound **13**, which has J values for the 3-H (δ 4.62) 6.7 and 1.4 Hz.

Indole and pyrrole derivatives act like enamines and smoothly react with nitrosoalkenes. The isolated products,[6a] however, are open chain 3-substituted indole and pyrroles, probably by eliminative rearomatization of the pyrrole ring, with exception of the 3-substituted indoles, which give the



Scheme 4. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$, Na_2CO_3, 20 °C, overnight; (ii) $NaCNBH_3$, AcOH, 0 °C→20 °C, overnight; (iii) Et_3N, $CHCl_3$, reflux, 8 h; (iv) $(Boc)_2O$, Et_3N, CH_2Cl_2, 20 °C, overnight; (v) Raney Ni, H_2, H_3BO_3 (20 equiv), $MgSO_4$, MeOH, 20 °C; (vi) (a) Raney Ni, H_2, H_3BO_3 (20 equiv), $MgSO_4$, MeOH, 20 °C; (b) $NaBH_4$, EtOH, 20 °C, 30 min; (c) Ac_2O, pyridine, 20 °C, overnight.

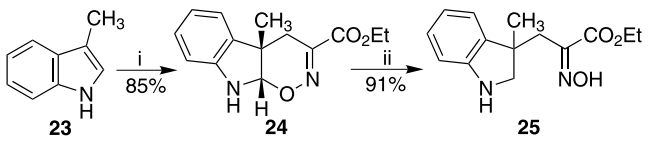


Scheme 5. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$, Na_2CO_3, 20 °C, overnight; (ii) $CH(OMe)_3$, TsOH, THF, 20 °C, overnight; (iii) $NaCNBH_3$, AcOH, 0 °C→20 °C, overnight; (iv) Et_3N, $CHCl_3$, reflux, 8 h; (v) $(Boc)_2O$, Et_3N, CH_2Cl_2, 20 °C, overnight. (vi) Raney Ni, H_2, H_3BO_3 (20 equiv), $MgSO_4$, MeOH, 2 h, 20 °C.

expected hetero-Diels–Alder adducts. Thus, the known adduct **24** of ethyl 2-nitrosoacrylate to 3-methylindole **23** (Scheme 6) was prepared according to the literature.[6a] However, treatment of this compound with $NaCNBH_3$ did not reduce the C=N bond and the product isolated **25** was that of the C–O bond scission.

It is known that allylsilanes[14] react smoothly with nitroso-alkenes to give hetero-Diels–Alder adducts in high yields. Thus, we prepared the oxazine **27** (Scheme 7) by adding ethyl 2-nitrosoacrylate to the parent allyltrimethylsilane, according to the literature.[14] Then, the reaction sequence discussed in Scheme 2 was applied to this adduct. First, the $NaCNBH_3$ reduction of **27** led to a mixture of **28** and its *syn*-stereoisomer in 84% yield; this upon treatment with a catalytic amount of Et_3N in refluxing $CHCl_3$ was completely converted to **28**. The *anti*-stereochemistry of this product was deduced from the ^1H NMR spectrum and the measured coupling constants, which indicate that both 3-H (δ 3.75, dd, $J=11.2$, 3.1 Hz) and 6-H (δ 3.68, dddd as ddt, $J=11.9$, 7.2, 7.1, 2.2 Hz) are in axial positions, the oxazine ring adopting a chair-like conformation.

In addition, chromatographic separation of the *syn*-isomer of **28** and inspection of its ^1H NMR spectrum reveals that this compound has equatorial the CO_2Et group and axial the CH_2SiMe_3 group. In this isomer, the 3-H, 6-H and N–H signals appeared at δ 3.64 (ddd as dt, $J=11.4$, 11.4, 3.1 Hz), 4.15 (m, partially hidden by the CH_2 of the EtO group) and 8.18 (d, $J=11.4$ Hz), respectively. Furthermore, the two methylene protons of the Me_3SiCH_2 group resonanced at 0.81 (dd, $J=14.3$, 7.5 Hz) and 0.98 (dd, $J=14.3$, 6.4 Hz), whereas the same protons of the *anti*-isomer **28** resonanced at 0.74 (dd, $J=14.5$, 7.2 Hz) and 0.89 (dd, $J=14.5$, 7.1 Hz).

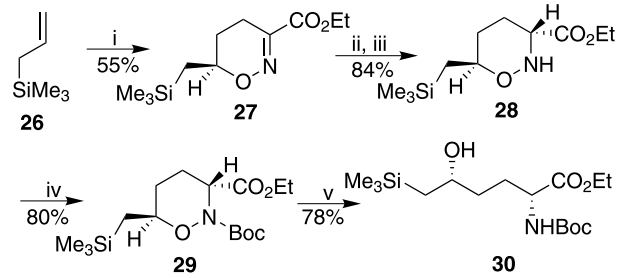


Scheme 6. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$, Na_2CO_3, 20 °C, overnight; (ii) $NaCNBH_3$, AcOH, 0 °C→20 °C, overnight.

The coupling constants of 3-H leave little doubt that this proton is in axial position. Also, comparing the chemical shifts of 3-H, 6-H and 6-CH_2 protons in both isomers, it is apparent that while the 3-H chemical shift remains practically unchanged, since in both cases this proton is equatorial, the 6-H and 6-CH_2 in the assigned as *cis*-isomer of **28** are shifted ~0.5 ppm downfield and ~0.15 ppm upfield, respectively, relative to **28**. This makes evident the equatorial position of 6-H and the axial position of 6-CH_2 in the *syn*-isomer of **28**, which was easily converted to the thermodynamically more stable **28**. In the next steps (Scheme 7), the N–H protection of **28** led to **29** in high yield, and this compound upon Raney Ni catalytic hydrogenation in MeOH at room temperature in the presence of boric acid afforded the δ,ε-bisfunctionalised protected amino acid **30** as a single diastereoisomer.

It is worth mentioning the presence of the trimethylsilyl group in **30**, not only for its high synthetic versatility, but also because of the current interest[15] in α-amino acids with silicon and trialkylsilyl side chains, which increase their hydrophobic properties. For this reason such α-amino acids can be used as suitable substitutes of natural lipophilic amino acids, or as replacements in naturally occurring peptides.

Since hetero-Diels–Alder additions to homochiral enol ethers have been reported in the literature,[6,16] it was most



Scheme 7. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$, Na_2CO_3, 20 °C, overnight; (ii) $NaCNBH_3$, AcOH, 0 °C→20 °C, overnight; (iii) Et_3N, $CHCl_3$, reflux, 2 h; (iv) $(Boc)_2O$, Et_3N, CH_2Cl_2, 20 °C, overnight; (v) Raney Ni, H_2, H_3BO_3 (20 equiv), $MgSO_4$, MeOH, 2 h, 20 °C.

likely that the addition of ethyl 2-nitrosoacrylate to chiral enol ethers could be extended to asymmetric synthesis of α-amino acids. By addition of ethyl 2-nitrosoacrylate to a chiral enol ether, the chirality is transferred to the C-6 stereocenter of the oxazine ring and thereof to the C-3 carbon (which is the α-carbon of the final amino acid) by $NaCNBH_3$ reduction and the subsequent isomerisation reaction. Thus, a homochiral alcohol could serve as a chiral auxiliary for the synthesis of the chiral enol ether, the asymmetric hetero-Diels–Alder addition to the heterodiene and the transferring of its chirality to the α-carbon of an amino acid precursor, being regenerated in the final step of the N–O bond cleavage.

To this aim, we selected the homochiral enol ether **31** (Scheme 8), whose enantiomer is known[16] to give adduct *ent*-**32** with ethyl 2-nitrosoacrylate in acceptable yield (56%) and satisfactory diastereoselectivity (6:1). In addition, both enantiomers of the final amino acid can be prepared, from the respective commercially available enantiomers of the parent alcohol. Applying the established procedures, **32** was prepared according to literature, separated from the minor diastereoisomer chromatographically and converted to the *cis*-oxazine **33**, by complete isomerisation of the *cis*/*trans* mixture intermediately formed after hydride reduction. In contrast to the previous examples, introducing the Boc group required the presence of a more nucleophilic base (DMAP), by which **33** was quantitatively converted to **34**. However, any attempt (Raney Ni/H_2, Pd-C/H_2, $Pd(OH)_2/H_2$, Zn/AcOH, etc) for N–O bond scission and formation of the chiral amino acid (*R*)-**8** failed. It is possible that the overcrowded environment of the N–O bond in **34** does not allow the approach of the catalyst and is responsible for the failure of this reaction. However, the unprotected chiral oxazine **33** was easily converted to D-proline derivative (*R*)-**9** in enantiomerically pure form,[17] under Raney Ni catalytic hydrogenation followed by N-Boc protection. The characteristic hindered rotation appeared clearly in this compound, like all N-Boc proline derivatives,[13] producing dublicated signals in the ^1H and ^{13}C NMR spectra.

Although compound *ent*-**32** is known in the literature, the absolute configuration of its C-3 stereocenter has not been determined. In addition, the absolute configuration of C-3 and C-6 stereocenters in compounds **33** and **34** could not be directly determined from their available spectroscopic and physical data. The conversion, however, of **33** to the D-proline derivative (*R*)-**9** {$[\alpha]_D = +42.3$ (*c* 0.5, $CHCl_3$); for (−)-**9**, lit.[17] $[\alpha]_D = -38.8$ (*c* 2.3, EtOH) and −47.7 (*c* 1.1, $CHCl_3$)}, revealed unequivocally the absolute configuration of C-3 and/or C-6 stereocenters in compounds **32**, **33** and **34**.

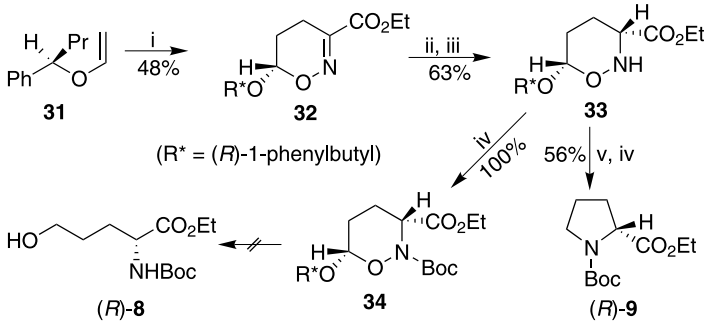
3. Conclusion

In this paper, we reported our results on the development of a new method for the synthesis of protected non-proteinogenic α-amino acids. The method involves (i) hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to electron rich alkenes such as enol ethers, enamines and allylsilanes, a known process, which proceeds efficiently and highly regio-selectively; (ii) $NaCNBH_3$ reduction of the C=N bond in the oxazines thus generated, the stereochemistry of the products being controlled by epimerisation of the thermodynamically less stable isomer to the more stable one; (iii) protection of the N–H group as N-Boc and (iv) finally, N–O bond cleavage by catalytic Raney Ni hydrogenation of both free and protected products to give proline or bis-homoserine derivatives, respectively. All proccesses gave good yields with step (ii) being crucial for having highly diastereoselected final products. The unsatisfactory stereoselection in the case of the enamine adduct is due to its hydrolysis during the working up. By using a homochiral enol ether and applying the above methodology, it was possible to prepare the protected parent proline in enantiomerically pure form, whereas we failed in the asymmetric synthesis of bis-homoserine. Our efforts are now focused to overcome the problems raised in attempting asymmetric synthesis.

4. Experimental

4.1. General

All reagents are commercially available and were used without further purification. Solvents were dried by standard methods. The progress of reactions was checked by thin layer chromatography (TLC) on Merck silica gel $60F_{254}$ glass plates (0.25 mm). The spots were visualised by heat staining with anisaldehyde in ethanol/ sulfuric acid. Column chromatography was performed with Merck silica gel 60 (0.063–0.200 mm). Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital



Scheme 8. Reagents and conditions: (i) $BrCH_2C(NOH)CO_2Et$, Na_2CO_3, 20 °C, overnight; (ii) $NaCNBH_3$, AcOH, 0 °C→20 °C, 24 h; (iii) Et_3N, $CHCl_3$, reflux, 8 h; (iv) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, 20 °C, overnight; (v) Raney Ni, H_2, H_3BO_3 (20 equiv), $MgSO_4$, MeOH, 48 h, 20 °C.

Polarimeter. Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as internal standard. Mass spectra were recorded under electron-impact (EI) conditions at 70 eV on a VG TS-250 spectrometer and microanalyses were performed on a Perkin–Elmer 2400-II Element analyser. High-resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE mass spectrometer under fast-atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix or on an IONSPEC FTMS spectrometer (matrix-assisted laser-desorption ionisation, MALDI) with 2,5-dihydroxybenzoic acid (DHB) as matrix.

4.2. General procedure for the hetero-Diels–Alder cycloadditions

A solution of $BrCH_2C(NOH)CO_2Et$ (1.48 g, 7.5 mmol) and the appropriate alkene (15 mmol) were dissolved in CH_2Cl_2 (100 mL) [ethyl vinyl ether (15 mL) was used as solvent], and to this mixture was added Na_2CO_3 (3.975 g, 37.5 mmol). After stirring overnight at room temperature the solids were removed by filtration through Celite and the filtrate was concentrated and chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give the hetero-Diels–Alder adducts as colorless or yellowish oils.

4.2.1. Ethyl 6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (5). This compound was isolated as a yellowish oil in 99% yield with IR and ^1H NMR spectra in agreement with those reported in the literature.[7a] ^{13}C NMR ($CDCl_3$) δ 14.1, 14.9, 15.6, 21.9, 61.9, 64.1, 95.7, 151.0, 163.4.

4.2.2. Ethyl *cis*-4a,6,7,8a-tetrahydro-4*H*,5*H*-pyrano[3,2-e]-1,2-oxazine-3-carboxylate (11). This compound was isolated as an oil in 50% yield IR and ^1H NMR spectra in agreement with those reported in the literature.[7a] ^{13}C NMR ($CDCl_3$) δ 13.9, 22.8, 24.3, 25.4, 27.4, 61.9, 63.1, 96.5, 147.9, 163.2.

4.2.3. Ethyl 8a-hydroxy-4a,5,6,7,8,8a-hexahydro-4*H*-benzo[e]-1,2-oxazine-3-carboxylate (17). This compound was isolated as an oil in 91% yield. IR (neat) 3400, 1720, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (m, 1H), 1.30 (m, 1H), 1.35 and 1.36 (two t, 3H, $J=7.3$ Hz), 1.5–1.8 (m, 5.7H), 1.95 (m, 1.3H), 2.12 (m, 0.7H), 2.17 (d, 0.3H, $J=18.3$ Hz), 2.25 (d, 0.7H, $J=18.9$ Hz), 2.47 (dd, 0.3H, $J=18.3$, 5.5 Hz), 2.75 (dd, 0.7H, $J=18.9$, 7.3 Hz), 3.05 (br s, 0.3H, OH), 4.32 (q, 2H, $J=7.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.9/23.1, 23.6/24.2, 24.9/25.2, 28.4/29.3, 32.6/34.5, 35.5/37.1, 61.9, 96.4/96.9, 149.3/151.2, 163.4/163.6; MS *m/z* (%) 227 (M^+, 13), 211 (40); HRMS (*m/z*) calcd for $C_{11}H_{18}NO_4$ 228.1230 ($M+H^+$), found 228.1228.

4.2.4. Ethyl 8a-methoxy-4a,5,6,7,8,8a-hexahydro-4*H*-benzo[e]-1,2-oxazine-3-carboxylate (18). A solution of **17** (1.14 g, 5 mmol), $CH(OMe)_3$ (1.06 g, 10 mmol) and TsOH (20 mg) in THF (50 mL) was stirred at room temperature overnight. The mixture was then added to H_2O (50 mL) and extracted with CH_2Cl_2 (2×50 mL). The organic layer was dried over Na_2SO_4, the solvent was then removed on a rotary evaporator and the residue was chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give **18** as a colorless oil (1.08 g, 82%). IR (neat) 1720, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 and 1.36 (two t, 3H, $J=7.3$ Hz), 1.1–1.95 (m, 8H), 2.15–2.45 (m, 2.5H), 2.75 (dd, 0.5H, $J=18.9$, 7.3 Hz), 3.23 and 3.28 (two s, ~1:1, 3H, OMe), 4.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.2/22.4, 23.6/24.6, 24.7/25.1, 28.3/28.3, 29.5/31.1, 33.3/35.3, 48.4/48.7, 61.8, 98.6/98.7, 150.1/151.6, 163.4/163.6; MS *m/z* (%) 241 (M^+, 10), 224 (35); HRMS (*m/z*) calcd for $C_{12}H_{20}NO_4$ 242.1387 ($M+H^+$), found 242.1389.

4.2.5. 3-Ethoxycarbonyl-4a-methyl-4,4a,9,9a-tetrahydro-1,2-oxazino[6,5-b]indole (24). This compound was isolated as colorless crystals in 85% yield with IR, MS and ^1H NMR spectra in agreement with those reported in the literature.[6a] Mp 69–70 °C (lit.[6a] mp 70–71 °C); ^{13}C NMR ($CDCl_3$) δ 13.9, 26.9, 29.2, 46.3, 62.1, 96.6, 108.9, 119.7, 122.1, 128.4, 132.4, 147.5, 159.1, 162.5.

4.2.6. Ethyl 6-[(trimethylsilyl)methyl]-5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (27). This compound was isolated as a colorless oil in 55% yield with ^1H NMR spectrum in agreement with that reported in the literature.[14] ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H, $SiMe_3$), 0.87 (dd, 1H, $J=14.5$, 6.8 Hz, 1H of CH_2SiMe_3), 1.06 (dd, 1H, $J=14.5$, 7.8 Hz, 1H of CH_2SiMe_3), 1.30 (t, 3H, $J=7.2$ Hz), 1.58 (m, 1H, 5-H_{axial}), 1.97 (ddt, 1H, $J=13.6$, 7.5, 2.1 Hz, 5-$H_{equatorial}$), 2.33 (ddd, 1H, $J=19.1$, 11.3, 7.8 Hz, 4-H_{axial}), 2.55 (ddd, 1H, $J=19.1$, 6.1, 2.0 Hz, 4-$H_{equatorial}$), 3.83 (dddd, 1H, $J=$ 10.7, 7.8, 6.8, 2.1 Hz, 6-H), 4.27 (q, 2H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ −0.9, 14.1, 21.3, 22.7, 26.2, 61.7, 75.4, 149.1, 163.7.

4.2.7. (+)-Ethyl (6*S*)-6-[(*R*)-1-phenylbutoxy]-5,6-dihydro-4*H*-1,2-oxazine-3-carboxylate (32). This compound was isolated as an oil in 48% yield with spectral and analytical data in agreement with those reported in the literature[16] for its enantiomer, separated chromatographically from its minor diastereoisomer (8%). $[\alpha]_D=+145.3$ (*c* 1, CH_2Cl_2) {for (−)-**32**, lit.[16] $[\alpha]_D^{22}=-148.2$ (*c* 5, CH_2Cl_2)}.

4.3. General procedure for the $NaCNBH_3$ reduction of the hetero-Diels–Alder adducts

To a solution of the adducts **5**, **11**, **18**, **24**, **27** or **32** (6 mmol) in glacial acetic acid (40 mL), $NaCNBH_3$ (1.18 g, 19 mmol) was added at 0 °C with vigorous stirring under Ar atmosphere and the resulting mixture was allowed to warm to room temperature and stirred for 6–12 h. The reaction mixture was then poured into a saturated solution of Na_2CO_3 (200 mL) and extracted with ethyl acetate ($2\times$ 50 mL). The organic layer was dried over Na_2SO_4, the solvent was then removed on a rotary evaporator and the residue was dissolved in $CHCl_3$ (10 mL). After adding a few drops of Et_3N, this solution was refluxed for 3 h, the volatiles were evaporated off and the residue was chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give products *cis*-**6**, **12**, **19**, **25**, **28** or **33** as colorless oils.

4.3.1. Ethyl *cis*-6-ethoxy-1,2-oxazinane-3-carboxylate (*cis*-6). This compound was isolated in 79% yield with IR, ^{1}H and ^{13}C NMR spectra in agreement with those reported in the literature.[8] ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.1 Hz), 1.29 (t, 3H, J=7.2 Hz), 1.85 (m, 4H, CH_2CH_2), 3.71 (dq, 1H, J=9.7, 7.1 Hz, 1H of CH_3CH_2O), 3.82 (m, 2H, 3-H and 1H of CH_3CH_2O), 4.20 (q, 2H, J=7.2 Hz), 4.73 (dd as t, 1H, J=2.6 Hz, 6-H), 5.75 (br s, 1H, N–H); ^{13}C NMR ($CDCl_3$) δ 14.1, 15.0, 22.1, 27.8, 58.9, 61.0, 63.7, 97.6, 171.1; HRMS (*m*/*z*) calcd for $C_9H_{17}NO_4Na$ 226.105 (M^++Na), found 226.1053.

4.3.2. Ethyl *trans*-6-ethoxy-1,2-oxazinane-3-carboxylate (*trans*-6). The mixture prepared by $NaCNBH_3$ reduction of **5** (1.20 g, 6 mmol) was chromatographed before the isomerisation on a silica gel column with hexane/ethyl acetate 2:1 as the eluent to give *cis*-**6** (625 mg, 51%) as a colorless oil followed by *trans*-**6** (337 mg, 28%) with ^{1}H and ^{13}C NMR spectra in agreement with those reported in the literature.[8] Mp 103–105 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J=7.1 Hz), 1.33 (t, 3H, J=7.2 Hz), 1.82, 2.05 and 2.20 (three m, 1H, 2H and 1H, CH_2CH_2), 3.71 (dq, 1H, J=9.7, 7.1 Hz, 1H of CH_3CH_2O), 3.98 (m, 2H, 3-H and 1H of CH_3CH_2O), 4.29 (m, 2H), 5.10 (dd as t, 1H, J=2.0 Hz, 6-H), 7.25 (br d, 1H, J=4.3 Hz, N–H); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.8, 20.4, 25.1, 62.8, 63.4, 65.6, 99.8, 168.2; Anal. Calcd for $C_9H_{17}NO_4$ C, 53.19,H, 8.43, N, 6.89. Found: C, 53.24,H, 8.36, N, 6.98.

4.3.3. Ethyl (3*R,4a*R**,8a*S**)-hexahydro-pyrano[3,2-e]-1,2-oxazine-3-carboxylate (12).** This compound was isolated in 58% yield. IR (neat) 3350, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.2 Hz), 1.75 (m, 5H), 2.0 (m, 2H), 3.62 (ddd as dt, 1H, J=11.6, 3.1 Hz, 7-H_{axial}), 3.84 (dd, 1H, J=9.8, 3.0 Hz, 3-H), 4.09 (dd, 1H, J=11.6, 3.7 Hz, 7-$H_{equatorial}$), 4.18 (q, 2H, J=7.2 Hz), 4.74 (s, 1H, 8a-H), 5.79 (br s, 1H, N–H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.3, 26.3, 27.3, 32.1, 58.8, 61.1, 67.2, 97.5, 170.7; HRMS (*m*/*z*) calcd for $C_{10}H_{18}NO_4$ 216.1230 ($M+H^+$), found 216.1229.

4.3.4. Ethyl (3*S,4a*R**,8a*S**)-8a-methoxyoctahydro-2*H*-benzo[e]-1,2-oxazine-3-carboxylate (*cis*-19) and ethyl (3*R**,4a*R**,8a*R**)-8a-methoxyoctahydro-2*H*-benzo[e]-1,2-oxazine-3-carboxylate (*trans*-19).** This inseparable mixture of diastereoisomers was isolated in 63% yield. IR (neat) 3330, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.3 Hz), 1.2–2.2 (m, 11H), 3.25 and 3.28 (two s, ~1:1, 3H, OMe), 3.90 (dd, 0.5H, J=9.8, 3.4 Hz), 4.01 (dd, 0.5H, J=12.7, 3.5 Hz), 4.18 (q, 2H, J=7.3 Hz), 5.57 (br s, 1H, N–H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6/22.7, 25.1/25.5, 28.1/28.7, 28.8/28.9, 29.4/32.0, 36.6/42.3, 47.3/47.6, 54.3, 60.2/60.9, 98.2/99.3, 170.9/171.7; MS *m*/*z* (%) 243 (M^+, 56), 212 (81); HRMS (*m*/*z*) calcd for $C_{12}H_{21}NO_4Na$ 266.1363 (M^++Na), found 266.1360.

4.3.5. Ethyl 2-hydroxyimino-3-(3-methyl-2,3-dihydro-1*H*-indol-3-yl-propionate (25). This compound was isolated in 91% yield. IR (neat) 3350, 3250, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, J=7.2 Hz), 1.37 (s, 3H), 2.96 (d, 1H, J=12.9 Hz, 1H of 3-CH_2), 3.09 (d, 1H, J=12.9 Hz, 1H of 3-CH_2), 3.20 (d, 1H, J=9.3 Hz, 1H of CH_2N), 3.59 (d, 1H, J=9.3 Hz, 1H of CH_2N), 4.10 (m, 2H), 6.65 (d, 1H, J=7.7 Hz), 6.73 (t, 1H, J=7.1 Hz), 7.02 (t, 1H, J=7.7 Hz), 7.07 (d, 1H, J=7.7 Hz), [NH and OH not appeared]; ^{13}C NMR ($CDCl_3$) δ 13.9, 25.4, 33.8, 46.0, 60.0, 61.7, 110.3, 119.0, 122.9, 127.8, 135.9, 150.2, 151.4, 164.2; MS *m*/*z* (%) 262 (M^+); Anal. Calcd for $C_{14}H_{18}N_2O_3$ C, 64.11,H, 6.92, N, 10.68. Found: C, 64.21,H, 7.10, N, 10.58.

4.3.6. Ethyl *anti*-6-[(trimethylsilyl)methyl]-1,2-oxazinane-3-carboxylate (28). This compound was isolated in 84% yield. IR (neat) 3350, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 9H, $SiMe_3$), 0.74 (dd, 1H, J=14.5, 7.2 Hz, 1H of CH_2SiMe_3), 0.89 (dd, 1H, J=14.5, 7.1 Hz, 1H of CH_2SiMe_3), 1.27 (t, 3H, J=7.2 Hz), 1.43, 1.77 and 2.12 (three m, 1H, 2H and 1H, CH_2CH_2), 3.68 (dddd as ddt, J=11.9, 7.2, 7.1, 2.2 Hz, 6-H), 3.75 (dd, J=11.2, 3.1 Hz, 3-H), 4.18 (q, 2H, J=7.2 Hz), 5.11 (br s, 1H, N–H); ^{13}C NMR ($CDCl_3$) δ −0.8, 14.1, 23.4, 27.4, 33.1, 59.4, 60.9, 78.0, 170.6; MS *m*/*z* (%) 245 (M^+, 48), 230 (81), 200 (39); HRMS (*m*/*z*) calcd for $C_{11}H_{24}NO_3Si$ 246.152 ($M+H^+$), found 246.1532.

4.3.7. (+)-Ethyl (3*R*,6*S*)-6-[(*R*)-1-phenylbutoxy]-1,2-oxazinane-3-carboxylate (33). This compound was isolated in 63% yield. $[\alpha]_D$=+141.4 (*c* 0.3, $CHCl_3$); IR (neat) 3350, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=7.0 Hz), 1.28 (t, 3H, J=7.2 Hz), 1.3–2.1 (m, 8H, two CH_2CH_2), 3.82 (dd, 1H, J=11.2, 3.4 Hz, 3-H), 4.21 (q, 2H, J=7.2 Hz), 4.55 (t, 1H, J=2.4 Hz, PhC*H*O), 4.69 (dd, 1H, J=7.9, 5.5 Hz, 6-H), 5.85 (br s, 1H, N–H), 7.3 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 19.4, 22.1, 27.6, 40.2, 59.0, 61.0, 77.9, 94.2, 126.9, 127.7, 128.5, 141.8, 171.1; MS *m*/*z* (%) 307 (M^+, 45), 291 (21), 249 (61), 158 (90), 92 (100); Anal. Calcd for $C_{17}H_{25}NO_4$ C, 66.43,H, 8.20, N, 4.56. Found: C, 66.35,H, 8.05, N, 4.29.

4.4. General procedure for the protection of oxazinanes *cis*-6, 12, 19, 28 and 33

To a solution of by *cis*-**6**, **12**, **19**, **28** or **33** (2.65 mmol) and Et_3N (0.6 mL) [and DMAP (20 mg) for the case of **33**] in dry CH_2Cl_2 (10 mL) $(Boc)_2O$ (1.16 g, 5.3 mmol) was added at 0 °C and the mixture was allowed to warm at room temperature and was then stirred for 12 h. The resulting solution was washed with aqueous HCl 5% (10 mL), the aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic layer was dried over Na_2SO_4. The solvent was subsequently evaporated off and the residue was chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give products *cis*-**7**, **13**, **20**, **29** or **34** as colorless or yellowish oils.

4.4.1. 2-(*tert*-Butyl) 3-ethyl *cis*-6-ethoxy-1,2-oxazinane-2,3-dicarboxylate (*cis*-7). This compound was isolated in 70% yield. IR (neat) 1745, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J=7.2 Hz), 1.31 (t, 3H, J=7.2 Hz), 1.52 (s, 9H), 1.62 and 1.90 (two m, 1 H and 2H, 4-H_{axial} and 5-CH_2), 2.41 (dddd, 1H, J=11.0, 4.9, 4.3, 1.8 Hz, 4-$H_{equatorial}$), 3.69 (dq, 1H, J=9.7, 7.2 Hz, 1H of CH_3CH_2O), 4.07 (dq, 1H, J=9.7, 7.2 Hz, 1H of CH_3CH_2O), 4.25 (m, 2H), 4.65 (dd 1H, J=9.7, 1.8 Hz, 3-H), 4.72 (d, 1H, J=4.2 Hz, 6-H). ^{13}C NMR ($CDCl_3$) δ 14.1, 15.0, 23.6, 27.3, 28.1, 55.6, 61.5, 65.4, 81.6, 103.7, 154.6, 169.4; HRMS (*m*/*z*) calcd for $C_{14}H_{25}NO_6Na$ 326.1574 (M^++Na), found 326.1571.

4.4.2. 2-(*tert*-Butyl) 3-ethyl (3*R,4a*R**,8a*S**)-hexahydro-**

pyrano[3,2-e]-1,2-oxazine-2,3-dicarboxylate (13). This compound was isolated in 43% yield. IR (neat) 1745, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H, $J=7.3$ Hz), 1.51 (s, 9H, CMe_3), 1.6 (m, 4H, 5-CH_2, 6-CH_2), 1.9 (m, 1H, 4a-H), 2.25 (m, 2H, 4-CH_2), 3.71 (ddd, 1H, $J=11.0$, 2.4, 1.8 Hz, 7-H_{axial}), 3.86 (dt, $J=11.0$, 2.4 Hz, 7-$H_{equatorial}$), 4.25 (m, 2H), 4.62 (dd, 1H, $J=6.7$, 1.4 Hz, 3-H), 5.00 (d, 1H, $J=1.8$ Hz, 8a-H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.9, 24.9, 28.2, 29.6, 32.9, 53.8, 61.6, 62.6, 82.0, 99.6, 154.9, 170.8; HRMS (*m/z*) calcd for $C_{15}H_{25}NO_6Na$ 338.1574 ($M^+ + Na$), found 338.1569.

4.4.3. 2-(*tert*-Butyl) 3-ethyl (3*R,4a*S**,8a*S**)-8a-methoxyoctahydro-2*H*-benzo[e]-1,2-oxazine-2,3-dicarboxylate (*cis*-20) and 2-(*tert*-butyl) 3-ethyl (3*S**,4a*S**,8a*R**)-8a-methoxyoctahydro-2*H*-benzo[e]-1,2-oxazine-2,3-dicarboxylate (*trans*-20).** This inseparable mixture of diastereoisomers was isolated as a colorless oil in 92% yield. IR (neat) 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, $J=7.3$ Hz), 1.46 and 1.50 (two s, 9H, CMe_3), 1.25–2.15 (m, 11H), 3.32 and 3.38 (two s, ~1:1, 3H, OMe), 4.04 (dd, 0.5H, $J=11.3$, 4.5 Hz), 4.22 (m, 2H), 4.73 (dd, 0.5H, $J=4.9$, 3.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.9, 22.6, 24.7, 26.7, 27.4, 28.3, 34.9, 49.3, 55.9, 61.5, 81.4, 105.0, 154.8, 170.0 (for one isomer) and 14.0, 22.5, 25.4, 27.8, 28.1, 28.3, 29.3, 42.4, 48.6, 55.9, 60.9, 81.9, 102.2, 155.3, 169.6 (for the second isomer); MS *m/z* (%) 343 (M^+, 34), 312 (52); HRMS (*m/z*) calcd for $C_{17}H_{29}NO_6Na$ 366.1887 ($M^+ + Na$), found 366.1885.

4.4.4. 2-(*tert*-Butyl) 3-ethyl *trans*-6-[(trimethylsilyl)-methyl]-1,2-oxazinane-2,3-dicarboxylate (29). This compound was isolated as a yellowish oil in 80% yield. IR (neat) 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H, $SiMe_3$), 1.00 (dd, 1H, $J=14.5$, 8.4 Hz, 1H of CH_2SiMe_3), 1.15 (dd, 1H, $J=14.5$, 6.3 Hz, 1H of CH_2SiMe_3), 1.28 (t, 3H, $J=7.2$ Hz), 1.48 (s, 9H, CMe_3), 1.42, 1.89 and 2.05 (three m, 1H, 1H and 2H, CH_2CH_2), 4.20 (m, 3H, 6-H and $CH_3CH_2O_2C$), 4.43 (dd as t, $J=5.4$ Hz, 3-H); ^{13}C NMR ($CDCl_3$) δ −0.9, 14.1, 20.9, 21.7, 28.3, 28.8, 58.5, 61.2, 77.5, 81.7, 155.8, 170.1; HRMS (*m/z*) calcd for $C_{16}H_{31}NO_5SiNa$ 368.1864 ($M^+ + Na$), found 368.1865.

4.4.5. (+)-2-(*tert*-Butyl) 3-ethyl (3*R*,6*S*)-6-[(*R*)-1-phenylbutoxy]-1,2-oxazinane-2,3-dicarboxylate (34). This compound was isolated as a colorless oil in quantitative yield. $[\alpha]_D = +121.3$ (*c* 0.3, $CHCl_3$); IR (neat) 1745, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, $J=7.3$ Hz), 1.30 (t, 3H, $J=7.1$ Hz), 1.47 and 1.53 (two s, 9H, CMe_3, restricted rotation),[13] 1.4–1.9 (m, 8H, two CH_2CH_2), 4.25 (m, 2H), 4.44 (dd, 1H, $J=7.8$, 3.4 Hz, 3-H), 4.66 (br d, 1H, $J=5.2$ Hz, 6-H), 4.92 (t, 1H, $J=6.8$ Hz, PhC*H*O), 7.3 (m, 5H, Ar–H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 18.7, 23.5, 27.3, 27.8 and 28.3 (CMe_3 restricted rotation), 39.6, 55.6, 61.5, 79.5, 80.9 and 81.6 (CMe_3 restricted rotation), 101.1, 127.0, 127.7, 128.3, 141.7, 152.1, 169.6; HRMS (*m/z*) calcd for $C_{22}H_{33}NO_6Na$ 430.22 ($M^+ + Na$), found 430.2201.

4.5. General procedure for the reduction of protected oxazinanes *cis*-7, 13, 19 and 29

To a solution of protected oxazinanes *cis*-**7**, **13**, **19** or **29** (1 mmol) in MeOH (30 mL) were added H_3BO_3 (1.23 g, 20 mmol), catalytic amount of Raney Ni and $MgSO_4$, and the mixture was stirred under H_2 atmosphere at room temperature for 2–12 h. H_3BO_3 was then neutralized by saturated aqueous Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3×50 mL) and the organic layer was dried over Na_2SO_4. The solvent was subsequently removed on a rotary evaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate as the eluent to give **8**, **20** or **30** as colorless oils or crystals. For the case of **13**, after neutralisation, the solvent was evaporated, EtOH (10 mL) and $NaBH_4$ (37 mg, 1 mmol) were added and the mixture was stirred at room temperature for 30 min. Drops of dilute aqueous HCl was added to neutralise the excess of $NaBH_4$ and the solvent was evaporated off. Pyridine (5 mL) and Ac_2O were added to this residue and the mixture was allowed to stir overnight. The mixture was disproportionated between H_2O (20 mL) and CH_2Cl_2 (20 mL), the organic layer was dried over Na_2SO_4, concentrated and chromatographed on a silica gel column with hexane/ethyl acetate as the eluent to give **14**.

4.5.1. Ethyl 2-[(*tert*-butoxycarbonyl)amino]-5-hydroxypentanoate (8). This compound was isolated as colorless crystals in 85% yield. Mp 58–59 °C; IR (nujol) 3350, 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, $J=7.1$ Hz), 1.43 (s, 9H, CMe_3), 1.64, 1.72 and 1.88 (three m, 2H, 1H and 1H, CH_2CH_2), 1.95 (br s, 1H, OH), 3.66 (t, 2H, $J=6.1$ Hz, C*H*$_2$OH), 4.19 (q, 2H, $J=7.1$ Hz, CH_3CH_2O), 4.29 (ddd as a br q, 1H, $J=7.5$ Hz, 2-H), 5.18 (br d, 1H, $J=7.5$ Hz, N–H); ^{13}C NMR ($CDCl_3$) δ 14.2, 28.3 29.6 (C-3 and C-4), 53.2, 61.4, 62.1, 80.0, 155.5, 172.8; HRMS (*m/z*) calcd for $C_{12}H_{23}NO_5Na$ 284.1468 ($M^+ + Na$), found 284.1470; Anal. Calcd for $C_{12}H_{23}NO_5$ C, 55.16,H, 8.87, N, 5.36. Found: C, 55.53,H, 8.81, N, 5.31.

4.5.2. (2*R,4*R**)-7-Acetoxy-4-acetoxymethyl-2-[(*tert*-butoxycarbonyl)amino]-heptyl acetate (14).** This compound was isolated as a colorless oil in 45% yield. IR (neat) 3350, 1745, 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3–1.8 (m, 6H, 3-CH_2, 5-CH_2, 6-CH_2), 1.45 (s, 9H, CMe_3), 2.06 and 2.08 (s, 3H and s, 6H, three Ac), 2.09 (m, 1H, 4-H), 4.05 (m, 7H, 2-H, three C*H*$_2$OAc), 4.54 (br d, 1H, $J=9.2$ Hz, N–H); ^{13}C NMR ($CDCl_3$) δ 20.8, 20.9 (two peaks), 25.7, 27.2, 28.3, 34.0, 34.1, 47.5, 64.3, 66.6, 67.0, 79.6, 155.3, 170.9, 171.0, 171.1; HRMS (*m/z*) calcd for $C_{19}H_{33}NO_8Na$ 426.2098 ($M^+ + Na$), found 426.2111.

4.5.3. Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3-(2-hydroxycyclohexyl)propanoate (21). This inseparable mixture of diastereoisomers was isolated as a colorless oil in 70% yield. IR (neat) 3450, 3350, 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, $J=7.1$ Hz), 1.25–2.45 (m, 12H), 3.19 and 3.93 (two m, ~1:3, 1H, C*H*OH), 4.15 (m, 2H), 5.14, 5.20, 5.30 and 5.51 (all as d, $J=7.5$ Hz, ~1:3:3:1, N–H); ^{13}C NMR ($CDCl_3$, selected data for the two major isomers) δ 51.4/51.8 (C-2), 61.1/61.2 (O*C*H_2CH_3), 68.5/74.7 (CHOH), 79.9 (*C*Me_3), 155.6 (*C*O_2CMe_3), 173.3/175.5 (*C*O_2Et); MS *m/z* (%) 315 (M^+, 21), 260 (45); HRMS (*m/z*) calcd for $C_{16}H_{29}NO_5Na$ 338.1938 ($M^+ + Na$), found 338.1934.

4.5.4. Ethyl (2*R,5*R**)-2-[(ethoxycarbonyl)amino]-5-hydroxy-6-(trimethylsilyl)hexanoate (30).** This

compound was isolated as a colorless oil in 78% yield. IR (neat) 3350, 1740, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 9H, $SiMe_3$), 0.86 (two dd as m, 2H, CH_2SiMe_3), 1.28 (t, 3H, $J=7.2$ Hz), 1.44 (s, 9H, CMe_3), 1.5–2.0 (m, 5H, OH and CH_2CH_2), 3.81 (m, 1H, 5-H), 4.19 (q, 2H, $J=7.2$ Hz) 4.23 (m, 1H, 2-H), 5.15 (br d, 1H, $J=7.5$ Hz, N–H); ^{13}C NMR ($CDCl_3$) δ −0.8, 14.1, 26.8, 28.3, 29.0, 36.0, 53.3, 61.3, 69.4, 79.8, 155.4, 172.9; MS *m/z* (%) 347 (M^+, 6), 332 (13), 275 (57); HRMS (*m/z*) calcd for $C_{16}H_{33}NO_5SiNa$ 370.202 ($M^+ + Na$), found 370.2021.

4.6. General procedure for the synthesis of protected proline derivatives 9, (*R*)-9, 15 and 22

To a solution of protected oxazinanes *cis*-**7**, **13**, **19** or **33** (1 mmol) in MeOH (10 mL) were added H_3BO_3 (0.465 g, 7.5 mmol), catalytic amount of Raney Ni and $MgSO_4$ and the mixture was stirred under H_2 atmosphere at room temperature for 24 h. The solvent was then evaporated and NaOH 1 M (5 mL) and THF (15 mL) were then added followed by the addition of $(Boc)_2O$ (0.872 g, 4 mmol) at 0 °C After stirring the mixture at room temperature for 24 h the solids were removed by filtration through Celite and the filtrate was disproportionated between H_2O (20 mL) and CH_2Cl_2 (20 mL). The organic layer was dried over Na_2SO_4, the solvent was subsequently removed on a rotary evaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate as the eluent to give compounds **9**, (*R*)-**9**, **15** or **22**.

4.6.1. 1-(*tert*-Butyl) 2-ethyl pyrrolidine-1,2-dicarboxylate (9). This compound was isolated as an oil in 55% yield. IR (neat) 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 and 1.26 (two t, 3H, $J=7.2$ Hz), 1.42 and 1.47 (two s, ~5:3, 9H, CMe_3), 1.9 (m, 3H), 2.22 (m, 1H), 3.5 (m, 2H), 4.2 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1/14.2, 23.6/24.2, 28.8/28.4, 29.6/30.8, 46.3/46.5, 58.8/59.2, 60.8, 79.6/79.8, 153.8/154.4, 172.9/173.2; MS *m/z* (%) 243 (M^+, 28); HRMS (*m/z*) calcd for $C_{12}H_{21}NO_4Na$ 266.1363 ($M^+ + Na$), found 266.1366.

4.6.2. (+)-1-(*tert*-Butyl) 2-ethyl (2*R*)-pyrrolidine-1,2-dicarboxylate [(*R*)-9]. This compound was isolated as an oil in 56% yield with IR, ^1H and ^{13}C NMR identical to those for (±)-**9**. $[\alpha]_D=+42.3$ (*c* 0.5, $CHCl_3$) {for (−)-**9**, lit.[17] $[\alpha]_D=-38.8$ (*c* 2.3, EtOH) and −47.7 (*c* 1.1, $CHCl_3$)}.

4.6.3. 1-(*tert*-Butyl) 2-ethyl (2*R,4*R**)-4-(3-hydroxypropyl)-pyrrolidine-1,2-dicarboxylate (15).** This compound was isolated as an oil in 66% yield. IR (neat) 3450, 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 and 1.21 (two t, 3H, $J=7.2$ Hz), 1.33 and 1.39 (two s, ~2:1, 9H, CMe_3), 1.45 (m, 5H), 1.85 (br s, 1H, OH), 2.10 (m, 1H), 2.38 (m, 1H), 2.94 (dd as t, 1H, $J=10.4$ Hz), 3.55–3.75 (m, 3H), 4.10 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.1/14.2, 28.2/28.4, 28.9/29.0, 31.2, 36.2/37.2, 37.7/38.4, 51.9/52.3, 59.1/59.4, 60.8, 62.5, 79.8/79.9, 153.6/154.1, 173.0/173.3; MS *m/z* (%) 301 (M^+, 17); HRMS (*m/z*) calcd for $C_{15}H_{27}NO_5Na$ 324.1781 ($M^+ + Na$), found 324.1781.

4.6.4. 1-(*tert*-Butyl) 2-ethyl octahydro-indole-1,2-dicarboxylate (22). This compound was isolated as an oil in 55% yield. IR (neat) 1745, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2–2.4 (m, 14H) overlapping with 1.40 and 1.45 (two s, 9H, CMe_3), 3.72 and 3.82 (two m, 1H), 4.18 (m, 3H); ^{13}C NMR ($CDCl_3$, data for the two major conformers) δ 14.1/14.2, 20.6, 23.7/23.8, 25.8/25.9, 28.3/28.4, 28.5, 31.6/32.5, 36.4/37.0, 57.1/57.4, 59.0/59.4, 60.8, 79.4/79.6, 153.3/154.0, 173.2/173.6; MS *m/z* (%) 297 (M^+, 45); HRMS (*m/z*) calcd for $C_{16}H_{27}NO_4Na$ 320.1832 ($M^+ + Na$), found 320.1835.

References and notes

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Banyasin A and banyasides A and B, three novel modified peptides from a water bloom of the cyanobacterium *Nostoc* sp.

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Abstract—Three new modified peptides banyasin A, banyaside A and banyaside B were isolated from the hydrophilic extract of a natural bloom of the cyanobacterium *Nostoc* sp. The planar structure of the new compounds was determined by homonuclear and inverse-heteronuclear 2D NMR techniques as well as high-resolution mass spectrometry. Banyasides A and B, are structurally closely related to the cyanobacteria metabolite, suomilide and to the sponge derived, dysinosins. The absolute configuration of the asymmetric centers was studied using Marfey's method for HPLC. Banyaside A and B were found to be trypsin and thrombin inhibitors.

1. Introduction

Cyanobacteria emerged as prolific producers of non-proteinogenic and modified amino acids. These amino acids are incorporated in a wide array of biologically active natural products that are produced by cyanobacteria. These amino acids can be divided into two categories: (1) modified proteogenic amino acids and (2) specially synthesized amino acids. Modified proteogenic amino acids can further be divided into two subcategories: (1a) trivial modifications, such as, D-amino acids (e.g., microcystins[1]), *N*-methylated amino acids (e.g., microginin SD755[2]), α-methylated amino acids (e.g., tantazoles[3]), iso-linked amino acids (e.g., microcystines[1]) or cyclized amino acids such as, oxazolines, oxazoles, thiazolines and thiazoles, derived from serine or threonine and cysteine, respectively (e.g., tenuecyclamides[4]) or (1b) unique modifications, such as the extension of the carboxylic end of amino acids with a ketide unit (e.g., mirabimides A–D[5], simplostatin 1[6]) or a methylene (e.g., homotyrosine in oscillopeptin[7]), and modification of the side-chains of the amino acids. Modifications of the side-chains of amino acids produce some of the more exciting metabolites of cyanobacteria. Modifications of the side-chains of amino acids include reduction of side-chain carboxyls (e.g., micropeptins[8]), reduction of aromatic rings (e.g., radiosumin[9]), alkylation[10] and halogenation[11] of aromatic rings, prenylation of side-chains oxygens (e.g., prenylagaramides[12]) and nitrogens (e.g., aeruginoguanidines[13]) and cyclization of reduced aromatic amino acids to azabicyclic systems (e.g., Choi moieties in aeruginosins[11] and the azabicyclicnonane moiety of suomilide[14]). Specially synthesized amino acids are usually long-chain polyketide-derived β-amino acids, such as β-amino acids (e.g., laxaphycins[15]), α-hydroxy-β-amino acids (e.g., schizothrin A[16]), α-methyl-β-aminoacids (lyngbyastatin 1[17]). In the future, gene encoding for the biosynthesis of these unique amino acids may be used in the combinatorial biosynthesis[18] of 'unnatural' natural products. Herein we report the isolation and structure determination of three novel peptides containing unique amino acids, banyasin A (**1**), banyaside A (**2**) and banyaside B (**3**), from the freshwater bloom of the cyanobacterium *Nostoc* sp. (IL-235) that previously yielded UV-absorbing pigments[19] and peptides.[20]

Banyasin A (**1**), was isolated as a glassy material with a molecular weight of 713 mass units. HRFABMS measurements of the protonated molecular ion (*m/z* 714.3983) suggested a $C_{34}H_{51}N_9O_8$ molecular formula for **1**, requiring 13 degrees of unsaturation. The NMR data was collected in 20% CD_3OH in $CDCl_3$. Eight exchangeable protons were observed in the proton NMR spectrum, four of which presented a fast exchange rate (δ_H 7.22, 8.38, 8.82 and 9.67 ppm) and four a much slower exchange rate (δ_H 7.84, 8.18, 8.32 and 8.47 ppm). Signals of five protons of a mono substituted phenyl ring appear in the aromatic region of the spectrum. Upfield from the aromatic region, two protons of a trans-substituted double bond and five methine protons next to nitrogen were observed. Two *N*-methyls, a singlet and a doublet, two doublet methyls and a triplet methyl appear at the high-field end of the spectrum. A broad one-

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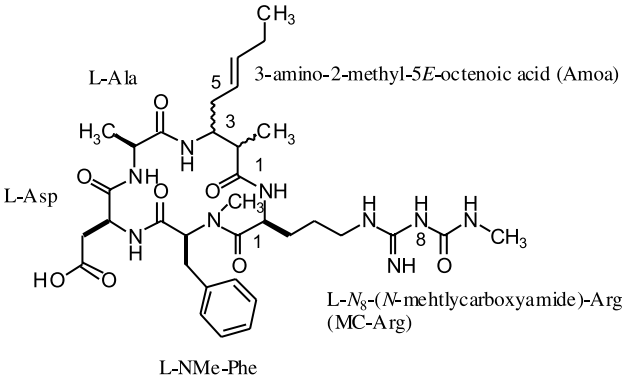
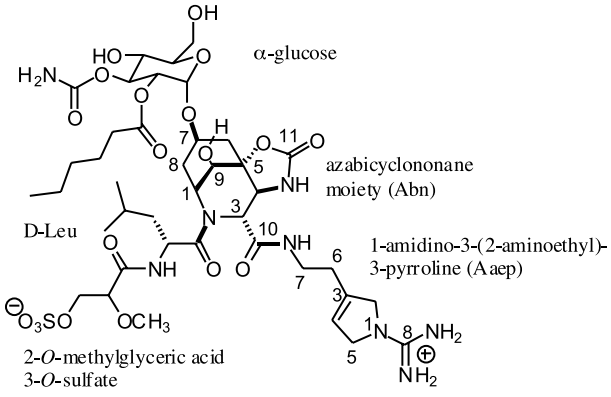
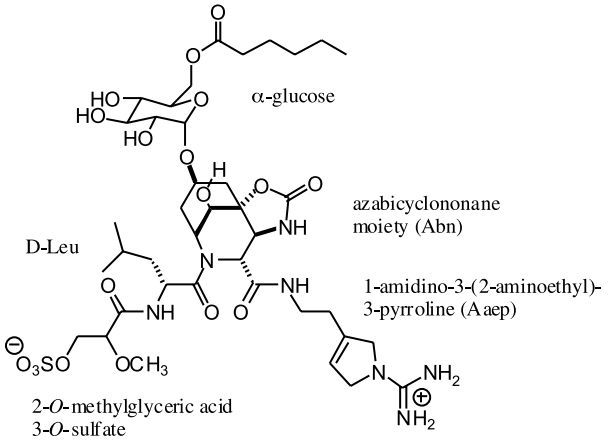
proton-signal resonates at δ_H −0.30 ppm, which may be attributed to an anisotropic effect such as diamagnetic shielding by the ring current of a neighboring aromatic moiety. In the carbon NMR spectrum, six carboxyl-carbons, two imine-carbons and eight vinyl carbons were observed at the low-field end of the spectrum. Six methines, seven methylenes and five methyls appear in the aliphatic region of the ^{13}C NMR spectrum. An H–H COSY experiment allowed the assignment of seven fragments, which account for 45 of the 51 protons of **1**. The fragments are: NHMe, α-NH to ε-NH of arginine (which include the proton at δ_H −0.30 ppm in the β-methylene), a mono substituted phenyl residue, an ABX spin system in agreement with an *N,N*-disubstituted aromatic amino-acid, α-NH to the β-methylene of aspartic acid, α-NH to the β-methyl of alanine and a sequence of protons in agreement with a novel amino acid, 3-amino-2-methyl-5*E*-octeneoic acid (Amoa). Assignment of the TOCSY spectrum confirms these assignments and added two connectivities between the proton at δ_H 8.38 ppm and the protons at δ_H 8.82 and 9.67 ppm. The correlations from the HMQC spectrum reinforced these assignments and confirmed the existence of another N-Me unit in **1**. HMBC correlations (see Table 1) allowed the full assignment of four of the five amino acid units of **1**, NMe-Phe, Asp, Ala and Amoa and connection of the doublet NMe to the imine carbon at δ_C 154.6 ppm. The HMBC experiment failed to show connectivity (although different mixing times were used) between the amide carbonyl and the α-carbon, and the imine-carbon at δ_C 154.8 ppm and the ε-NH of arginine, although the chemical shifts of these carbons matched those of an arginine unit. Furthermore, correlations between carbonyl groups and amide NH-groups of the neighboring amino acids allowed the assignment of the sequence: CO-Amoa-Ala-Asp-Phe-NMe. The remaining amide-carbonyl group, at δ_C 173.6 ppm, presents connectivities with Phe-NMe and an α-proton. No correlation was observed between Amoa-carbonyl and a neighboring NH-group. NOE correlations from a ROESY experiment allowed the assignment of the full structure of **1**. Correlation between the α-protons of NMe-Phe and Arg established their vicinity and assigned the amide-carbonyl (at δ_C 173.6 ppm) as the carbonyl of the arginine unit. Correlations of arginine-α-NH with the Amoa α-proton and α-methyl established their connection and closure of the cyclic penta-peptide. The NOE correlations, of the imide proton at δ_H 9.67 ppm with those at δ_H 7.22, 8.38 and 8.82 ppm, of the proton at δ_H 7.22 ppm with a doublet methyl at δ_H 2.74 ppm and that of the proton at δ_H 8.38 ppm with Arg-5-H_2, are adequate only with the proposed N_8-(*N*-methylcarboxyamide)arginine structure. The latter structure is supported by the generation of arginine upon acid hydrolysis of the peptide (see below) and the EI, CI and FAB MS fragmentations (see Fig. 1). Acid hydrolysis of **1** and derivatization with Marfey's reagents, followed by HPLC analysis, demonstrated the L-stereochemistry of the alanine, aspartic acid, NMe-phenylalanine and arginine.[21] The stereochemistry of positions 2 and 3 in Amoa remains to be solved. 3-Alkyl-3-amino-2-methyl carboxy-acids are common in cyanobacteria cyclic peptides,[17] although Amoa is presented for the first time in banyasin A (**1**). N_8-(*N*-Methylcarboxyamide)arginine is a unique amino acid that is presented here for the first time.



Banyasin A (**1**)



Banyaside A (**2**)



Banyaside B (**3**)

Banyasides A (**2**) and B (**3**), are structurally closely related to suomilide,[14] which was isolated from the brackish-water cyanobacterium *Nodularia spumigena* HKVV, and dysinosins,[22,23] which were isolated from a Dysideidae sponge. Banyaside A (**2**) was purified as an optically active colorless glassy solid with a molecular composition of $C_{40}H_{64}N_8O_{19}S$. A molecular ion was observed for **2** only in the negative FABMS (obsd $[M-H]^-$ at *m/z* 991).

In the positive ion mode, a cluster ion derived from a neutral loss of sulfur trioxide from the molecular cluster ion was observed (*m/z* 913). The molecular composition of **2** was

Table 1. NMR data of Banyasin A (**1**) in 20% CD_3OH in $CDCl_3$[a]

Position	δ_C, mult[b]	δ_H, mult (J, Hz)	HMBC[c]	ROESY[d]
Amoa-1[e]	177.1 s		Amoa-3,9	
2	41.5 d	2.48 m	Amoa-4	MC-Arg-α-NH
3	52.2 d	3.74 m	Amoa-9	Amoa-2,4,9,NH
	37.3 t	1.96 m	Amoa-3,5,6	
4		2.03 m		
5	124.9 d	5.26 dt 15.2,6.9	Amoa-4,6,7	
6	135.5 d	5.41 dt 15.2,6.0	Amoa-4,5,7,8	Amoa-8
7	25.7 t	1.90 dq 6.0, 7.4	Amoa-5,6,8	MC-Arg-N_8H
8	13.8 q	0.86 t 7.4	Amoa-6,7	Amoa-6
9	15.6 q	0.91 d 6.9		Amoa-2,3,NH, MC-Arg-α-NH
NH		7.84 d 9.5		Ala-2,NH
Ala-1	173.0 s		Amoa-NH, Ala-2,3	
2	48.6 d	4.44 dq 7.8, 7.2	Ala-3	Ala-NH,Amoa-NH
3	14.4 q	1.26 d 7.2	Ala-2	
NH		8.32 d 7.8		Amoa-4, Asp-2,3
Asp-1	170.8 s		Ala-NH, Asp-2,3	
2	48.6 d	4.65 ddd 7.6, 4.9, 2.8	Asp-3	Ala-NH, Asp-NH
3	35.8 t	2.59 dd 17.8, 2.8	Asp-2	Ala-NH
		3,26 dd 17.8, 4.9		
4	173.1 s		Asp-2,3	
NH		8.47 d 7.6		Phe-2, NMe
NMe-Phe-1	170.0 s		Asp-NH,Phe-2	
2	62.1 d	5.07 dd 11.2, 3.2	Phe-3, NMe	Asp-NH,MC-Arg-2
3	35.0 t	3.08 dd 14.4, 2.3	Phe-2,5,5′	
		3.11 dd 14.4, 11.6		
4	138.2 s		Phe-2,3,3′,6,6′	
5,5′	130.0 d×2	7.19 d×2 7.2	Phe-3.3′,6,6′,7	MC-Arg-3, Phe-NMe
6,6′	129.2 d×2	7.29 t×2 7.2	Phe-5,5′,7	MC-Arg-3
7	127.2 d	7.23 t 7.2	Phe-5,5′,6,6′	
NMe	29.3 q	2.88 s	Phe-2	Asp-NH,Phe-5,5′
MC-Arg-1[f]	173.6 s		Phe-2	
2	48.5 d	4.17 m		MC-Arg-NH, Phe-2
3	27.1 t	−0.30 brm	CM-Arg-2,4	Phe-5,5′,6,6′
		1.08 m		
4	25.0 t	1.09 m		
		1.40 m		
5	40.8 t	2.85 m		CM-Arg-N_9H
		2.93 m		
α-NH		8.18 brs		CM-Arg-2, Amoa-2,9
ε-NH		8.82 brs		CM-Arg-N_8H
7	154.8 s			
N_8H		9.67 brs		CM-Arg-ε-NH, N_9H, N_{11}H
N_9H		8.38 brs		CM-Arg-5,5′, N_8H
10	154.6 s		CM-Arg-12	
N_{11}H		7.22 m		CM-Arg-N_8H,12
12	26.3 q	2.74 d 4.1		

[a] Carried out on an ARX-500 Bruker instrument.
[b] Multiplicity and assignment from HMQC experiment.
[c] Determined from HMBC experiment, $^nJ_{CH}=8$ Hz, recycle time 1 s.
[d] By ROESY experiment, mixing time 400 ms. The HMBC correlations are reported as correlations of the protons printed in the column with the carbons in the rows.
[e] 3-Amino-2-methyl-5*E*-octeneoic acid.
[f] N_8-(*N*-Methylcarboxyamide)arginine.

determined by HRFABMS of the latter cluster ion (obsd $[M+H-SO_3]^+$ at m/z 913.4512). In DMSO-d_6, **2** appears as a ca. 1:7 mixture of *cis*- and *trans*-rotamers of the azabicyclononane-Leu peptidic bond. The glycopeptidic nature of banyaside A is evident from the proton and carbon NMR spectra of **2**, namely the signals of three amide protons between 7.5 and 8.5 ppm, an anomeric proton at 4.86 ppm and the carbinol protons between 3 and 5 ppm in the proton NMR spectrum and the carbonyl signals, an anomeric carbon at 94.6 ppm and carbinol carbon signals between 75 and 60 ppm, in the carbon NMR spectrum. Analysis of the NMR spectra of **2** in DMSO-d_6 allowed the construction of six partial structures: hexanoic acid, 1,2,3-trisubstituted-α-glucose, an azabicyclononane moiety,[24] leucine, 2-*O*-methyl-3-sulfoglyceric acid and 1-amidino-3-(2-aminoethyl)-3-pyrroline (see Table 2). The structure of the hexanoic acid was deduced from the COSY, TOCSY, HMQC and HMBC correlations (see Table 2). The α-glucose structure is based on the COSY correlations and H–H J-values. The chemical shifts of the protons at positions 1, 2 and 3 of the glucose unit (δ_H 4.86, 4.49 and 4.96 ppm, respectively) indicated that the oxygen at position 1 is alkylated while the oxygens at positions 2 and 3 are esterified. HMBC correlation of Glu-H-3 with a carbonyl resonance, at δ_C 156.5 ppm, and an NOE correlation of protons of an NH_2 group with Glu-H-2 and H-3, established a carbamoyl substituent at position 3. NOE correlation of the glucose H-1 with methylene-2 of the hexanoic acid,

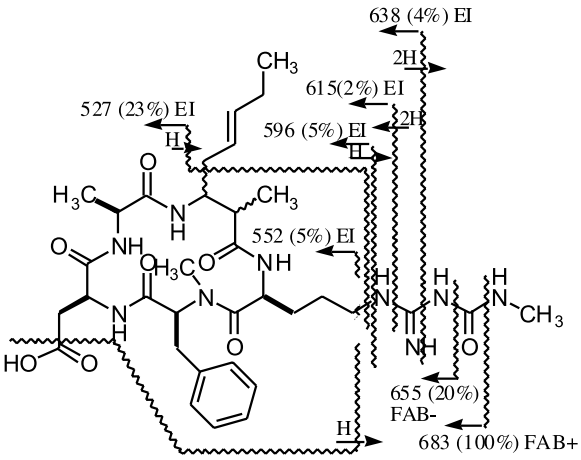


Figure 1. Mass spectra fragmentations of banyasin A (**1**).

established it as the substituent at position 2 of the glucose unit. Two fragments, H-3 to 4-NH and H_2-6 through H-9 of the azabicyclononane moiety, were elucidated based on proton connectivities from COSY and TOCSY experiments. The two fragments were connected by HMBC correlations: those of H-1 to C-3 and H-3 to C-1, establishing the aza-bridge between C-1 and C-3, and those of H-4 to C-5, C-6 and C-9 and H-6a and H-6e to C-5 establishing the oxygen-bearing quaternary carbon, C-5, as the second bridgehead of the bicyclic-moiety. The HMBC correlations of the amide carbonyl group (C-10, δ_C 169.1 ppm) with H-3 and H-4 established its connection to C-3. Correlation of 4-NH with a carbonyl group (C-11, δ_C 156.9 ppm), the chemical shifts of C-5 and C-11 and the molecular formula of **2**, suggested the closure of the latter carbonyl to a urethane between C-4-NH and C-5-oxygen. The relative stereochemistry of the azabicyclononane moiety is based on NOEs from a ROESY experiment of **2** (see Fig. 2). The most important connectivites were those of H-3 with H-9 and H-4 with H-7 (bold lines in Fig. 2). The D-leucine unit was deduced on the basis of the data from COSY, HMQC and HMBC experiments and Marfey's analysis[21] of the acid hydrolysate of **2**. COSY correlations of an ABC system and the data from the HMQC experiment established the spin system of positions 2 and 3 of the glyceric acid unit. The HMBC correlation of H-2, H-3 and H-3′ with a carbonyl-carbon and of H-2 with a methoxyl-carbon established the partial structure of this segment as 2-*O*-methylglyceric acid. Comparison of the proton and carbon chemical shifts of this moiety with the NMR data of 2-*O*-methylglyceric acid and 2-*O*-methylglyceric acid 3-*O*-sulfate[10] and, taking into account the natural loss of sulfur trioxide, in the positive FABMS of **2**, established the structure of this unit as 2-*O*-methylglyceric acid 3-*O*-sulfate. The structure of the amidino aminoethyl pyrroline (Aaep) moiety is based on the COSY correlation of the vinylic proton, H-4, with H_2-5 and HMBC correlations of this proton (H-4) with carbons 2, 3, 5 and 6. The structure of the aminoethyl fragment is based on the COSY correlation of H_2-6 with H_2-7 and of H_2-7 with 7-NH. Finally, the amidino group was attached to the pyrroline nitrogen by HMBC correlations of H_2-2 and H_2-5 to the singlet sp^2-carbon at 154.3 ppm and the NOE between the imidino-protons and H_2-2 and H_2-5. The five segments, Glu, Abn, Leu, Mgs and Aaep, were assembled to give the full structure by HMBC and NOE correlations. The glucose H-1 shows an HMBC correlation with Abn C-7, suggesting that the glucose is attached to the latter carbon (Abn-7). Glu-H-1 shows an NOE correlations with Abn-H-7, 8a and 8e and Glu-H-5 shows an NOE with H-6a and 6e suggesting a restricted rotation around the Abn-7-*O*-Glu-1 bonds. Abn-H-3 shows HMBC correlation with Leu-carbonyl (C-1) and Abn-H-1 shows NOE correlation with Leu-H-2, 3, 3′ suggesting that the major rotamer of these two units is *trans* oriented as shown in the drawing of compound **2** (see additional NOEs in Table 2). The HMBC correlation of Abn-3 with Aaep-7-NH attaches the Aaep segment to the carbonyl (C-3) of the Abn moiety. The HMBC correlation between Leu-NH and Mgs-carbonyl as well as NOEs between these two segments (see Table 2), conclude the structure elucidation of banyaside A (**2**). The absolute stereochemistry of the α-glucose, Abn and Mgs remain unresolved.

Banyaside B (**3**) was obtained as optically active colorless glassy solid with a molecular composition of $C_{39}H_{63}N_7O_{18}S$. A molecular ion was observed for **3** only in the negative FABMS (obsd $[M-H]^-$ at *m/z* 948). In the positive ion mode, a cluster ion derived from a neutral loss of sulfur trioxide from the molecular cluster ion was observed (*m/z* 870). The molecular composition of **3** was determined by HRFABMS of the latter cluster ion (obsd $[M+H-SO_3]^+$ at *m/z* 870.4461). Comparison of the NMR data for compounds **2** and **3** suggested that they differ only in the substitution pattern of the glucose unit. In banyaside B, **3**, the carbamoyl substituent is missing and the hexanoic acid is attached to Glu-6-oxygen. This assignment is based on the chemical shifts of Glu-H-2 and -3, which are upfield shifted relative to those of compound **2**, and Glu-6-H_2 which are downfield shifted relative to those of **2**. On the basis of these observations structure **3** was assigned to banyaside B.

The azabicyclicnonane (Abn) moiety of suomilide and banyasides A and B, like the Choi moiety of the aeruginosins, is most probably derived from the aromatic amino acid, tyrosine. While, in the case of the aeruginosins, Choi is produced by reduction of the phenol ring to the cyclohexenol moiety followed by addition of the amine to the double bond, we suggest that Abn is rather produced by oxidation of the aromatic ring (see Fig. 3). Tyrosine is first oxidized to the quinone methide II. Such an oxidative step is most probably also an initial step in the biosynthesis of the trypsin inhibitors radiosumin[9] and dehydroradiosumin.[25] Reduction of the ketone affords the triene III, which is oxidized to the triepoxide IV. Nucleophilic attack of carbamoyl phosphate on the exocyclic-epoxide followed by cyclization affords the urethane VI. Attack of the α-amine on the endocyclic-epoxide, produces the aza-bicyclic system and reduction of the last epoxide to alcohol gives the Abn moiety. These unique transformations of aromatic amino acids furnish novel amino acids, which are key elements in bioactive natural products. They may be used in the synthesis of peptido-mimetics and, in the future, the genes of their biosynthetic machinery may be utilized in 'combinatorial biosynthesis' of 'unnatural' natural products.

Compounds **1–3** were isolated through a serine protease

Table 2. NMR data of banyaside A (**2**) in DMSO-d_6[a]

Position	δ_C, mult[b]	δ_H, mult (*J*, Hz)	HMBC[c]	ROESY[d]
Glu-1[e]	94.6 d	4.86 d 3.6		Glu-2, HA-2, Abn-4-NH,7,8a,8e
2	71.3 d	4.49 dd 10.4, 3.6	Glu-3	Glu-1,4,7-NH_2
3	71.8 d	4.96 dd 10.4, 9.6	Glu-1,2,4	Glu-5,7-NH_2
4	68.0 d	3.36 dd 9.6, 9.0	Glu-3,5,6,6′	Glu-2
5	73.3 d	3.53 brd 9.0	Glu-1,4	Glu-3, Abn-6
6	60.3 t	3.54 brd 9.9		
7	156.5 s		Glu-3	
7-NH_2		6.45 brs		Glu-2,3
HA-1[f]	172.8 s		HA-2,3	
2	33.7 t	2.24 t 7.3	HA-3	Glu-1, HA-3,4,5
3	24.3 t	1.50 tt 7.3, 7.0	HA-2	HA-2,4,5,6
4	30.7 t	1.23 m	HA-2,3,5,6	HA-2,3,5,6
5	21.9 t	1.24 m	HA-3,4,6	HA-2,3,4,6
6	13.9 q	0.81 t 6.9	HA-4,5	HA-3,4,5
Abn-1[g]	53.8 d	4.07 brs	Abn-3,8e	Abn-4-NH,8a,8e,9, Leu-2,3,6
3	56.9 d	4.55 brs	Abn-1	Abn-4,6e,9
4	58.1 d	4.28 brs	Abn-3,4-NH,6a	Abn-3,6e,6a,7
4-NH		8.00 brs		Abn-1,3,4,4-NH,9
5	80.6 s		Abn-1,3,4,6a,6e	
6	34.7 t	e 2.00 brdd 10.0, 6.3	Abn-4	Abn-6a,7, Glu-5
		a 2.30 m		Abn-5e,7,8a, Glu-5
7	69.5 d	3.70 m	Abn-6e,6a, Glu-1	Abn-4,6e,8e, Glu-1, Aaep-7-NH
8	28.9 t	a 1.71 brt 11.3		Abn-1,6a,7, Glu-1
		e 2.12 brd 11.3		Abn-1,7, Glu-1
9	65.9 d	3.74 m	Abn-4	Abn-1,3,9-OH
9-OH		6.08 brs		Abn-9
10	169.1 s		Abn-3,4, Aaep-7,7-NH	
11	156.9 s		Abn-4-NH	
Leu-1	172.6 s		Leu-2, Abn-3	
2	48.6 d	4.58 m	Leu-NH	Leu-3,4,5,6, Abn-1
3	39.1 t	1.33 m	Leu-5,6	Leu-3′,4,5,6, Abn-1
		1.62 m		Leu-3,5,6, Abn-1,8e,9
4	24.4 t	1.66 m	Leu-5,6	Leu-2,5,6, Abn-8e
5	21.3 q	0.88 d 6.0	Leu-6	Leu-3,3′,4
6	23.3 q	0.88 d 6.0	Leu-5	Leu-3,3′,4
NH		8.36 d 6.1		Leu-2,3,3′,4,5,6, Mgs-2, OMe, Abn-1,3,8e, Glu-1
Mgs-1[h]	170.2 s		Mgs-2,3,3′,Leu-NH	
2	80.3 d	3.89 dd 2.5, 9.5	Mgs-3,3′,OMe	Mgs-Ome, Leu-NH
3	66.5 t	3.73 dd 11.0, 9.5	Mgs-2	Leu-NH
		3.91 dd 11.0, 2.5		Leu-NH
OMe	57.5 q	3.20 s	Mgs-2	Mgs-2, Leu-NH
Aaep-2[i]	55.6 t	4.11 brs	Aaep-4,6	Aaep-6,7,8-NH_2
3	136.0 s		Aaep-2,4,5,6,7	
4	119.1 d	5.64 brs	Aaep-2,5,6	Aaep-5,6,7, Glu-1, Abn-4
5	54.5 t	4.11 brs	Aaep-4	Aaep-4, 8-NH_2
6	27.9 t	2.26 m	Aaep-4	Aaep-2,4,7
7	37.5 t	3.21 m	Aaep-6,7-NH	Aaep-6,7-NH
7-NH		7.55 t 6.0		Aaep-6,7, Abn-1,3,4,7,8e
8	154.3 s		Aaep-2,5	
8-NH_2		7.16 m		Aaep-2,5

[a] Carried out on an Avance-400 Bruker instrument.
[b] Multiplicity and assignment from HMQC experiment.
[c] Determined from HMBC experiment, $^nJ_{CH}=8$ Hz, recycle time 1 s. The HMBC correlations are reported as correlations of the protons printed in the column with the carbons in the rows.
[d] By ROESY experiment, mixing time 400 ms.
[e] α-Glucose.
[f] Hexanoic acid.
[g] 4-Amino-5,7,9-trihydroxy-2-azabicyclo[3.3.1]nonane-3-carboxylic acid.
[h] 2-*O*-Methylglyceric acid-3-*O*-sulfae.
[i] 1-Amidino-3-(2-aminoethyl)-3-pyrroline.

(chymotrypsin and trypsin) inhibition-guided separation. The final fractions that yielded compounds **1–3**, inhibited only trypsin. Pure **1**, was found to be inactive in the assay, while **2** and **3** completely inhibited the proteolytic activity of trypsin at a concentration of 45 μg/mL. The IC_{50} values were determined only for compound **2**, against the serine proteases trypsin and thrombin. Banyaside A (**2**) inhibited trypsin activity with an IC_{50} value of 1.48 μg/mL and thrombin with an IC_{50} value of 0.39 μg/mL.

The three novel compounds (**1–3**) described in this work deepen our knowledge regarding the chemistry and biosynthetic capabilities of cyanobacteria. Banyasin A (**1**) contains an unprecedented modified arginine and a unique β-amino acid that add to the constantly growing collection of modified amino acids produced by cyanobacteria. The activity revealed by Banyasides A (**2**) and B (**3**)—inhibition of serine proteases—defines a new class of cyanobacterial protease inhibitors and adds a new chemical motif, which

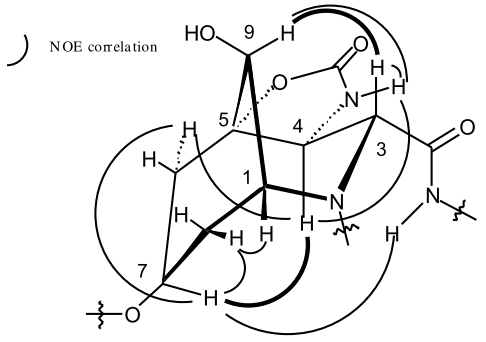


Figure 2. NOEs of the azabicyclononae moiety of Banyside A (**2**).

may be used in the synthesis of protease inhibitors for pharmaceutical use. The structural similarity of the cyanobacteria-derived banyasides and suomilide[3] with the dysinosins isolated from the sponge *Lamellodysidea chlorea*[22,23] clearly points to the possibility that the dysinosins are biosynthesized by a symbiotic cyanobacteria within the sponge as was demonstrated in the case of 13-demethylisodysidenin in *Dysidea herbacea*.[26]

2. Experimental

2.1. General experimental procedures

High resolution MS were recorded on a Fisons VG AutoSpecQ M 250 instrument. UV spectra were recorded on a Kontron 931 plus spectrophotometer. Optical rotation values were obtained on a Jasco P-1010 polarimeter at the sodium D line (589 nm). NMR spectra were recorded on a Bruker ARX-500 spectrometer at 500.136 MHz for ^{1}H and 125.76 MHz for ^{13}C and a Bruker Avance 400 spectrometer at 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 40.55 MHz for ^{15}N. ^{1}H, ^{13}C, DEPT, gCOSY, gTOCSY, gROESY, gHMQC and gHMBC spectra were recorded using standard Bruker pulse sequences. HPLC separations were performed on an ISCO HPLC system (model 2350 pump and model 2360 gradient programmer) equipped with an Applied

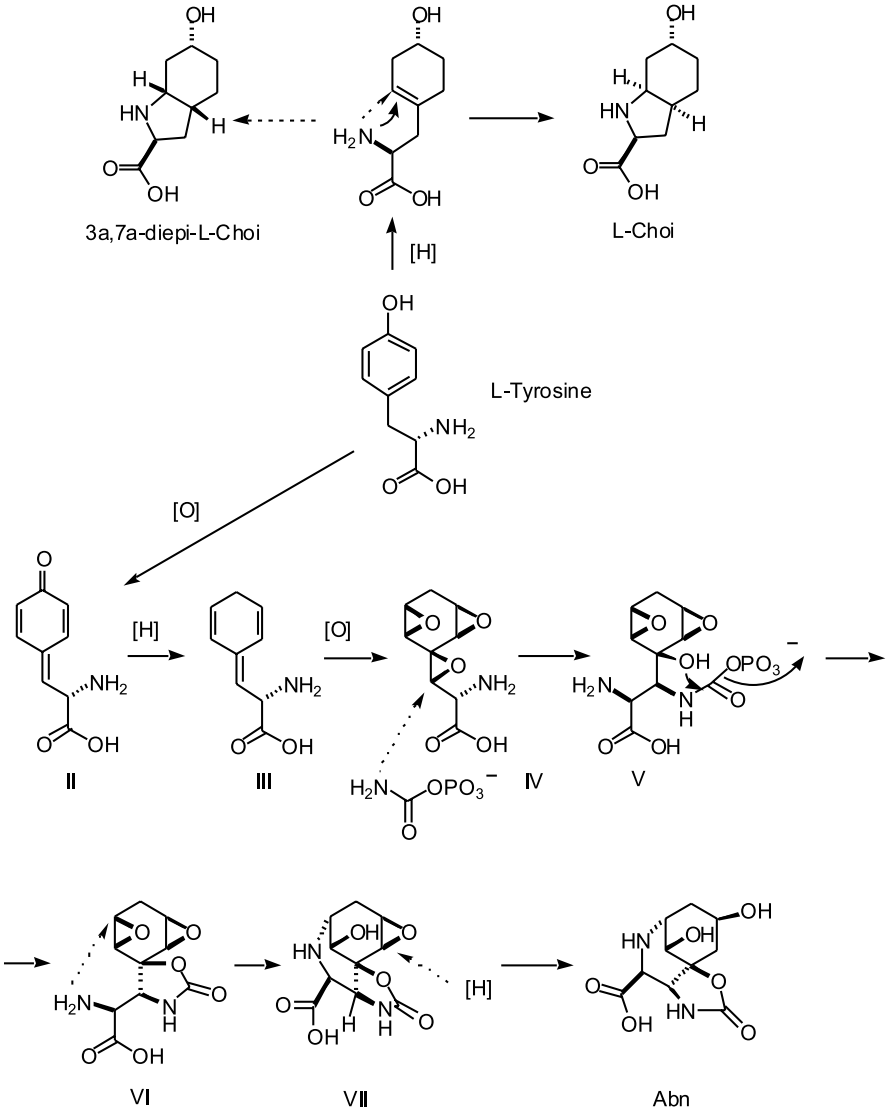


Figure 3. Proposed biogenesis of the Choi and Abn moieties.

Biosystems Inc. diode-array detector and Merck-Hitachi HPLC system (model L-4200 UV–vis detector and model L-6200A Intelligent pump).

2.2. Waterbloom material

Nostoc sp., TAU strain IL-235, was collected, in July 1999, from the spring pool of the Banyas stream, one of the tributaries that flow into the Jordan River, in Israel.

2.3. Isolation procedure

The naturally-collected, freeze-dried cells (146 g) were extracted with MeOH: H_2O (7:3) ($\times$3) and then with MeOH:chloroform (1:1) ($\times$3). The combined hydrophilic extract was concentrated under reduced pressure to afford 5.1 g of crude extract. The crude extract was separated on an ODS (YMC-GEL, 120A, 4.4$\times$6.4 cm) flash column with increasing amounts of MeOH in water. Fractions 4 and 5

Table 3. NMR data of banyaside B (**3**) in DMSO-d_6[a]

Position	δ_C, mult[b]	δ_H, mult (J, Hz)	HMBC[c]	ROESY[d]
Glu-1[e]	98.7 d	4.58 d 3.6	Glu-2,3,5	Glu-2, Abn-7,8a,8e
2	71.6 d	3.15 dd 9.9, 3.6		Glu-1
3	73.0 d	3.33 dd 9.9, 9.3	Glu-1	
4	70.6 d	3.00 t 9.3	Glu-3,5	Glu-5,6
5	70.2 d	3.62 dd 9.3, 3.0	Glu-1,4	
6	64.0 t	3.96 dd 11.3, 3.0		Glu-4,5,6′
		4.26 d 11.3		Glu-6
HA-1[f]	173.2 s		HA-2,3	
2	33.5 t	2.29 t 7.4	HA-3	
3	24.4 t	1.49 tt 7.4, 7.1	HA-2	
4	30.8 t	1.24 m	HA-2,3,5,6	
5	21.6 t	1.24 m	HA-4,6	
6	14.0 q	0.84 t 6.3	HA-4,5	
Abn-1 [g]	53.8 d	4.10 m	Abn-3	Abn-8a,8e,9, Leu-2, NH
3	56.7 d	4.61 brs		Abn-4-NH,9, Aaep-7-NH
4	58.3 d	4.30 brs	Abn-3,4-NH,6a	Abn-4-NH,6e
4-NH		8.01 brs		Abn-3,4
5	80.7 s		Abn-3,4,4NH,6a,6e	
6	35.0 t	e 1.95 brdd 10.3, 4.6	Abn-4	Abn-4,7
		a 2.30 m		Abn-5e,7,8a
7	70.2 d	3.62 m		Abn-4,6e,8e, Glu-1
8	28.9 t	a 1.77 bt 10.9		Abn-1,6a,7
		e 2.12 brdd 10.9, 6.9		Abn-1,7, Glu-1
9	66.0 d	3.75 m	Abn-4	Abn-1,3
9-OH		6.05 brs		
10	168.9 s		Abn-3,4	
11	156.8 s		Abn-4-NH	
Leu-1	172.4 s		Leu-2, NH	
2	48.8 d	4.54 m		Leu-NH, Abn-1
3	39.1 t	1.34 m	Leu-5,6	Leu-3′,4,5,6, Abn-1
		1.60 m		Leu-3,5,6, Abn-1,8e,9
4	24.4 t	1.65 m	Leu-5,6	
5	21.3 q	0.89 d 6.0	Leu-6	Leu-3,3′,4
6	23.3 q	0.89 d 6.0	Leu-5	Leu-3,3′,4
NH		8.50 d 6.1		Leu-2,3,3′,4,5,6, Abn-1,3,8e
Mgs-1[h]	170.4 s		Mgs-2, Leu-NH	
2	80.3 d	3.90 dd 2.8, 8.3	Mgs-3,3′,OMe	Mgs-3, OMe
3	66.5 t	3.78 dd 12.1, 8.3	Mgs-2	Mgs-2
		3.92 dd 12.1, 2.8		
OMe	57.7 q	3.20 s	Mgs-2	Mgs-2
Aaep-2[i]	55.7 t	4.10 brs	Aaep-4	Aaep-8-NH_2
3	136.2 s		Aaep-2,5,6	
4	118.9 d	5.62 brs	Aaep-6	Aaep-5
5	54.4 t	4.10 brs	Aaep-4	Aaep-4, 8-NH_2
6	27.9 t	2.27 m	Aaep-7	Aaep-7
7	37.5 t	3.13 m	Aaep-6	Aaep-6,7-NH
		3.25 m		Aaep-6,7-NH
7-NH		7.53 t 5.5		Aaep-7, Abn-3
8	154.3 s			
8-NH_2		7.24 m		Aaep-5

[a] Carried out on an Avance-400 Bruker instrument.
[b] Multiplicity and assignment from HMQC experiment.
[c] Determined from HMBC experiment, $^nJ_{CH}$=8 Hz, recycle time 1 s. The HMBC correlations are reported as correlations of the protons printed in the column with the carbons in the rows.
[d] By ROESY experiment, mixing time 400 ms.
[e] α-Glucose.
[f] Hexanoic acid.
[g] 4-Amino-5,7,9-trihydroxy-2-azabicyclo[3.3.1]nonane-3-carboxylic acid.
[h] 2-*O*-Methylglyceric acid-3-*O*-sulfae.
[i] 1-Amidino-3-(2-aminoethyl)-3-pyrroline.

(3:7 and 1:1 MeOH:H_2O) were found to be active in a protease inhibition assay (trypsin) and, thus, separated on a Sephadex LH-20 gel-filtration column with 1:1 $CHCl_3$:MeOH. Fraction 1 (50 mg), from the Sephadex LH-20 column was subjected to a reversed-phase HPLC (YMC ODS-A 10 μm, 250 mm×20.0 mm, DAD at 230 nm, flow rate 5.0 mL/min) in 35:35:30 MeOH/acetonitrile/water to obtain pure compound **1**. Compound **1** (9.0 mg), 0.0062% yield based on the dry weight of the cyanobacteria cells, was eluted from the column with a retention time of 14.5 min. Fraction 2 (72 mg), from the Sephadex LH-20 column was subjected to a reversed-phase HPLC (YMC ODS-A 10 μm, 250 mm×20.0 mm, DAD at 210 nm, flow rate 5.0 mL/min) in 1:1 MeOH/water to obtain pure **2** (8.3 mg) and **3** (2.7 mg). Compound **2**, 0.0056% yield, and compound **3**, 0.0018% yield, based on the dry weight of the cyanobacteria cells, were eluted from the column with retention times of 37.1 and 30.0 min, respectively.

2.3.1. Banyasin A (1). Colorless glassy solid; $[\alpha]_D^{20}=-45.3$ (*c* 0.7, MeOH); UV (MeOH) λ_{max} (ε) 214 (10,000) nm; for ^1H and ^{13}C NMR data see Table 1; Negative FAB MS *m/z* 712 $(M-H)^-$; HR positive FAB MS *m/z* 714.3983 $[MH^+]$ (calcd for $C_{34}H_{52}N_9O_8$, 714.3938).

2.3.2. Banyaside A (2). Colorless glassy solid; $[\alpha]_D^{20}=+28.7$ (*c* 1.0, MeOH); UV (MeOH) λ_{max} (ε) 218 (4000), 271 (2400) nm; for ^1H and ^{13}C NMR data see Table 2; Negative FAB MS *m/z* 991 $(M-H)^-$; HR positive FAB MS *m/z* 913.4512 $[MH-SO_3]^+$ (calcd for $C_{40}H_{65}N_8O_{16}$, 913.4518).

2.3.3. Banyaside B (3). Colorless glassy solid; $[\alpha]_D^{20}=+17.3$ (*c* 0.3, MeOH); UV (MeOH) λ_{max} (ε) 234 (3600), 268 (2300) nm; for ^1H and ^{13}C NMR data see Table 3; Negative FAB MS *m/z* 948 $(M-H)^-$; HR positive FAB MS *m/z* 870.4461 $[MH-SO_3]^+$ (calcd for $C_{39}H_{64}N_7O_{15}$, 870.4460).

2.4. Protease inhibition assays

Trypsin, thrombin and chymotrypsin were purchased from Sigma Chemical Co. Trypsin was dissolved in 50 mM Tris–HCl/100 mM NaCl/1 mM $CaCl_2$ to prepare a 1 mg/mL solution. Thrombin was dissolved in 200 mM Tris–HCl, pH 8.0 to prepare a 0.5 mg/mL solution. Chymotrypsin was dissolved in 50 mM Tris–HCl/100 mM NaCl/1 mM $CaCl_2$/1 mM HCl to prepare a 1 mg/mL solution. A 2 mM solution of *N*-benzoyl-D,L-arginine-*p*-nitroanilide (for trypsin) and Suc-Gly-Gly-*p*-nitroanilide (for chymotrypsin), and 0.5 mg/mL *N*-carbobenzyloxy-Gly-Pro-Arg-4-methyl-β-nitroanilide (for thrombin) in the appropriate buffer solution was used as a substrate solution. The test sample was dissolved in ethanol and diluted with the same buffer solution as that used for the enzyme and substrate. For the testing of trypsin and chymotrypsin, 100 μL buffer solution, a 10 μL enzyme solution and 10 μL of test solution were added to each microtiter plate well and preincubated at 37 °C for 5 min. Then, 100 μL of substrate solution was added to begin the reaction. The absorbance of the well was immediately measured at 405 nm. The developed color was measured after incubation at 37 °C for 30 min. For the thrombin inhibition assay, a 170 μL buffer solution, 10 μL thrombin solution and 10 μL of test solution were added to each microtiter plate well and preincubated at 25 °C for 10 min. Then, 10 μL of substrate solution was added to begin the reaction. The absorbance of the well was immediately measured at 405 nm. The developed color was measured after incubation at 25 °C for 20 min.

Acknowledgements

We thank the Israel Nature and National Parks Protection Authority, for the permission to collect the cyanobacterium within the Banyas Reservation, Dr. Alex Livne for the initial collection of the cyanobacterium, Olga Gratz-Pogrebinsky, Ela Zafrir and Ronit Kazenstein-Nahmiyas for the bioassays and Mr. Shimon Hauptman for mass spectra measurements. This study was supported by the European Community grant ERBIC18-CT98-0293 and the Israel Ministry of Science grant 432-201 for the HTS laboratory at Tel Aviv University.

Supplementary data

^1H, ^{13}C NMR, COSY, TOCSY, NOESY or ROESY, HMQC or HSQC and HMBC spectra of banyasin A, banyaside A and banyaside B are available.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.11.016

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An easy ABD → ABCD strategy to indolo[2,3-*a*]quinolizin-4-one. Synthesis of deplancheine and yohimbane

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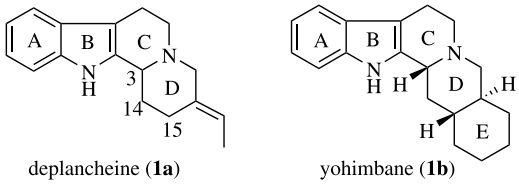
Abstract—The efficient synthesis of indolo[2,3-*a*]quinolizin-4-ones **2** is described in two steps via formal [3+3] cycloaddition reaction of α-sulfonyl tryptaminylacetamide **4** with various α,β-unsaturated esters **5** and the regioselective reduction of the resulting glutarimides **3** with sodium borohydride then sequent further dehydrated cyclization in the presence of boron trifluoride etherate. The useful building block is applied to synthesize deplancheine (**1a**) and yohimbane (**1b**).

1. Introduction

The development of synthetic methodology for constructing the tetracyclic indolo[2,3-*a*]quinolizin-4-one type alkaloids has attracted much attention[1,2] for several decades because of their important pharmacological properties.[3] Recently, we developed a facile methodology to produce a wide variety of α-sulfonyl piperidine-2,6-diones (glutarimides) by formal [3+3] cycloaddition reaction.[4] We also explored the application of these various glutarimides to different clinical drugs and natural products.[5–7] In the synthetic field of piperidine-2,6-dione, the regioselective reduction of asymmetrically substituted piperidine-2,6-dione to their corresponding hydroxypiperidinone[8–10] is an important course to the formation of *N*-acyliminium ions.

However, it is difficult to generate specific *N*-acyliminium ions from imide systems.[1] Thus, it is important to select appropriate piperidine-2,6-diones with α-sulfonyl group that features higher selectivity in reduction. To solve the imide reduction, we have developed the regioselective reduction with sodium borohydride to the various α-sulfonyl piperidine-2,6-diones derived from the formal [3+3] cycloaddition reaction under the milder condition (4–7 °C). The resulting hydrolactam was sequent dehydrated into ene-lactam by the catalytic amount of boron trifluoride etherate solution. This approach has been successfully employed in the synthesis of 8a-*epi*-dendroprimine[6a] and 3-PPP.[7a] Here, applications of this methodology have been realized in the synthesis of indolo[2,3-*a*]quinolizine alkaloid family with potential biological activities.

In continuing the previous investigations and building upon these observations on the chemistry of α-sulfonyl piperidine-2,6-dione, we envisaged that a rapid entry into tetracyclic indolo[2,3-*a*]quinolizin-4-one skeleton could be achieved based on the formal [3+3] cycloaddition reaction between α-sulfonyl tryptaminylacetamide and various α,β-unsaturated esters, and the regioselective reduction of the resulting piperidine-2,6-diones with sodium borohydride, followed by further dehydration with the catalytic amount of boron trifluoride etherate. Thus, the tetracyclic indolo[2,3-*a*]quinolizin-4-one system could be assembled in a key step by Bischler–Napieralski cyclization to establish the C ring and obtained as a single diastereomer in which the substituents at C3 and C14 and C14 and C15 are *trans* to each other (Fig. 1).



deplancheine (**1a**) yohimbane (**1b**)

Figure 1. Structural characteristics of deplancheine (**1a**) and yohimbane (**1b**).

Keywords: Indolo[2,3-*a*]quinolizin-4-one; Formal [3+3] cycloaddition reaction; Regioselective reduction; Deplancheine; Yohimbane.
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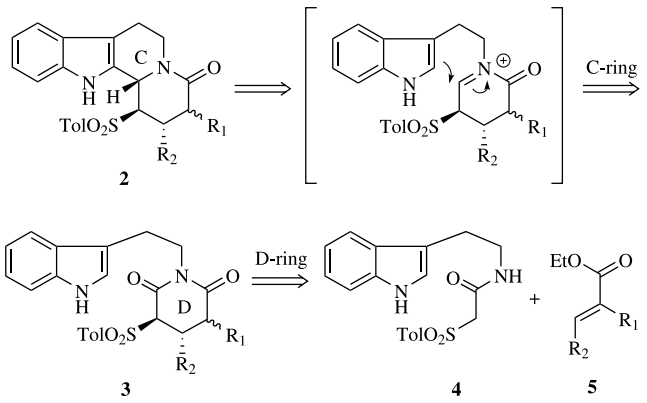
Here, we also demonstrate the three-step technique toward synthesis of deplancheine and yohimbane based on the tetracyclic indolo[2,3-*a*]quinolizin-4-one skeleton.

2. Results and discussion

2.1. Retrosynthetic approach to indolo[2,3-*a*]quinolizin-4-one 2

We describe the stepwise reduction leading to tetracyclic indolo[2,3-*a*]quinolizin-4-one **2** as illustrated in Scheme 1.



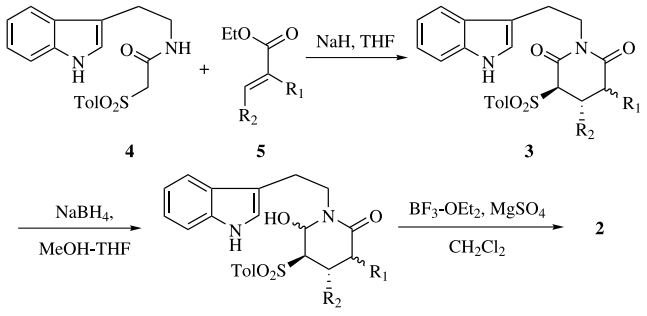
Scheme 1. Retrosynthetic study of tetracyclic indolo[2,3-*a*]quinolizin-4-one **2**.

There are two remarkable steps for the synthesis of compound **2**. One is the rapid access to produce a wide variety of α-sulfonyl piperidine-2,6-dione **3** with ABD-ring by formal [3+3] cycloaddition reaction. The other is the regioselective reduction of α-sulfonyl piperidine-2,6-dione **3** to α-sulfonyl hydroxypyridinone followed by acidic dehydration. The approach for ABD→ABCD ring was achieved by the dehydration and Bischler–Napieralski cyclization under the acidic condition.

2.2. Three-step synthesis of indolo[2,3-*a*]quinolizin-4-one 2 from 4

The synthesis of indolo[2,3-*a*]quinolizin-4-one began from the piperidine-2,6-diones **3** which were the cycloadducts of formal [3+3] cycloaddition reaction as shown in Scheme 2.

Tryptamine was treated with chloroacetyl chloride and triethylamine to produce α-chloro tryptaminylacetamide. The chloro compound was treated with *p*-toluenesulfinic acid sodium salt to give α-sulfonyl tryptaminylacetamide **4**. Compound **4** was deprotonated with sodium hydride to produce the dianion intermediate. The dianion of **4** was reacted with different α,β-unsaturated ester **5** to yield the various piperidine-2,6-dione **3** with different substitent in an efficient procedure.



Scheme 2. Synthesis of indolo[2,3-*a*]quinolizin-4-one **2**.

In the next step, the piperidine-2,6-dione **3** was treated with sodium borohydride followed by dehydration with boron trifluoride etherate yielded the indolo[2,3-*a*]quinolizin-4-one **2**. According to related reports,[12] regioselective reduction with sodium borohydride was effected by the α-substituted group at glutarimide ring. In our case, chelation between α-sufonyl and adjacent carbonyl group position of piperidine-2,6-dione **3** was induced by sodium borohydride to produce the regioselective 6-hydroxy piperidinone at 4–7 °C. The 6-hydroxy piperidinone was dehydrated and intramolecularly cyclized with boron trifluoride etherate to give **2** as a sole product. The two steps from **3** to **2** gave 62–85% overall yield. Some representative results are shown in Table 1.

Table 1. The substitutents and yields of piperidine-2,6-diones **3** and indolo[2,3-*a*]quinolizin-4-ones **2**

Entry	Compound **2**, R_1, R_2	**3** (%)	**2** (%)
1	R_1=H, R_2=H	**3a**, 72	**2a**, 74
2	R_1=H, R_2=CH_3	**3b**, 84	**2b**, 81
3	R_1=H, R_2=$CH_2CH_2CH_2CH_2$–OH	**3c**, 80	**2c**, 82
4	R_1=H, R_2=$CH_2CH_2CH_2CH_2$–OBn	**3d**, 90	**2d**, 85
5	R_1=H, R_2=$CH_2CH_2CH_2CH_2$–OMs	**3e**, 56	**2e**, 69
6	R_1=H, R_2=$CH(OCH_3)_2$	**3f**, 67	**2f**, 81
7	R_1=H, R_2=CO_2Et	**3g**, 66	**2g**, 62
8	R_1=CH_3, R_2=H	**3h**, 82	**2h**, 80
9	R_1=H, R_2=C_6H_5	**3i**, 78	**2i**, 84
10	R_1=(*E*)-ethylidene, R_2=H	**3j**, 72	**2j**, 78

The stereochemistry of **3j** was established by X-ray analysis.[13] Reduction of the **2f** to yield **6**, fortunately, the structure of **6** could be determined by single-crystal X-ray analysis (Diagram 1).[13] The relative stereochemical relationship of three contiguous chiral centers on **6** can be

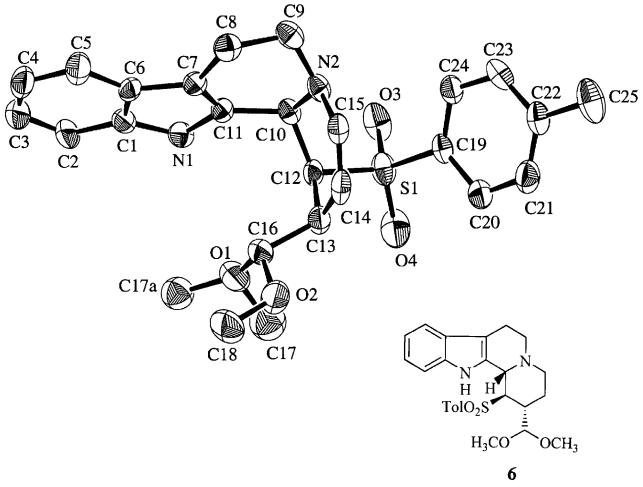


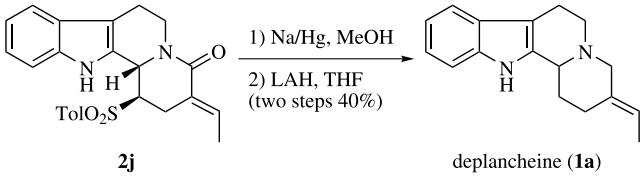
Diagram 1. X-ray crystallography of **6**.

confirmed as the *trans* orientation to each other. By the one-pot intramolecular Bischler–Napieralski cyclization reaction, we provide a rapid entry for constructing C-ring with three contiguous chiral centers on the tetracyclic indolo[2,3-*a*]quinolizin-4-one skeleton.

2.3. Synthesis of deplancheine (1a)

Deplancheine (**1a**) was isolated from the New Caledonian plant *Alstonia deplanchei* van Heurck et Mueller Arg. (Apocyanaceae) and assigned as the *trans* configuration on the basis of an analogy with the majority of indole alkaloids.[14a] After its structure elucidation, a number of total syntheses were reported.[14] Both deplancheine and 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine[15] are simple skeleton of indolo[2,3-*a*]quinolizine alkaloid family with interesting biological functions. In structural comparison, two alkaloids have a common characteristic tetracycle framework comprised indole ABC ring and their only difference is the *exo*-olefin substitutent of the D-ring.

Desulfonation of **2j** with an excess of sodium amalgam in methanol yielded the piperidinone. Without further purification, reduction of the corresponding piperidinone by lithium aluminum hydride produced the deplancheine (**1a**) and its side product **7** in the ratio of 4:1. Under the condition, the over-reduced product **7** was obtained. We exchanged the sequence of the two-step to avoid the problem but a similar result was still obtained. Although Martin had provided the related reaction conditions to solve the generated problems,[16] we could not obtain the desired sole **1a** by the reported methods and the mixture of **1a** and **7** still was generated (Scheme 3).

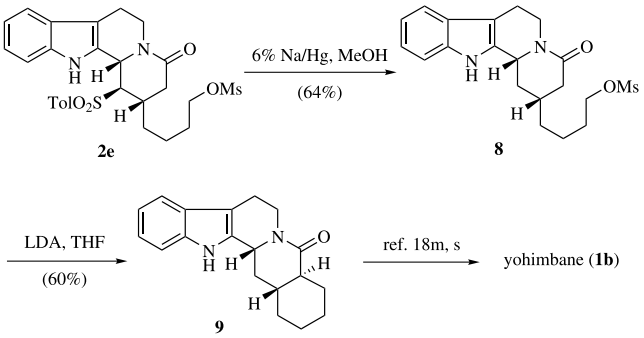


Scheme 3. Synthesis of deplancheine (**1a**).

2.4. Synthesis of yohimbane (1b)

Yohimbane (**1b**), allo-yohimbane, pseudo-yohimbane, and 3-*epi*-allo-yohimbane are simple skeleton of *Rauwolfia* alkaloid family.[17] The family possesses a wide range of biological activities and has been served as an important pharmacological tool. The interesting biological functions have induced many attempts to synthesize these compounds with pentacyclic ring system.[18]

We choose **2e** as the starting material for synthesizing **1b** as shown in Scheme 4. Desulfonation of **2e** with an excess of 6% sodium amalgam in methanol yielded the resulting piperidinone **8**. According to the Hua's method, treatment of **8** with lithium diisopropylamide was furnished completely to **9** via intramolecular alkylation.[18s]



Scheme 4. Synthesis of yohimbane (**1b**).

3. Conclusion

In summary, a concise synthesis of tetracyclic indolo[2,3-*a*]quinolizin-4-one **2** skeleton has been accomplished which demonstrates the utility of the formal [3+3] cycloaddition reaction of α-sulfonyl tryptaminylacetamide to provide the D-ring and regioselective reduction of the resulting piperidine-2,6-dione then followed by further dehydration and intramolecular cyclization reaction to establish C-ring. Syntheses of deplancheine (**1a**) and yohimbane (**1b**) are also described using the methodology. Further applications of the formal [3+3] cycloaddition reaction toward other alkaloids will be reported in due course.

4. Experimental

4.1. General

Dichloromethane (DCM) and tetrahydrofuran (THF) were distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. All reported melting temperatures are uncorrected.

4.2. Procedure of formal [3+3] cycloaddition reaction

A solution of α-sulfonyl tryptaminylacetamide **4** (357 mg, 1.0 mmol) in THF (30 mL) was added to a rapidly stirred suspension of sodium hydride (132 mg, 3.3 mmol, 60%) in THF (40 mL). After the reaction mixture was stirred at rt for 15 min, a solution of α,β-unsaturated ester **5** (1.2 mmol) in THF (10 mL) was added. The resulting mixture was refluxed for 30 min, quenched with saturated ammonium chloride solution (2 mL) in an ice bath, and concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (2× 20 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) produced glutarimides **3a–j** in 56–90% yield.[5–7]

4.3. Procedure of regioselective reduction [$NaBH_4$] and acidic dehydration [BF_3-OEt_2]

A solution of **3** (1.0 mmol) in a co-solvent of THF (10 mL) and methanol (5 mL) was stirred at 4–7 °C. Sodium borohydride (110 mg, 3.0 mmol) was added at 4–7 °C. The mixture was stirred for 2 h at that temperature. Saturated sodium bicarbonate solution (1 mL) was added to the mixture and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with DCM (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Without further purification, the crude hydroxy-lactam was dissolved in DCM (10 mL), and a catalytic amount of boron trifluoride etherate (0.1 mL) and anhydrous magnesium sulfate (0.5 g) were added. The mixture was stirred for 5 h at rt. Saturated sodium bicarbonate solution (5 mL) was added to the resulting mixture and concentrated under reduced pressure. The residue was diluted with water (5 mL) and extracted with DCM (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over anhydrous magnesium sulfate, filtered and evaporated. Purification on silica gel (hexane/ethyl acetate=4/1–2/1) produced tetracycles **2a–j** in 62–85% yield.

4.3.1. 1-(4-Methylphenyl)sulfonyl-1,2,3,4,6,7,12,12b-octahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2a). Mp 258–260 °C; IR ($CHCl_3$) 3240, 1610 cm^{-1}; ESI-MS: $C_{22}H_{22}N_2O_3S$ *m/z* (%)=58 (48), 136 (50), 149 (88), 238 (72), 391 (57), 395 (M^++1, 100); HRMS (ESI, M^++1) calcd for $C_{22}H_{23}N_2O_3S$ 395.1431, found 395.1436; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (br s, 1H), 7.87 (d, *J*=8.3 Hz, 2H), 7.48 (d, *J*=7.8 Hz, 1H), 7.44 (d, *J*=8.2 Hz, 2H), 7.42 (d, *J*=8.4 Hz, 1H), 7.21 (t, *J*=8.0 Hz, 1H), 7.11 (t, *J*=7.8 Hz, 1H), 5.39 (d, *J*=8.3 Hz, 1H), 4.95 (dd, *J*=4.8, 13.2 Hz, 1H), 3.67–3.62 (m, 1H), 3.03–2.90 (m, 2H), 2.75–2.70 (m, 1H), 2.57 (dt, *J*=4.5, 17.2 Hz, 1H), 2.49 (s, 3H), 2.20–2.12 (m, 1H), 2.07–1.97 (m, 1H), 1.95–1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.32, 146.44, 136.11, 132.46, 131.49, 130.46 (2×), 129.29, 129.12, 126.47, 122.61, 119.85, 118.45, 111.65, 111.03, 64.32, 52.18, 42.75, 30.08, 22.10, 21.78, 20.56; Anal. Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10. Found: C, 66.72; H, 5.66; N, 7.31.

4.3.2. 1-(4-Methylphenyl)sulfonyl-2-methyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2b). Mp> 260 °C (decomp.); IR ($CHCl_3$) 3250, 1640 cm^{-1}; EI-MS: $C_{23}H_{24}N_2O_3S$ *m/z* (%)=91 (100), 237 (52), 252 (23), 408 (M^+, 2); HRMS (EI, M^+) calcd for $C_{23}H_{24}N_2O_3S$ 408.1508, found 408.1505; ^1H NMR (500 MHz, $CDCl_3$) δ 9.55 (br s, 1H), 7.88 (d, *J*=8.5 Hz, 2H), 7.53 (d, *J*=7.5 Hz, 1H), 7.45 (d, *J*=8.5 Hz, 3H), 7.24 (td, *J*=1.0, 7.5 Hz, 1H), 7.16 (dd, *J*=1.0, 7.5 Hz, 1H), 5.50 (d, *J*=6.0 Hz, 1H), 5.16 (dt, *J*=3.0, 12.5 Hz, 1H), 3.53 (d, *J*=6.0 Hz, 1H), 2.97–2.92 (m, 1H), 2.87–2.81 (m, 3H), 2.50 (s, 3H), 2.41–2.35 (m, 1H), 2.27 (ddd, *J*=1.5, 3.5, 16.0 Hz, 1H), 0.90 (d, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.82, 146.10, 136.29, 132.95, 131.54, 130.39 (2×), 128.80 (2×), 126.24, 122.45, 119.75, 118.31, 111.47, 110.37, 69.52, 49.59, 40.50, 35.72, 27.48, 21.67, 20.63, 20.48; Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.66; H, 6.03; N, 7.02.

4.3.3. 1-(4-Methylphenyl)sulfonyl-2-(4-hydroxy)butyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2c). Mp>230 °C (decomp.); IR ($CHCl_3$) 3430, 1635 cm^{-1}; EI-MS: $C_{26}H_{30}N_2O_4S$ *m/z* (%)=91 (100), 237 (54), 310 (8), 466 (M^+, 1); HRMS (ESI, M^++1) calcd for $C_{26}H_{31}N_2O_4S$ 467.2004, found 467.2006; ^1H NMR (500 MHz, $CDCl_3$) δ 9.61 (br s, 1H), 7.86 (d, *J*=8.5 Hz, 2H), 7.54 (d, *J*=8.0 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 7.46 (d, *J*=8.5 Hz, 2H), 7.26 (td, *J*=1.0, 8.0 Hz, 1H), 7.16 (dd, *J*=1.0, 8.0 Hz, 1H), 5.50 (d, *J*=6.5 Hz, 1H), 5.14 (ddd, *J*=1.5, 4.5, 11.5 Hz, 1H), 3.47 (d, *J*=6.0 Hz, 1H), 3.28–3.18 (m, 2H), 2.97–2.84 (m, 3H), 2.80–2.73 (m, 1H), 2.51 (s, 3H), 2.38 (dt, *J*=1.5, 16.0 Hz, 1H), 2.20–2.15 (m, 1H), 1.42–1.26 (m, 4H), 1.16–1.09 (m, 1H), 1.02–0.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.13, 146.45, 136.39, 132.78, 131.44, 130.50 (2×), 128.97 (2×), 126.22, 122.61, 119.86, 118.41, 111.60, 110.55, 69.50, 49.26, 44.27, 40.20, 34.40, 33.16, 32.65, 31.40, 23.66, 21.78, 20.53; Anal. Calcd for $C_{26}H_{30}N_2O_4S$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.33; H, 6.54; N, 5.83.

4.3.4. 1-(4-Methylphenyl)sulfonyl-2-(4-benzoyloxy)butyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2d). Mp 141–142 °C; IR ($CHCl_3$) 3250, 1630 cm^{-1}; FAB-MS: $C_{33}H_{36}N_2O_4S$ *m/z* (%)=91 (100), 136 (66), 154 (61), 237 (52), 309 (14), 401 (4), 557 (M^++1, 7); HRMS (ESI, M^++1) calcd for $C_{33}H_{37}N_2O_4S$ 557.2474, found 557.2470; ^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (br s, 1H), 7.82 (d, *J*=8.4 Hz, 2H), 7.52 (d, *J*=7.8 Hz, 1H), 7.44 (d, *J*=8.3 Hz, 1H), 7.39 (d, *J*=8.4 Hz, 1H), 7.36–7.12 (m, 7H), 5.47 (d, *J*=6.5 Hz, 1H), 5.12 (dt, *J*=2.9, 12.7 Hz, 1H), 4.31 (s, 2H), 3.46 (d, *J*=6.5 Hz, 1H), 3.16 (t, *J*=6.3 Hz, 2H), 2.91 (td, *J*=3.6, 12.1 Hz, 1H), 2.84–2.74 (m, 3H), 2.44 (s, 3H), 2.36 (d, *J*=15.6 Hz, 1H), 2.15–2.13 (m, 1H), 1.28–1.07 (m, 4H), 0.94–0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.20, 146.25, 138.37, 136.45, 132.97, 131.58, 130.45, 130.41, 130.12, 129.01 (2×), 128.36 (2×), 127.58, 127.56, 126.33, 122.59, 119.86, 118.45, 111.62, 110.54, 72.92, 69.61, 68.64, 49.36, 40.28, 34.24, 33.76, 32.67, 28.89, 23.04, 21.75, 20.57; Anal. Calcd for $C_{33}H_{35}N_2O_4S$: C, 71.19; H, 6.52; N, 5.03. Found: C, 71.33; H, 6.82; N, 5.44.

4.3.5. 1-(4-Methylphenyl)sulfonyl-2-(4-methylsulfonyl)-butyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2e). Mp 211–212 °C; IR ($CHCl_3$) 3230, 1640 cm^{-1}; FAB-MS: $C_{27}H_{32}N_2O_6S_2$ *m/z* (%)=136 (60), 154 (61), 237 (100), 389 (9), 545 (M^++1, 19); HRMS (ESI, M^++1) calcd for $C_{27}H_{33}N_2O_6S_2$ 545.1780, found 545.1781; ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (br s, 1H), 7.87 (d, *J*=8.0 Hz, 2H), 7.53 (d, *J*=7.5 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 3H), 7.25 (td, *J*=1.0, 8.0 Hz, 1H), 7.15 (dd, *J*=1.0, 8.0 Hz, 1H), 5.50 (d, *J*=6.0 Hz, 1H), 5.14 (ddd, *J*=1.5, 4.5, 12.5 Hz, 1H), 3.93 (t, *J*=6.5 Hz, 2H), 3.51 (d, *J*=6.5 Hz, 1H), 2.97–2.75 (m, 4H), 2.84 (s, 3H), 2.51 (s, 3H), 2.37 (dt, *J*=2.0, 15.5 Hz, 1H), 1.39–1.26 (m, 4H), 1.16–1.09 (m, 1H), 1.00–0.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.89, 146.47, 136.36, 132.65, 131.39, 130.52 (2×), 128.89 (2×), 126.19, 122.54, 119.80, 118.34, 111.60, 110.43, 69.00, 68.13, 49.33, 40.26, 37.07, 34.17,

33.21, 32.54, 28.18, 22.25, 21.72, 20.48; Anal. Calcd for $C_{27}H_{32}N_2O_6S_2$: C, 59.54; H, 5.92; N, 5.14. Found: C, 58.96; H, 6.31; N, 4.70.

4.3.6. 1-(4-Methylphenyl)sulfonyl-2-dimethoxymethyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2f). Gum; IR ($CHCl_3$) 3330, 1618 cm^{-1}; ESI-MS: $C_{25}H_{28}N_2O_5S$ *m/z* (%)=75 (100), 237 (30), 468 (M^+, 2); HRMS (ESI, M^+) calcd for $C_{25}H_{28}N_2O_5S$ 468.1719, found 468.1719; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 7.86 (d, J=8.0 Hz, 2H), 7.52 (d, J=7.5 Hz, 1H), 7.46–7.42 (m, 3H), 7.24 (t, J=8.0 Hz, 1H), 7.14 (t, J=8.0 Hz, 1H), 5.50 (d, J=6.0 Hz, 1H), 5.16–5.12 (m, 1H), 3.99 (d, J=7.5 Hz, 1H), 3.95 (d, J=6.0 Hz, 1H), 3.08 (s, 3H), 2.95–2.89 (m, 1H), 2.85–2.76 (m, 3H), 2.79 (s, 3H), 2.54 (d, J=16.5 Hz, 1H), 2.48 (s, 3H), 2.41–2.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.64, 164.11, 136.35, 132.70, 131.22, 130.29 (2×), 129.16 (2×), 126.32, 122.40, 119.68, 118.37, 111.48, 110.67, 104.31, 64.03, 55.29, 53.54, 49.49, 40.53, 36.38, 30.59, 21.73, 20.54.

4.3.7. 1-(4-Methylphenyl)sulfonyl-2-ethoxycarbonyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2g). Gum; IR ($CHCl_3$) 3345, 2531 cm^{-1}; ESI-MS: $C_{25}H_{26}N_2O_5S$ *m/z* (%)=236 (100), 310 (41), 466 (M^+, 11); HRMS (ESI, M^+) calcd for $C_{25}H_{26}N_2O_5S$ 466.1562, found 466.1557; ^1H NMR (500 MHz, $CDCl_3$) δ 9.17 (br s, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.51 (d, J=8.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.0 Hz, 1H), 7.23 (t, J=7.5 Hz, 1H), 7.14 (t, J=7.5 Hz, 1H), 5.32 (d, J=8.0 Hz, 1H), 4.54 (dd, J=5.0, 13.0 Hz, 1H), 4.03–3.99 (m, 1H), 3.97 (q, J=7.0 Hz, 2H), 3.20–3.16 (m, 1H), 3.11–3.05 (m, 1H), 2.90–2.83 (m, 2H), 2.62 (dd, J=3.5, 13.5 Hz, 1H), 2.52 (s, 3H), 2.04 (dd, J=5.5, 13.5 Hz, 1H), 1.09 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.26, 169.26, 146.69, 136.21, 132.99, 130.69 (2×), 130.02, 129.44, 129.21 (2×), 126.54, 122.61, 119.76, 118.57, 111.47, 109.24, 67.46, 60.85, 52.21, 41.02, 38.43, 32.09, 21.81, 20.75.

4.3.8. 1-(4-Methylphenyl)sulfonyl-3-methyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2h). Mp 183–184 °C; IR ($CHCl_3$) 3230, 1630 cm^{-1}; EI-MS: $C_{23}H_{24}N_2O_3S$ *m/z* (%)=130 (74), 143 (100), 267 (4), 408 (M^+, 1); HRMS (EI, M^+) calcd for $C_{23}H_{24}N_2O_3S$ 408.1508, found 408.1507; ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (br s, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.52 (d, J=7.5 Hz, 1H), 7.46 (d, J=8.0 Hz, 2H), 7.45 (d, J=7.5 Hz, 1H), 7.24 (td, J=1.0, 8.0 Hz, 1H), 7.15 (dd, J=1.0, 8.0 Hz, 1H), 5.41 (d, J=8.0 Hz, 1H), 5.02–4.99 (m, 1H), 3.81 (dd, J=7.5, 14.0 Hz, 1H), 2.96–2.87 (m, 2H), 2.78–2.69 (m, 2H), 2.51 (s, 3H), 2.10–2.08 (m, 1H), 1.80–1.75 (m, 1H), 1.07 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.38, 146.29, 136.15, 132.51, 131.29, 130.41 (2×), 129.12 (2×), 126.33, 122.47, 119.71, 118.36, 111.55, 110.82, 62.46, 51.05, 42.02, 33.06, 28.75, 21.72, 20.48, 15.92; Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.87; H, 6.22; N, 6.99.

4.3.9. 1-(4-Methylphenyl)sulfonyl-2-phenyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2i). Mp>260 °C (decomp.); IR ($CHCl_3$) 3240, 1645 cm^{-1}; EI-MS: $C_{28}H_{26}N_2O_3S$ *m/z* (%)=91 (100), 169 (25), 223 (11), 314 (10), 470 (M^+, 1); HRMS (EI, M^+) calcd for $C_{28}H_{26}N_2O_3S$ 470.1664, found 470.1662; ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (br s, 1H), 7.79 (d, J=8.0 Hz, 2H), 7.55 (d, J=8.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H), 7.36 (d, J=8.0 Hz, 2H), 7.26 (td, J=1.0, 8.0 Hz, 1H), 7.17 (dd, J=1.0, 8.0 Hz, 1H), 7.07–7.03 (m, 3H), 6.79–6.77 (m, 2H), 5.65 (d, J=7.0 Hz, 1H), 5.11 (ddd, J=1.5, 6.0, 12.5 Hz, 1H), 4.14–4.11 (m, 1H), 3.59 (dd, J=5.0, 8.5 Hz, 1H), 3.05–2.97 (m, 2H), 2.90–2.80 (m, 2H), 2.62 (ddd, J=1.5, 5.0, 16.5 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.61, 146.05, 140.05, 136.50, 133.23, 131.44, 130.38 (2×), 128.83 (2×), 128.73 (2×), 127.25, 126.89 (2×), 126.41, 122.65, 119.89, 118.54, 111.62, 110.29, 68.76, 50.23, 41.02, 38.40, 36.84, 21.73, 20.31; Anal. Calcd for $C_{28}H_{26}N_2O_3S$: C, 71.46; H, 5.57; N, 5.95. Found: C, 71.66; H, 5.87; N, 6.33.

4.3.10. 3-Ethylidene-1-(4-methylphenyl)sulfonyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (2j). Mp>260 °C (decomp.); s: $C_{24}H_{24}N_2O_3S$ *m/z* (%)=91 (100), 169 (30), 249 (33), 264 (61), 420 (M^+, 5); HRMS (EI, M^+) calcd for $C_{24}H_{24}N_2O_3S$ 420.1508, found 420.1504; ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (br s, 1H), 7.91 (d, J=8.5 Hz, 2H), 7.49 (d, J=8.0 Hz, 1H), 7.48 (d, J=8.5 Hz, 2H), 7.41 (d, J=8.0 Hz, 1H), 7.21 (td, J=1.0, 8.0 Hz, 1H), 7.12 (td, J=1.0, 8.0 Hz, 1H), 6.78 (qd, J=1.5, 7.0 Hz, 1H), 5.38 (d, J=8.5 Hz, 1H), 4.89 (dd, J=4.5, 12.5 Hz, 1H), 3.74–3.69 (m, 1H), 3.13–3.06 (m, 1H), 3.01 (td, J=3.5, 12.0 Hz, 1H), 2.82 (dd, J=4.5, 13.5 Hz, 1H), 2.72 (d, J=13.5 Hz, 1H), 2.53 (s, 3H), 2.51–2.45 (m, 1H), 1.60 (dd, J=1.5, 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.25, 146.39, 135.92, 135.04, 132.24, 131.52, 130.36 (2×), 129.33 (2×), 126.41, 125.63, 122.46, 119.68, 118.38, 111.53, 111.05, 63.47, 52.59, 43.65, 24.07, 21.76, 20.37, 13.51; Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.55; H, 5.75; N, 6.66. Found: C, 68.37; H, 5.47; N, 6.83.

4.4. Reduction of compound 2f

Lithium aluminum hydride (20 mg, 0.5 mmol) was added to a solution of **2f** (94 mg, 0.2 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 2 h at rt, quenched with saturated ammonium chloride solution (1 mL) under cooling, and then concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude compound. Purification on silica gel (hexane/ethyl acetate=2/1–1/1) produced **6** (56 mg, 62%).

4.4.1. 1-(4-Methylphenyl)sulfonyl-2-dimethoxymethyl-2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine (6). ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 7.85 (d, J=9.0 Hz, 1H), 7.48 (d, J=6.0 Hz, 2H), 7.41–7.36 (m, 3H), 7.20–7.07 (m, 2H), 4.60 (br d, J=8.4 Hz, 1H), 4.41 (br s, 1H), 3.81 (br d, J=6.3 Hz, 1H), 3.16 (s, 3H), 3.09–2.54 (m, 6H), 2.88 (s, 3H), 2.45 (s, 3H), 2.21–2.05 (m, 2H), 1.87–1.84 (m, 1H) Single-crystal X-ray diagram:[13] crystal of **6** was grown by slow diffusion of ethyl acetate into a solution of **6** in dichloromethane to yield orange prisms. The compound crystallizes in the monoclinic crystal system, space group. $P2_1/n$(#14), a=13.701 (2)Å, b=9.718 (3)Å, c=17.823 (3)Å, β=100.81 (1)°, V=2330.8 (8) Å^3, Z=4, d_{calcd}=1.295 mg/m^3, $F(000)$=968.00, 2γ range 20 (8.7–14.0°), R=0.116.

4.5. Reduction of compound 2j

Sodium amalgam (Na/Hg, 300 mg) was added to a stirred solution of **2j** (210 mg, 0.5 mmol) in methanol (15 mL), and vigorously stirred for 2 h at rt The residue was filtered and washed with methanol (2×10 mL). The combined organic layers were concentrated to obtain the crude products. Without further purification, lithium aluminum hydride (20 mg, 0.5 mmol) was added to a solution of the resulting compound in THF (10 mL) at 0 °C. The mixture was stirred for 2 h at rt, quenched with saturated ammonium chloride solution (1 mL) under cooling, and then concentrated. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×30 mL). The organic layer was washed with brine and water, dried, filtered and concentrated to produce crude compound. The crude products were slowly recrystallized sequentially from the mixture by the solvent system of hexane and ethyl acetate (v/v=1/3–1/1) to yield **1a** (50 mg, 40%) and **7** (13 mg, 10%).

4.5.1. (*E*)-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydro indolo[2,3-*a*]quinolizidine (1a), (deplancheine).[10,11] EI-MS: $C_{17}H_{20}N_2$ *m/z* (%)=108 (100), 143 (25), 158 (16), 252 (M^+, 34); HRMS (EI, M^+) calcd for $C_{17}H_{20}N_2$ 252.1621, found 252.1622; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.47 (d, J=7.0 Hz, 1H), 7.29 (d, J=7.5 Hz, 1H), 7.14–7.08 (m, 2H), 5.38 (br d, J=3.5 Hz, 1H), 3.29 (br d, J=12.0 Hz, 1H), 3.16 (br d, J=12.0 Hz, 1H), 3.07–3.03 (m, 2H), 2.99–2.91 (m, 3H), 2.70 (dd, J=6.0, 16.0 Hz, 1H), 2.59 (br s, 1H), 2.39 (t, J=11.0 Hz, 1H), 2.32–2.27 (m, 1H), 1.61 (d, J=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.31, 134.49, 134.32, 128.82, 121.05, 119.29, 117.54, 114.93, 112.72, 110.42, 63.87, 63.61, 55.51, 36.48, 35.03, 24.55, 14.39. The ^{1}H NMR spectral data of **1a** were in accordance with those reported in the literature.

4.5.2. *Trans*-3-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine (7).[14j] EI-MS: $C_{17}H_{22}N_2$ *m/z* (%)=118 (29), 169 (63), 225 (19), 253 (100), 254 (M^+, 76); HRMS (EI, M^+) calcd for $C_{17}H_{22}N_2$ 254.1778, found 254.1779; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (br s, 1H), 7.48 (d, J=7.5 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.13 (t, J=7.0 Hz, 1H), 7.09 (t, J=7.0 Hz, 1H), 3.15 (d, J=11.5 Hz, 1H), 3.12–3.00 (m, 3H), 2.73 (dd, J=4.5 Hz, 1H), 2.63 (td, J=4.5 Hz, 11.5 Hz, 1H), 2.09 (dq, J=3.0, 13.0 Hz, 1H), 2.02 (t, J=11.5 Hz, 1H), 1.94 (d, J=12.0 Hz, 1H), 1.71–1.64 (m, 1H), 1.58 (q, J=11.0 Hz, 1H), 1.32–1.23 (m, 2H), 1.12–1.04 (m, 1H), 0.95 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.99, 135.00, 127.36, 121.20, 119.27, 118.05, 110.73, 107.96, 61.70, 60.25, 53.44, 37.64, 30.73, 29.73, 27.25, 21.63, 11.33. The ^{1}H and ^{13}C NMR spectral data of **7** were in accordance with those reported in the literature.

4.6. Yohimban-21-one (9).[18m,s]

Sodium amalgam (Na/Hg, 300 mg) was added to a stirred solution of **2e** (163 mg, 0.3 mmol) in methanol (15 mL), and vigorously stirred for 2 h at rt The residue was filtered and washed with methanol (2×10 mL). The combined organic layers were concentrated to obtain the crude products. Initially, careful purification on silica gel (hexane/ethyl acetate=1/1) produced **8** (75 mg, 64%) as a viscous gum. HRMS (EI, M^+) calcd for $C_{20}H_{26}N_2O_4S$ 390.1613, found 390.1616; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.33 (d, J=7.8 Hz, 1H), 7.20–7.09 (m, 2H), 5.15–5.12 (m, 1H), 4.81–4.78 (m, 1H), 4.28–4.22 (m, 1H), 4.27 (t, J=6.0 Hz, 2H), 3.00 (s, 3H), 3.04–2.77 (m, 4H), 2.56–2.49 (m, 1H), 2.12–2.05 (m, 1H), 1.81–1.75 (m, 1H), 1.56–1.38 (m, 6H). The **8** (40 mg, 0.1 mmol), dissolved in dried THF (5 mL), was added a solution of lithium diisopropylamide (LDA) which was generated in situ from diisopropylamine (200 mg, 2.0 mmol) in dried THF (10 mL) and *n*-butyllithium (1.6 M, 1 mL, 1.6 mmol) at −78 °C. After storage of this mixture for 30 min, acetic acid (0.5 mL) in THF (5 mL) was added. The reaction mixture was stirred at −78 °C for an additional 5 min, and the reaction was quenched with saturated aqueous sodium bicarbonate (15 mL). The liquid layers were separated, and aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (ethyl acetate/methanol=20/1) produced **9** (18 mg, 60%). The ^{1}H NMR data was in accordance with the reported in the literature.

5. Supplementary Material

Additional spectroscopic data for compounds **3a–j**, **2a–j**, **6**, **7**, **8**, **1a** (^{1}H NMR in $CDCl_3$) were supported.

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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.2004.11.005

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Concise synthetic strategy toward cyclic α,α-disubstituted α-amino acids bearing a δ-nitrogen atom: chiral 1-substituted 4-aminopiperidine-4-carboxylic acids

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Abstract—A concise synthetic strategy toward cyclic α,α-disubstituted α-amino acids, 1-substituted 4-aminopiperidine-4-carboxylic acids have been developed. The synthetic route is a reductive amination of dimethyl bis(dioxolanemethyl)malonate with various amines, followed by Curtius rearrangement. This synthetic route is capable of synthesizing 4-aminopiperidine-4-carboxylic acids bearing a bulky substituent and optically active ones bearing a pendent chiral substituent, by the change of condensed amines.

1. Introduction

α,α-Disubstituted α-amino acids are non-proteinogenic amino acids,[1] and attract many synthetic, peptide, and medicinal chemists because of their characteristic properties such as biological activities, conformational restriction of side-chains, and the stable secondary structure of their peptides.[2] We have already reported an asymmetric synthesis of α-methylated and α-ethylated α,α-disubstituted α-amino acids,[3] and conformational study of their peptides.[4] Besides acyclic α-alkylated α,α-disubstituted α-amino acids, cyclic α,α-disubstituted α-amino acids (1-amino-cycloalkanecarboxylic acid; Ac_nc), in which the side-chain of the amino acids construct a cycloalkane-ring, have been reported.[1b,5] Among cyclic α,α-disubstituted α-amino acids, 4-aminopiperidine-4-carboxylic acid (Pip), which is an achiral α-amino acid bearing a δ-nitrogen atom, has been focused upon because of the anti-microbial activity of its helical peptides.[6] However so far, the Pip derivatives have just been synthesized from piperidone derivative, by the Strecker, or Bücherer–Bergs methods.[7] Herein, we describe a new concise synthetic route for various achiral and chiral 1-substituted 4-aminopiperidine-4-carboxylic acids. Some of them, especially chiral α,α-disubstituted α-amino acids are a new class of optically active cyclic α,α-disubstituted α-amino acids bearing a pendent chiral center, and they could not be easily prepared by the known synthetic route from 4-piperidone,[7] or from heterospirocyclic azirines as synthons (Fig. 1).[8]

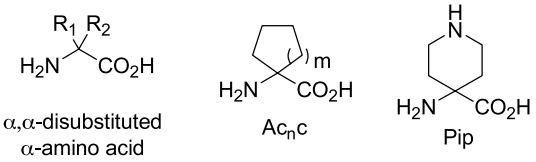

Figure 1. Acyclic and cyclic α,α-disubstituted α-amino acids.

2. Results and discussion

2.1. Synthetic strategy for Pip derivatives

At first, we envisaged that cyclic α,α-disubstituted α-amino acids (Pip derivatives) could be prepared from a bis-(formylmethyl)glycine derivative (ii) by reductive condensation with various amines. Also, it was thought that the dialdehyde (ii) could be prepared from protected intermediate (i). Unfortunately, several attempts to prepare the intermediate (i) from the protected glycines by bisalkylation failed. Next, we thought that cyclic diester intermediate (iv) could be converted into the Pip derivatives by Curtius rearrangement, and diester (iv) may be prepared by a reductive condensation of dimethyl bis(formylmethyl)-malonate (iii) and amines. Preparation of the intermediate (iii) was thought to be easier than that of glycine (ii) because the alkylated dimethyl malonate seemed to be stable (Scheme 1).

Keywords: Cyclic α,α-disubstituted α-amino acid; Piperidine; Curtius rearrangement; Unnatural amino acid; Chiral amino acid.
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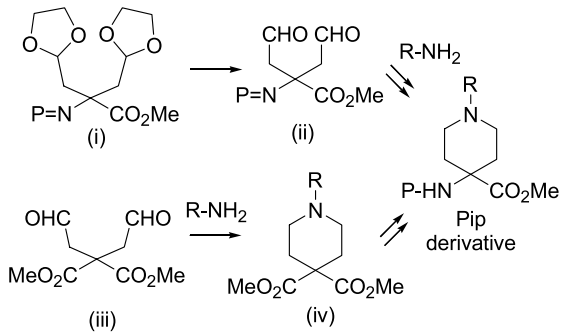
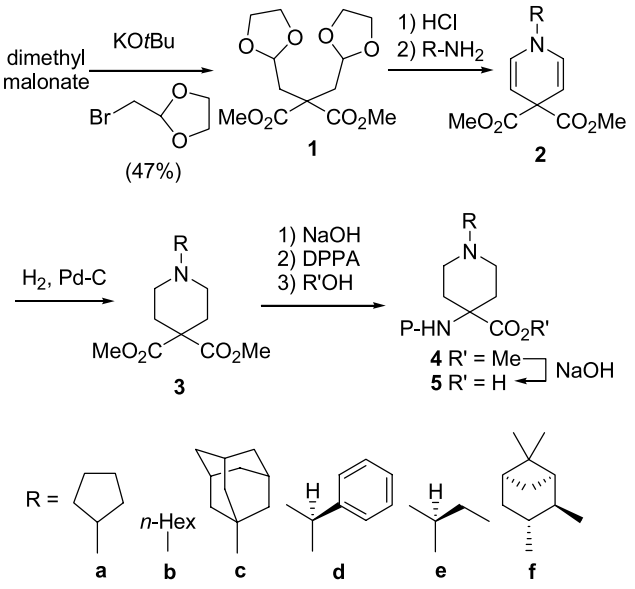


Scheme 1. Synthetic strategy for the Pip derivatives.

2.2. Preparation of achiral Pip derivatives

Bisalkylation of dimethyl malonate by treatment with KO*t*Bu and 2-bromomethyl-1,3-dioxolane in DMSO at 80 °C afforded a bis(dioxolanemethyl) diester **1** in 47% yield (Scheme 2).



Scheme 2. Synthetic scheme of various Pip derivatives.

The dioxolane group in **1** could be deprotected by 10% aqueous HCl to give a dialdehyde, which seemed to be unstable to purification by column chromatography on silica gel. Thus, the crude dialdehyde was subjected to the next reaction without purification. The deprotection of the dioxolane group, followed by condensation of the dialdehyde with cyclopentylamine, *n*-hexylamine, or 1-adamantanylamine afforded cyclic dienamines **2a** (57%), **2b** (55%), and **2c** (36%), respectively. The isolated dienamines **2a–c** were subjected to hydrogenation with Pd-C to afford the desired cyclic diesters **3a–c** in 73, 80 and 82% yields. Hydrolysis of the diester **3a–c** with aqueous NaOH gave monocarboxylic acids, and subsequent Curtius rearrangement using diphenylphosphoryl azide (DPPA),[9,3] followed by quenching with benzyl alcohol afforded Cbz-protected 1-cyclopentyl-Pip-OMe Cbz-**4a** (50%), 1-*n*-hexyl-Pip-OMe Cbz-**4b** (40%), and 1-adamantanyl-Pip-OMe Cbz-**4c** (50%), respectively. Work up with *t*-BuOH afforded a Boc-protected 1-cyclopentyl-Pip-OMe Boc-**4a** in 51% yield, and with 9-fluorenemethanol yielded a Fmoc-protected 1-cyclopentyl-Pip-OMe Fmoc-**4a** in 59% yield (Table 1).

Table 1. Preparation of various cyclic α,α-disubstituted α-amino acid; Pip derivatives **4**

Entry	Amine	Dienamine **2** % yield	Diester **3** % yield	Cbz-protected Pip-OMe **4** % yield
1	**a**	**2a**: 57	**3a**: 73	Cbz-**4a**: 50
2	**b**	**2b**: 55	**3b**: 80	Cbz-**4b**: 40
3	**c**	**2c**: 36	**3c**: 82	Cbz-**4c**: 50
4	**d**	**2d**: 60	**3d**: 67	Cbz-**4d**: 41
5	**e**	**2e**: 41	**3e**: 86	Cbz-**4e**: 61
6	**f**	**2f**: 56	**3f**: 76	Cbz-**4f**: 30

a: cyclopentylamine; **b**: *n*-hexylamine; **c**: 1-adamantanylamine; **d**: (*S*)-phenylethylamine; **e**: (*S*)-(+)-2-aminobutane; **f**: (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine.

2.3. Preparation of optically active Pip derivatives

The aforementioned strategy was applied to the synthesis of optically active cyclic α,α-disubstituted α-amino acids **4d–f** in which asymmetric carbons exist in the appendant substituent of amines. So far, no such chiral cyclic α,α-disubstituted α-amino acids have been designed, nor synthesized in optically active form. The crude dialdehyde prepared from **1** was condensed with chiral amines (*S*)-phenylethylamine **d**, (*S*)-2-aminobutane **e**, and (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine **f** to give dienamines **2d** (60%), **2e** (41%), and **2f** (56%), respectively. Hydrogenation of **2d–f** afforded the corresponding cyclic diesters **3d–f** in 67, 86 and 76% yields. Partial hydrolysis of the diesters, followed by Curtius rearrangement with DPPA[9] afforded optically active 1-substituted Pip-OMe **4d–f**. Work up with benzyl alcohol gave Cbz-protected Pip-OMe Cbz-**4d** (41%), Cbz-**4e** (61%), and Cbz-**4f** (30%), and with *t*-BuOH produced a Boc-protected 1-(*S*)-phenylethyl-Pip-OMe Boc-**4d** (43%). Furthermore, work up with concentrated HCl afforded an N-terminal free amine H_2N-1-(*S*)-phenylethyl-Pip-OMe H_2N-**4d** in 40% yield. The HPLC analysis of Cbz-(*S*)-**4d** using a chiral column indicated that no epimerization occurred in the synthetic sequences, and the enantiomeric excesses of Cbz-(*S*)-**4d** was >99% ee. Hydrolysis of the ester in Cbz-Pip-OMe **4d** afforded a C-terminal free cyclic α,α-disubstituted α-amino acid Cbz-protected 1-(*S*)-phenylethyl-Pip-OH **5d** (quant.).[10]

3. Conclusion

We succeeded in developing a concise synthetic route toward cyclic α,α-disubstituted α-amino acids bearing a δ-nitrogen atom. By using amines, it is possible to synthesize various 1-substituted 4-aminopiperidine-4-carboxylic acid derivatives. In particular, this strategy can be applied to the synthesis of optically active cyclic α,α-disubstituted α-amino acids bearing a pendent chirality,[11] which have not been designed nor synthesized so far. Application of the synthetic route to the combinatorial chemistry, and the use of cyclic α,α-disubstituted α-amino

acids having a pendent chiral moiety for the synthesis of peptide-foldamers[12] are currently underway in our group.

4. Experimental

4.1. General

^{1}H NMR spectra were determined at 270, 400 or 500 MHz. Infrared spectra were recorded on a NICOLET AVATAR-320 spectrometer. EIMS, FABMS, EI(+)HRMS and FAB(+)HRMS spectra were taken on a JEOL HMS 610H or JEOL SX102 spectrometer.

4.1.1. Dimethyl 2,2-bis(1,3-dioxolan-2-ylmethyl)malonate (1). A mixture of dimethyl malonate (4.33 mL, 37.9 mmol) and KO*t*Bu (5.10 g, 45.4 mmol) in DMSO (100 mL) was stirred at room temperature for 1 h. Then, 2-bromomethyl-1,3-dioxolane (4.7 mL, 45.4 mmol) was added, and the mixture was stirred at 80 °C for 12 h. The solution was cooled to room temperature, and then KO*t*Bu (5.10 g, 45.4 mmol) was added, and stirred for 1 h. 2-Bromomethyl-1,3-dioxolane (4.7 mL, 45.4 mmol) was added again, and the solution was stirred at 80 °C for 12 h. The solution was diluted with H_2O, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (40% EtOAc in hexane) to give **1** (5.25 g, 47%) as colorless crystals: mp 36–37 °C; IR (KBr) 2955, 2891, 1738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (t, J=4.8 Hz, 2H), 3.89–3.93 (m, 4H), 3.78–3.82 (m, 4H), 3.71 (s, 6H), 2.45 (d, J=4.8 Hz, 4H); EI-MS m/z 305 (M^+, 1), 273 (2), 215 (2), 73 (100); FAB(+)HRMS calcd for $C_{13}H_{21}O_8$ ($[M+H]^+$) 305.1236, found 305.1241.

4.1.2. 1-Cyclopentyl-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2a). A solution of **1** (1.0 g, 3.29 mmol) in 10% aqueous HCl (20 mL) and THF (20 mL) was stirred at room temperature for 12 h. The solution was neutralized with powdered $NaHCO_3$, and then cyclopentylamine (280 mg, 3.29 mmol) in THF (5 mL) was added. After being stirred at room temperature for 3 h, the solution was extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (15% EtOAc in hexane) to give **2a** (497 mg, 57%) as colorless crystals: mp 41–42 °C; IR (KBr) 2955, 2874, 1734, 1676, 1599, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (d, J=8.1 Hz, 2H), 4.74 (d, J=8.1 Hz, 2H), 3.73 (s, 6H), 3.56 (quintet, J=7.0 Hz, 1H), 1.85–1.89 (m, 2H), 1.66–1.69 (m, 2H), 1.51–1.60 (m, 4H); FAB(+)HRMS calcd for $C_{14}H_{20}NO_4$ ($[M+H]^+$) 266.1392, found 266.1392.

4.1.3. 1-Hexyl-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2b). Compound **2b** was prepared from **1** and *n*-hexylamine in a manner similar to that described for the preparation of **2a**. **2b**: 55%. A colorless oil; IR (neat) 2953, 2928, 2858, 1736, 1679, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (d, J=7.9 Hz, 2H), 4.71 (d, J=7.9 Hz, 2H), 3.73 (s, 6H), 3.08 (t, J=7.2 Hz, 2H), 1.50 (quintet, J=6.8 Hz, 2H), 1.26–1.32 (m, 6H), 0.88 (t, J=6.8 Hz, 3H); FAB(+)HRMS calcd for $C_{15}H_{24}NO_4$ ($[M+H]^+$) 282.1705, found 282.1710.

4.1.4. 1-Adamantanyl-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2c). Compound **2c** was prepared from **1** and adamantanylamine in a manner similar to that described for the preparation of **2a**. **2c**: 36%. Colorless crystals; mp 155–156 °C (recryst from $CHCl_3$); IR (KBr) 2911, 2852, 1734, 1674, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (d, J=8.3 Hz, 2H), 4.72 (d, J=8.3 Hz, 2H), 3.72 (s, 6H), 2.14 (br s, 3H), 1.80 (br d, J=2.4 Hz, 6H), 1.68 (br d, J=12.1 Hz, 3H), 1.61 (br d, J=12.1 Hz, 3H) FAB(+) HRMS calcd for $C_{19}H_{26}NO_4$ ($[M+H]^+$) 332.1862, found 332.1860.

4.1.5. 1-[(1*S*)-Phenylethyl]-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2d). Compound **2d** was prepared from **1** and (*S*)-phenylethylamine in a manner similar to that described for the preparation of **2a**. **2d**: 60%. A colorless oil; $[\alpha]_D^{28}=-7.53$ (*c* 0.95, $CHCl_3$); IR (neat) 2978, 2954, 2902, 1739 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.22–7.37 (m, 5H), 6.18 (d, J=8.0 Hz, 2H), 4.77 (d, J=8.0 Hz, 2H), 4.45 (q, J=6.9 Hz, 1H), 3.73 (s, 6H), 1.56 (d, J=6.9 Hz, 3H); EI-MS m/z 302 (M^++H), 6), 289 (51), 273 (24), 245 (83), 199 (70), 185 (74), 139 (93), 97 (93), 59 (100); FAB(+)HRMS calcd for $C_{17}H_{20}NO_4$ ($[M+H]^+$) 302.1392, found 302.1397.

4.1.6. 1-[(1*S*)-1-Methylpropyl]-4,4-bis(methoxy-carbonyl)-1,4-dihydropyridine (2e). Compound **2e** was prepared from **1** and (*S*)-2-aminobutane in a manner similar to that described for the preparation of **2a**. **2e**: 41%. A colorless oil; $[\alpha]_D^{25}=+12.5$ (*c* 0.94, $CHCl_3$); IR (neat) 2967, 2877, 1737, 1677, 1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (d, J=7.7 Hz, 2H), 4.72 (d, J=7.7 Hz, 2H), 3.73 (s, 6H), 3.06 (m, 1H), 1.43–1.53 (m, 2H), 1.16 (d, J=6.7 Hz, 3H), 0.86 (t, J=7.4 Hz, 3H); FAB(+)HRMS calcd for $C_{13}H_{20}NO_4$ ($[M+H]^+$) 254.1392, found 254.1388.

4.1.7. 1-[(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl]-4,4-bis-(methoxycarbonyl)-1,4-dihydropyridine (2f). Compound **2f** was prepared from **1** and (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine in a manner similar to that described for the preparation of **2a**. **2f**: 56%. Colorless crystals; mp 80–81 °C (recryst from $CHCl_3$–MeOH); $[\alpha]_D^{23}=-22.5$ (*c* 0.70, $CHCl_3$); IR (KBr) 2985, 2972, 2935, 2893, 1733, 1675, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, J=8.1 Hz, 2H), 4.77 (d, J=8.1 Hz, 2H), 3.73 (s, 6H), 3.48 (td, J=7.6, 10.1 Hz, 1H), 2.40 (m, 1H), 2.32 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.75–1.83 (m, 2H), 1.23 (s, 3H), 1.04 (d, J=7.1 Hz, 3H), 1.00 (s, 3H), 0.92 (d, J=10.1 Hz, 1H); FAB(+)HRMS calcd for $C_{19}H_{28}NO_4$ ($[M+H]^+$) 334.2018, found 334.2019. Anal. Calcd for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16; N 4.20. Found: C, 68.21; H, 8.16; N, 4.20.

4.1.8. 1-Cyclopentyl-4,4-bis(methoxycarbonyl)piperidine (3a). A mixture of **2a** (213 mg, 0.80 mmol) and 5% Pd-C (100 mg) in MeOH (10 mL) was vigorously stirred under H_2 atmosphere for 12 h. The Pd-catalyst was filtered off, and the filtrate was evaporated to leave an oily residue. Purification by column chromatography on silica gel (EtOAc) gave **3a** (159 mg, 73%) as colorless crystals; mp 59–60 °C (recryst from $CHCl_3$); IR (KBr) 3446, 2963, 2869,

2806, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 6H), 2.40–2.46 (m, 5H), 2.17 (t, $J=5.6$ Hz, 4H), 1.80–1.86 (m, 2H), 1.63–1.71 (m, 2H), 1.50–1.57 (m, 2H), 1.33–1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 67.4, 53.2, 52.5, 49.4, 30.8, 30.5, 24.1; FAB(+)HRMS calcd for $C_{14}H_{24}NO_4$ ($[M+H]^+$) 270.1705, found 270.1705. Anal. Calcd for $C_{14}H_{24}O_4N$: C, 62.43; H, 8.61; N 5.20. Found: C, 62.59; H, 8.60; N, 5.09.

4.1.9. 1-Hexyl-4,4-bis(methoxycarbonyl)piperidine (3b). Compound **3b** was prepared from **2b** in a manner similar to that described for the preparation of **3a**. **3b**: 80%. A colorless oil; IR (neat) 2952, 2930, 2857, 2812, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 6H), 2.41 (br m, 4H), 2.27 (t, $J=7.7$ Hz, 2H), 2.16 (t, $J=4.8$ Hz, 4H), 1.45 (m, 2H), 1.27–1.30 (m, 6H), 0.88 (t, $J=7.2$ Hz, 3H); FAB(+)HRMS calcd for $C_{15}H_{28}NO_4$ ($[M+H]^+$) 286.2018, found 286.2014.

4.1.10. 1-Adamantanyl-4,4-bis(methoxycarbonyl)piperidine (3c). Compound **3c** was prepared from **2c** in a manner similar to that described for the preparation of **3a**. **3c**: 82%. Colorless crystals; mp 68–69 °C (recryst from $CHCl_3$–MeOH); IR (KBr) 2905, 2849, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.71 (s, 3H), 2.62 (br s, 4H), 2.14 (br s, 4H), 2.07 (br s, 3H), 1.67 (br s, 6H), 1.64 (br d, $J=12.0$ Hz, 3H), 1.58 (br d, $J=12.0$ Hz, 3H); FAB(+)HRMS calcd for $C_{19}H_{30}NO_4$ ($[M+H]^+$) 336.2175, found 336.2179.

4.1.11. 1-[(1*S*)-Phenylethyl]-4,4-bis(methoxycarbonyl)-piperidine (3d). Compound **3d** was prepared from **2d** in a manner similar to that described for the preparation of **3a**. **3d**: 67%. A colorless oil; $[\alpha]_D^{24}=-15.4$ (*c* 0.30, $CHCl_3$); IR (neat) 3026, 2972, 2953, 2811, 1733 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.21–7.30 (m, 5H), 3.71 (s, 6H), 3.31 (q, $J=6.7$ Hz, 1H), 2.31–2.47 (m, 4H), 2.12 (t, $J=5.6$ Hz, 4H), 1.32 (d, $J=6.7$ Hz, 3H); EI-MS *m/z* 306 (M^++H, 21), 305 (M^+, 14), 291 (59), 290 (100), 228 (52); FAB(+)HRMS calcd for $C_{17}H_{24}NO_4$ ($[M+H]^+$) 306.1705, found 306.1701.

4.1.12. 1-[(1*S*)-1-Methylpropyl]-4,4-bis(methoxy-carbonyl)piperidine (3e). Compound **3e** was prepared from **2e** in a manner similar to that described for the preparation of **3a**. **3e**: 86%. A colorless oil; $[\alpha]_D^{28}=+9.91$ (*c* 0.91, $CHCl_3$); IR (neat) 2961, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 6H), 2.48–2.54 (m, 2H), 2.38–2.46 (m, 3H), 2.10–2.16 (m, 4H), 1.51 (m, 1H), 1.25 (m, 1H), 0.92 (d, $J=6.6$ Hz, 3H), 0.87 (t, $J=7.4$ Hz, 3H); FAB(+)HRMS calcd for $C_{13}H_{24}NO_4$ ($[M+H]^+$) 258.1705, found 258.1710.

4.1.13. 1-[(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl]-4,4-bis-(methoxycarbonyl)piperidine (3f). Compound **3f** was prepared from **2f** in a manner similar to that described for the preparation of **3a**. **3f**: 76%. Colorless crystals; mp 69–70 °C (recryst from $CHCl_3$–MeOH); $[\alpha]_D^{24}=-24.2$ (*c* 1.60, $CHCl_3$); IR (KBr) 2992, 2935, 2873, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 6H), 2.86 (td, $J=6.4$, 9.9 Hz, 1H), 2.51–2.61 (m, 4H), 2.22 (m, 1H), 2.15 (t, $J=5.4$ Hz, 4H), 1.98–2.06 (m, 2H), 1.90 (m, 1H), 1.74–1.80 (m, 2H), 1.18 (s, 3H), 1.06 (d, $J=7.1$ Hz, 3H), 0.97 (s, 3H), 0.87 (d, $J=9.5$ Hz, 1H); FAB(+)HRMS calcd for $C_{19}H_{32}NO_4$ ($[M+H]^+$) 338.2331, found 338.2328. Anal. Calcd for $C_{19}H_{31}O_4N$: C, 67.63; H, 9.26; N 4.15. Found: C, 67.59; H, 9.26; N, 4.14.

4.1.14. Methyl 1-cyclopentyl-4-(benzyloxycarbonyl-amino)piperidine-4-carboxylate (Cbz-4a). A solution of **3a** (200 mg, 0.743 mmol) and 0.1 N aqueous NaOH (7.43 mL, 0.743 mmol) in MeOH (7 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of H_2O in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, diphenylphosphoryl azide (DPPA, 0.192 mL, 0.89 mmol), Et_3N (0.124 mL, 0.891 mmol), and BnOH (0.092 mL, 0.891 mmol) in benzene (7 mL) was refluxed for 6 h. After removal of the solvent, the oily residue was purified by column chromatography (EtOAc) to afford Cbz-**4a** (133 mg, 50%) as colorless crystals: mp 78–79 °C (recryst from $CHCl_3$–MeOH); IR (KBr) 3331, 2951, 2870, 2814, 1735, 1715, 1690, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.34 (m, 5H), 5.09 (s, 2H), 5.02 (s, 1H), 3.68 (br s, 3H), 2.75–2.85 (m, 2H), 2.50 (quintet, $J=7.9$ Hz, 1H), 2.15–2.30 (m, 4H), 2.01 (m, 2H), 1.84 (m, 2H), 1.63–1.73 (m, 2H), 1.54 (m, 2H), 1.40 (m, 2H); FAB(+)HRMS calcd for $C_{20}H_{29}N_2O_4$ ($[M+H]^+$) 361.2127, found 361.2128.

4.1.15. Methyl 1-hexyl-4-(benzyloxycarbonylamino)-piperidine-4-carboxylate (Cbz-4b). Compound Cbz-**4b** was prepared from **3b** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4b**: 40%. A colorless oil; IR (neat) 3348 (br), 2953, 2930, 2857, 1739, 1716, 1522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.34 (m, 5H), 5.09 (s, 2H), 5.02 (s, 1H), 3.68 (br s, 3H), 2.71 (m, 2H), 2.31 (t, $J=7.7$ Hz, 2H), 2.12–2.28 (m, 4H), 2.01 (m, 2H), 1.49 (m, 2H), 1.25–1.36 (m, 6H), 0.88 (t, $J=6.5$ Hz, 3H); FAB(+)HRMS calcd for $C_{21}H_{33}N_2O_4$ ($[M+H]^+$) 377.2440, found 377.2445.

4.1.16. Methyl 1-adamantanyl-4-(benzyloxycarbonyl-amino)piperidine-4-carboxylate (Cbz-4c). Compound Cbz-**4c** was prepared from **3c** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4c**: 50%. Colorless crystals; mp 112–113 °C; IR ($CDCl_3$) 3438 (br), 2908, 2853, 1736, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.39 (m, 5H), 5.09 (s, 2H), 4.95 (br s, 1H), 3.68 (br s, 3H), 2.90 (m, 2H), 2.42 (br t, $J=10.8$ Hz, 2H), 1.97–2.18 (m, 7H), 1.73 (br s, 6H), 1.68–1.74 (m, 6H), 1.59 (d, $J=12.1$ Hz, 3H), 1.67 (d, $J=12.1$ Hz, 3H); FAB(+)HRMS calcd for $C_{25}H_{35}N_2O_4$ ($[M+H]^+$) 427.2597, found 427.2599.

4.1.17. Methyl 1-[(1*S*)-phenylethyl]-4-(benzyloxy-carbonylamino)piperidine-4-carboxylate (Cbz-4d). Compound Cbz-**4d** was prepared from **3d** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4d**: 41%. A colorless oil; $[\alpha]_D^{25}=-23.2$ (*c* 0.49, $CHCl_3$); IR (neat) 3346 (br), 3030, 2952, 2815, 1732, 1710, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22–7.37 (m, 10H), 5.02 (s, 2H), 4.91 (br s, 1H), 3.67 (br s, 3H), 3.41 (q, $J=6.4$ Hz, 1H), 2.83 (m, 1H), 2.62 (m, 1H), 2.11–2.25 (m, 4H), 2.05 (m, 1H), 1.93 (m, 1H), 1.36 (d, $J=6.4$ Hz, 3H); EI-MS *m/z* 396 (M^+, 5), 381 (57), 319 (8), 291 (47), 273 (12), 140 (97), 105

(41), 91 (100); FAB(+)HRMS calcd for $C_{23}H_{29}N_2O_4$ ($[M+H]^+$) 397.2127, found 397.2126; HPLC analysis: column, Chiralcel OD 0.46$\phi\times$25 cm; eluent, 5% *iso*-PrOH in hexane; flow rate, 1 mL/min; detection, $UV_{254\ nm}$; retention time (t_R), Cbz-(±)-**4d**: 36 and 42 min, Cbz-(*S*)-**4d**: 42 min.

4.1.18. Methyl 1-[(1*S*)-1-methylpropyl]-4-(benzyloxycarbonylamino)piperidine-4-carboxylate (Cbz-4e). Compound Cbz-**4e** was prepared from **3e** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4e**: 61%. A colorless oil; $[\alpha]_D^{25}=+8.75$ (*c* 1.0, $CHCl_3$); IR (neat) 3350 (br), 2961, 1739, 1715, 1523 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.35 (m, 5H), 5.09 (s, 2H), 4.93 (br s, 1H), 3.69 (br s, 3H), 2.60–2.65 (m, 2H), 2.42–2.51 (m, 2H), 2.36 (m, 1H), 2.10–2.20 (m, 2H), 1.98–2.01 (m, 2H), 1.54 (m, 1H), 1.26 (m, 1H), 0.96 (d, $J=6.6$ Hz, 3H), 0.88 (t, $J=7.4$ Hz, 3H); FAB(+)HRMS calcd for $C_{19}H_{29}N_2O_4$ ($[M+H]^+$) 349.2127, found 349.2130.

4.1.19. Methyl 1-[(1*R*,2*R*,3*R*,5S)-isopinocampheyl]-4-(benzyloxycarbonylamino)piperidine-4-carboxylate (Cbz-4f). Compound Cbz-**4f** was prepared from **3f** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4f**: 30%. Colorless crystals; mp 106–107 °C (recryst from MeOH); $[\alpha]_D^{24}=-21.7$ (*c* 0.89, $CHCl_3$); IR (KBr) 3356, 2952, 2920, 1735, 1712, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.36 (m, 5H), 5.09 (s, 2H), 4.97 (br s, 1H), 3.69 (br s, 3H), 2.90 (td, $J=6.4$, 4.5 Hz, 1H), 2.78 (br t, $J=11.4$ Hz, 2H), 2.47 (td, $J=10.9$, 21.8 Hz, 2H), 2.13–2.25 (m, 3H), 1.92–2.09 (m, 6H), 1.76–1.84 (m, 2H), 1.19 (s, 3H), 1.08 (d, $J=6.9$ Hz, 3H), 0.97 (s, 3H), 0.88 (d, $J=9.6$ Hz, 1H); FAB(+)HRMS calcd for $C_{25}H_{37}N_2O_4$ ($[M+H]^+$) 429.2753, found 429.2758.

4.1.20. Methyl 1-cyclopentyl-4-(t-butoxycarbonylamino)piperidine-4-carboxylate (Boc-4a). A solution of **3a** (254 mg, 0.943 mmol) and 0.1 N aqueous NaOH (9.43 mL, 0.743 mmol) in MeOH (10 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of H_2O in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, DPPA (0.447 mL, 2.08 mmol), Et_3N (0.158 mL, 1.13 mmol) in *t*-BuOH (10 mL) was refluxed for 6 h. After removal of the solvent, the oily residue was purified by column chromatography (4% MeOH in $CHCl_3$) to afford Boc-**4a** (156 mg, 51%) as a colorless oil: IR (neat) 3354 (br), 2956, 1732, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (br s, 1H), 3.72 (s, 3H), 2.80 (br d, $J=12.2$ Hz, 2H), 2.54 (quintet, $J=7.8$ Hz, 1H), 2.29 (m, 2H), 2.18 (dt, $J=3.1$, 12.2 Hz, 2H), 1.97 (br d, $J=12.7$ Hz, 2H), 1.82–1.89 (m, 2H), 1.64–1.72 (m, 2H), 1.49–1.59 (m, 2H), 1.37–1.45 (m, 2H), 1.43 (s, 9H); FAB(+)HRMS calcd for $C_{17}H_{31}N_2O_4$ ($[M+H]^+$) 327.2284, found 327.2279.

4.1.21. Methyl 1-[(1*S*)-phenylethyl]-4-(*t*-butoxycarbonylamino)piperidine-4-carboxylate (Boc-4d). Compound Boc-**4d** was prepared from **3d** in a manner similar to that described for the preparation of Boc-**4a**. Boc-**4d**: 43%. A colorless oil; $[\alpha]_D^{26}=-18.2$ (*c* 0.68, $CHCl_3$); IR (neat) 3367 (br), 2975, 2813, 1740, 1705, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, $J=4.3$ Hz, 4H), 7.23 (m, 1H), 4.61 (br s, 1H), 3.71 (s, 3H), 3.38 (q, $J=6.6$ Hz, 1H), 2.84 (m, 1H), 2.59 (m, 1H), 2.08–2.26 (m, 4H), 1.97 (m, 1H), 1.87 (m, 1H), 1.42 (s, 9H), 1.34 (d, $J=6.6$ Hz, 3H); FAB(+)HRMS calcd for $C_{20}H_{31}N_2O_4$ ($[M+H]^+$) 363.2284, found 363.2282.

4.1.22. Methyl 1-cyclopentyl-4-[(9-fluorenylmethoxycarbonyl)amino]piperidine-4-carboxylate (Fmoc-4a). A solution of **3a** (124 mg, 0.460 mmol)) and 0.1 N aqueous NaOH (4.60 mL, 0.460 mmol) in MeOH (10 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of H_2O in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, DPPA (0.119 mL, 0.553 mmol), and Et_3N (0.077 mL, 0.553 mmol) in benzene (3 mL) was refluxed for 1 h. Then, 9-fluorenylmethanol (108 mg, 0.553 mmol) was added, and the solution was refluxed for 5 h. After removal of the solvent, the oily residue was purified by column chromatography (4% MeOH in $CHCl_3$) to afford Fmoc-**4a** (121 mg, 59%) as colorless crystals; mp 160 °C (decomp.); IR (KBr) 3371 (br), 2953, 2867, 1729, 1605, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (br d, $J=7.5$ Hz, 2H), 7.59 (br d, $J=7.5$ Hz, 2H), 7.40 (br t, $J=7.5$ Hz, 2H), 7.31 (br t, $J=7.5$ Hz, 2H), 4.93 (s, 1H), 4.42 (d, $J=6.5$ Hz, 2H), 4.23 (t, $J=6.5$ Hz, 1H), 3.68 (br s, 3H), 2.71–2.82 (m, 2H), 2.51 (quintet, $J=8.0$ Hz, 1H), 2.11–2.29 (m, 4H), 1.91–2.09 (m, 2H), 1.84–1.86 (m, 2H), 1.65–1.73 (m, 2H), 1.54–1.60 (m, 2H), 1.35–1.44 (m, 2H); FAB(+)HRMS calcd for $C_{27}H_{33}N_2O_4$ ($[M+H]^+$) 449.2440, found 449.2436.

4.1.23. Methyl 1-[(1*S*)-phenylethyl]-4-aminopiperidine-4-carboxylate (H_2N-4d). A solution of **3d** (200 mg, 0.655 mmol) and 0.1 N aqueous NaOH (6.55 mL, 0.655 mmol) in MeOH (8 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of H_2O in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, DPPA (0.169 mL, 0.786 mmol), and Et_3N (0.110 mL, 0.786 mmol) in benzene (5 mL) was refluxed for 2 h. Removal of the solvent afforded an oily residue, which was dissolved in 10% aqueous HCl (3 mL), and stirred at room temperature for 1 h. Then, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent and purification by column chromatography afforded H_2N-**4d** (69 mg, 40%) as a colorless oil: $[\alpha]_D^{26}=-14.9$ (*c* 1.70, $CHCl_3$); IR (neat) 3375 (br), 3305 (br), 2951, 2816, 1729, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.32 (m, 5H), 3.70 (s, 6H), 3.41 (q, $J=6.7$ Hz, 1H), 2.60 (m, 1H), 2.42–2.52 (m, 3H), 2.03–2.15 (m, 2H), 1.63 (br s, 2H), 1.48–1.57 (m, 2H), 1.36 (d, $J=6.7$ Hz, 3H); FAB(+)HRMS calcd for $C_{15}H_{23}N_2O_2$ ($[M+H]^+$) 263.1760, found 263.1758.

4.1.24. 1-[(1*S*)-Phenylethyl]-4-(benzyloxycarbonylamino)piperidine-4-carboxylic acid (5d). 0.1 N Aqueous NaOH solution (1.6 mL) was added to the stirred solution of Cbz-**4d** (41 mg, 0.105 mmol) in MeOH (1 mL), and the whole was refluxed for 6 h. After evaporation of MeOH, the aqueous solution was washed with hexane, neutralized with 5% aqueous HCl, and the solution was concentrated in vacuo. The residue was dissolved in MeOH, and filtered. Evaporation of MeOH afforded an acid **5d** (40 mg, quant.) as a yellowish powder: $[\alpha]_D^{25}=-25.8$ (*c* 0.66, $CHCl_3$); IR

(KBr) 3307 (br), 1705, 1588 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.21–7.40 (m, 10H), 5.01 (s, 2H), 3.45 (q, J= 6.9 Hz, 1H), 2.89 (m, 1H), 2.60 (m, 1H), 2.20–2.35 (m, 2H), 1.90–2.20 (m, 4H), 1.39 (d, J=6.9 Hz, 3H); FAB(+)MS *m/z* 405 ($[M+Na]^+$), 383 ($[M+H]^+$); FAB(+)HRMS calcd for $C_{22}H_{27}N_2O_4$ ($[M+H]^+$) 383.1971 found 383.1952.

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Enantiospecific access to 10-*N*-substituted camphors

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Dedicated to Professor Jose L. Soto, our dear colleague, on the occasion of his retirement

Abstract—A general and straightforward enantiospecific access to synthetically valuable 10-*N*-substituted camphors (amines and secondary amides) has been developed. The synthetic method uses camphor as the starting enantiopure material and takes place in five individual steps with a high overall yield. The process involves a stereocontrolled double-Wagner–Meerwein-rearrangement strategy to generate key-intermediate 10-(triflyloxy)camphor, a peculiar and highly-reactive primary triflate, which is able to alkylate soft *N*-nucleophiles, such as amines and nitriles, easily and without producing Grob-like fragmentation of the β-(triflyloxy)ketone-based norbornane system.

1. Introduction

Among the great number of well known chirality-transfer agents based on 10-substituted camphor **1(X)**,[1,2] the 10-*N*-substituted one constitute an interesting new family, whose members have been used as valuable chiral auxiliaries (e.g. Chen's cyclohydrazide **2**[3]) and chiral catalysts (e.g. aminal **3**,[4] or bisamide **4**[5]), (Fig. 1). Additionally, some members of this class of camphor derivatives show interesting biological activities with application in the pharmaceutical field [i.e. antispasmodic aminoketone **1(NMe$_2$)**].[6]

Unfortunately, and differently to other 10-heteroatom-susbtituted-camphors,[7] the synthetic access to 10-*N*-substituted camphors is not easy. In fact, the only readily accessible 10-*N*-substituted camphors are amides derived from commercially available ketopinic acid (see amides **5** in Fig. 2),[8] as well as ketopinic nitrile (**6** in Fig. 2).[9] This fact has made such ketopinic-acid derivatives the only disposable synthetic intermediates for the preparation of other 10-*N*-substituted-camphor derivatives.[3–6,8,10]

On the other hand, the only previously described access to 10-aminocamphors **1(NR$_2$)**, based on ketopinic acid and developed by Schenone et al. in 1975, presents a problematic oxidation step of an amino alcohol intermediate.[6]

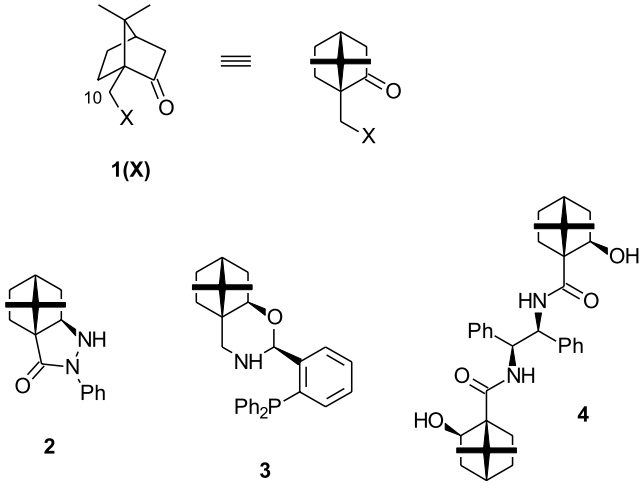

Figure 1. Some relevant chirality transfers based on 10-*N*-substituted camphor.

It is, therefore, easy to understand that the establishment of general and straightforward synthetic procedures to enantiopure 10-aminocamphors (amines and amides) would be of a great interest, due to the utility of such compounds as valuable alternative starting materials for the preparation of new valuable unexplored 10-*N*-substituted-camphor-based compounds.

Keywords: Camphor; Chirality; Enantiospecific synthesis; Amines; Amides; Alkylations.
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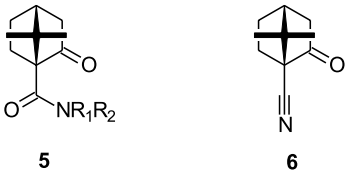
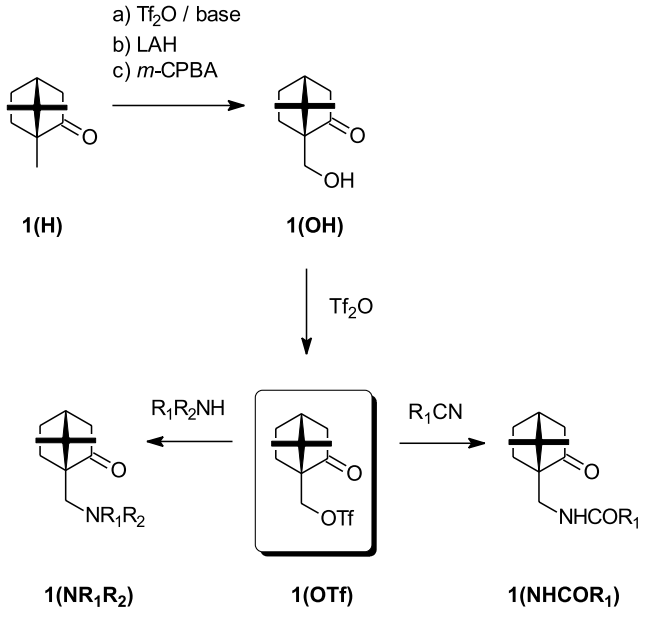


Figure 2. Classic starting intermediate for the preparation of 10-*N*-substituted-camphor derivatives.

2. Results and discussion

In relation with this interest, and continuing with our research effort on establishing Wagner–Meerwein-rearrangement-based procedures for the preparation of 10-substituted camphors **1(X)**,[7a] we have now developed a general and divergent synthetic procedure for enantiopure 10-aminocamphors (including secondary amides) (Scheme 1).

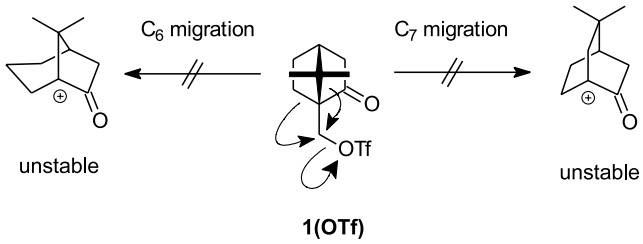


Scheme 1. Enantiospecific synthesis of 10-aminocamphors.

The synthetic route uses commercial camphor **1(H)** as enantiopure starting material, involving an initial enantiospecific transformation of such chiral-pool material into 10-hydroxycamphor **1(OH)** (70% yield), according to a three-step double-Wagner–Meerwein-rearrangement-based methodology described previously by us.[7a] Initial intermediate **1(OH)** was then quantitatively converted into key-intermediate 10-(triflyloxy)camphor **1(OTf)** by a straightforward treatment with triflic anhydride (Tf_2O) under mild reaction conditions (Scheme 1).

Neopentylic-like triflate **1(OTf)** resulted to be peculiarly stable. Thus, it did not undergo any possible Wagner–Meerwein rearrangement of its framework (C6 or C7 alkyl migrations),[11] probably due to the destabilizing effect caused by the α-carbonyl group on the emergent bridgehead carbocation intermediate (see Scheme 2).

Finally, the neopentylic-like triflyloxyl group of **10** (**OTf**) can undergo an easy nucleophilic substitution by the action



Scheme 2. Possible Wagner–Meerwein rearrangements of neopentylic-like triflate **1(OTf)**.

of soft *N*-nucleophile amines and nitriles (Ritter Reaction),[12] such as diethylamine, pyperidine and acetonitrile, to give the corresponding *N*-alkylated amines **1(NR$_1$R$_2$)** or secondary amides **1(NHCOR$_1$)** with good yields. This neopentylic-like nucleophilic substitution takes place under mild reaction conditions and without producing Grob-like fragmentation of the β-(triflyloxy)ketone-based norbornane framework, due the high nucleofugacity of the triflyloxyl group.[13]

3. Summary

In summary, for the first time, a straightforward and general synthetic methodology for the enantiospecific preparation of valuable enantiopure 10-aminocamphors (including amide derivatives) has been established. As validation of such methodology, (1*R*)-10-(diethylamino)camphor (61% overall yield), (1*R*)-10-(pyperidin-1-yl)camphor (63% overall yield) and (1*R*)-10-(acetilamino)camphor (60% overall yield) has been obtained from (1*R*)-camphor. This easy access to 10-aminocamphors will allow the preparation of new non-explored types of 10-*N*-substituted-camphor-based chirality-transfer agents and drugs (i.e. anticonvulsants and antispasmodics).[2–6] Further research in this interesting last aspect is in progress.

4. Experimental

4.1. General

All starting materials and reagents were obtained from well-known commercial suppliers and were used without further purification. Anhydrous solvents were properly dried under standard conditions. Chromatography was performed over silica gel (Flash, 150 mesh) or neutral alumina. ^{1}H and ^{13}C NMR were recorded on 200 and 300 MHz spectrometers. Chemical shifts (δ) for ^{1}H and ^{13}C NMR were recorded in ppm downfield relative to the internal standard tetramethylsilane (TMS), and coupling constants (J) are in Hz. IR spectra were recorded on a FT spectrometer. HRMS were recorded in a mass VG Autospec spectrometer, using the FAB technique.

4.1.1. (1*R*)-10-(Triflyloxy)camphor 1(OTf). Over a cold (0 °C) solution of primary alcohol **1(OH)**[7a] in dry CH_2Cl_2 was added triflic anhydride (1.2 mequiv). The reaction mixture was stirred for 10 min and hydrolyzed with saturated sodium hydrogen carbonate solution. After standard work up and purification by elution

chromatography (silica gel, hexane/CH_2Cl_2 40:60) **1(OTf)** was obtained as a colorless liquid (ca. quantitative). $[\alpha]_D^{20}+30.8$ (1.27 CH_2Cl_2). IR, ^1H and ^{13}C NMR, and MS agree with the structure.

4.1.2. (1*R*)-10-(Diethylamino)camphor 1(NEt_2). A solution of **1(OTf)** and diethylamine (2.0 mequiv) in dry acetonitrile was refluxed for 6 h. After standard hydrolysis (sat. sodium hydrogen carbonate solution), work up and purification by elution chromatography (neutral alumina, ether/methanol 95:5), pure 10-(diethylamino)camphor **1(NEt_2)** (87% yield) was obtained as a colorless liquid. $[\alpha]_D^{20}+44.5$ (0.58, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ 2.66 (AB, $J=14.4$ Hz, 1H), 2.65–2.34 (several m, 4H), 2.41 (AB, $J=14.4$ Hz, 1H), 2.33–2.25 (m, 1H), 2.18–1.81 (several m, 3H), 1.81 (d, $J=18.1$ Hz, 1H), 1.40–1.16 (several m, 2H), 1.04 (s, 3H), 0.96 (t, $J=7.1$ Hz, 6H), 0.90 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 219.3, 61.4, 49.2, 48.1 (two signals), 47.5, 43.6, 43.5, 26.9, 26.3, 20.4, 19.9, 11.7 (two signals) ppm. IR (CCl_4) ν 2966, 1742, 1387, 1371 cm^{-1}. HRMS 223.1936 (calcd 223.1936 for $C_{14}H_{25}NO$).

4.1.3. (1*R*)-10-(Piperidin-1-yl)camphor 1(N–(CH_2)$_5$–). A solution of **1(OTf)** and pyperidine (2.0 mequiv) in dry acetonitrile was refluxed for 6 h. After standard hydrolysis (sat. sodium hydrogen carbonate solution), work up and purification by elution chromatography (neutral alumina, ether/methanol 95:5), pure 10-(piperidin-1-yl)camphor **1(N–(CH_2)$_5$–)** (90% yield) was obtained as a colorless liquid. $[\alpha]_D^{20}+40.1$ (1.23, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ 2.48 (AB, $J=14.2$ Hz, 1H), 2.46–2.31 (several m, 4H), 2.35 (AB, $J=14.2$ Hz, 1H), 2.10–1.92 (several m, 4H) 1.81 (d, $J=18.1$ Hz, 1H), 1.52–1.45 (several m, 4H), 1.40–1.29 (several m, 4H) 1.04 (s, 3H), 0.92 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.2, 61.4, 56.7 (two signals), 54.4, 47.5, 43.6, 43.5, 26.8, 26.3 (two signals), 26.2, 24.1, 20.6, 20.0 ppm. IR (CCl_4) ν 2933, 1743, 1443, 1389, 1371 cm^{-1}. HRMS 235.1932 (calcd 235.1936 for $C_{15}H_{25}NO$).

4.1.4. (1*R*)-10-(Acetylamino)camphor 1(NHCOMe). A solution of **1(OTf)** in dry acetonitrile was refluxed for 6 h. After standard hydrolysis (sodium hydrogen carbonate), work up and purification by elution chromatography (silica gel, CH_2Cl_2 to elute impurities and then MeOH), pure 10-(acetylamino)camphor **1(NHCOMe)** (85% yield) was obtained as a pale-yellow colorless oil. $[\alpha]_D^{20}+15.6$ (0.64, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ 5.61 (br s, 1H), 2.96 (AB, $J=18.0$ Hz, 1H), 2.96 (AB, $J=18.0$ Hz, 1H), 2.62 (ddd, $J=18.0$, 3.2, 3.2 Hz, 1H), 2.43–1.87 (several m, 5H), 1.95 (s, 3H), 1.46–1.27 (m, 1H), 1.21 (s, 3H), 1.07 (s, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.4, 170.0, 62.8, 50.1, 46.2, 44.1, 43.1, 35.3, 26.7, 24.0, 23.0, 19.4 ppm. IR ($CHCl_3$) ν 3342, 2964, 1709, 1666, 1539 cm^{-1}. HRMS 209.1422 (calcd 209.1416 for $C_{12}H_{19}NO_2$).

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Comparison of AB_2 and AB_4 monomers in ferrocene-cored benzyl ether dendrimers

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Abstract—Ferrocene-cored unsymmetric and symmetric arylalkyl ether dendrimers based on an AB_2 monomer (3,5-dihydroxybenzyl alcohol) were prepared. Their electrochemical properties were compared with the unsymmetric and symmetric ferrocene-cored dendrimers based on a relatively rigid and three-dimensionally disposed AB_4 monomer. The thermodynamics and kinetics of heterogeneous electron transfer in these dendrimers show that G_{2n} of AB_2 dendrimers behave similar to G_n of AB_4 dendrimers. For example, the redox reaction shows significant irreversibility especially at higher scan rates in the case of G_4 didendron based on AB_2 monomer and G_2 didendron based on AB_4 monomer. Despite the fact that AB_4 building blocks are more rigid, the effective encapsulation in both these dendrimers are similar. This result is attributed to the three dimensional disposition of the branching points in the AB_4 monomer.

1. Introduction

The hyperbranched architecture of dendrimers has received much attention in recent years for a wide variety of applications.[1–7] Of particular interest is the covalent encapsulation of redox active core functionalities by branching units in the dendrimer, thus creating specific site-isolated micro environments.[8–12] This type of dendritic shielding may serve as model systems to better understand the mechanism of metalloproteins controlling the behavior of the active site. Also, it could find applications in miniaturizing information storage circuits.[13] The conformation around the core moiety plays a crucial role in determining the efficiency of encapsulation in dendrimers. The electron transfer rate attenuation has been an important factor in deciding the efficiency of encapsulation in redox active core dendrimers.[8–10,12,13] We recently reported that significant variations in redox potential and heterogeneous electron transfer rate constants were observed even at lower generations in the case of dendrimers based on a three-dimensionally disposed AB_4 monomer **12**.[14] The motivation for the study reported here stems from the suggestion that the thermodynamics and kinetics of heterogeneous electron transfer are essentially unperturbed in arylalkyl ether dendrimers, whereas significant variations were observed in dendrimers with aliphatic amide or ether amide backbones.[15–19] This difference was attributed to the relative rigidity of the arylalkyl ether dendrimers. Since AB_4 monomer has a relatively rigid structure compared to the corresponding AB_2 monomer derived from 3,5-dihydroxybenzyl alcohol (**11**), we have been interested in comparing the efficiency of encapsulation between the dendrimers (**1–10**) obtained from these two monomer types (Chart 2). A schematic representation of dendrons based on AB_2 and AB_4 monomer is shown in Chart 1.

2. Results and discussion

The obvious difference between the AB_2 and AB_4 monomer is the number of branching points in the dendrimer. Monomer **12** has four branching points in which two of the phenolic moieties are disposed in an orthogonal plane to

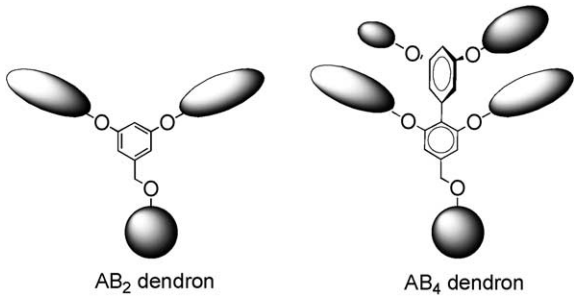

Chart 1. Schematic representation of dendrons based on AB_2 and AB_4 monomer.

Keywords: Dendrimers; Ferrocene; Encapsulation; Rigidity; Three-dimensionality.
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the other two phenolic moieties due to the biaryl twist. This relative positioning of the branching phenolic functionalities provides the three-dimensionality to the AB_4 monomer based dendrimers. On the other hand, the phenolic groups of AB_2 monomer **11** are in the same plane. However, note that due to the difference in the number of branching units, generation G_n of dendrimers derived from **12** are similar in molecular weights to generation G_{2n} of those derived from **11**. Therefore, while the branching units of G_1 dendron **4** from the AB_4 monomer are three-dimensionally disposed because of the biaryl twist, the comparable G_2 dendron **2** from the AB_2 monomer is also three-dimensionally disposed in space due to the benzyl ether connectivities between the dendrimer layers. Also, all dendrimers in Chart 2 are based on benzyl ether linkages; therefore we obviate any possible differences in the properties of the ferrocene core due to the difference in backbone functionalities. Thus, the only difference between the two classes of dendrimers seems to be rigidity. The source of conformational flexibility in these dendrimers is from the benzyl ether linkages. Note that the G_4-didendron **8** from the AB_2 monomer possesses 62 benzyl ether linkages, while the comparable AB_4 monomer based G_2-didendron **10** has only 42 benzyl ether functionalities. From this comparison, the AB_4 monomer based dendrimers seem to be more rigid than the AB_2-based counterparts. Thus the study would directly address the role of rigidity in encapsulation.

Both unsymmetrical and symmetrical dendrimers based on an AB_2 monomer (generation 2 and 4) were synthesized with a ferrocene core, structures of which are shown in Chart 2 (Scheme 1). Also shown are the structures of dendrimers (generation 1 and 2) based on an AB_4 monomer.[14] The dendrons were synthesized starting from 3,5-dihydroxybenzyl alcohol, using the convergent approach reported by Fréchet.[20] Ferrocene was attached to the focal point of the dendrons symmetrically and unsymmetrically by employing ferrocene-1,1′-diacid fluoride or fluorocarbonylferrocene[21] as the electrophilic species, respectively. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and MALDI-ToF mass spectrometry. The dendrimers were also analyzed using GPC as an additional check for purity. Electrochemical measurements were performed with 0.2 M $TBA^+PF_6^-$ in CH_2Cl_2. Electrochemical data for compounds are given in Table 1. Half wave potentials ($E_{1/2}$) were measured relative to F_c/F_c^+ using square wave voltammetry. Experimental cyclic voltammograms were simulated using Digisim to determine diffusion coefficients (D_0) and heterogeneous electron transfer rate constants (k^0). Diffusion coefficients, estimated using the Randles–Sevcik equation $\{i_p=(2.69\times10^5)\ ACD^{1/2}v^{1/2}\}$, were used as the starting point for the simulation. The $E_{1/2}$ and the k^0 values are shown in Table 1.

First, we will discuss the unsymmetrical compounds **1**–**5**. The redox potentials of the dendrimers **2**–**5** are essentially unchanged compared to the control ferrocene carboxylic ester **1**. This result suggests that the difference between the stability of ferrocene and the ferrocenium species is similar in all generations in dendrimers **2**–**5**. That is, no special microenvironment is provided by dendrons for the ferrocene core within the generations studied. The electron transfer rate constants decrease with increase in size of the dendrimers as seen from **2** to **3** and from **4** to **5**. Compared to the control molecule **1** with $k^0=4.6\times10^{-3}$ cm/s, the AB_2 dendrimers **2** and **3** exhibit k^0 of 3.6×10^{-3} and 1.8×10^{-3} cm/s, respectively. The biaryl dendrimers **4** and **5** exhibit k^0 of 3.1×10^{-3} and 2.1×10^{-3} cm/s, respectively. These results could be attributed to the steric inhibition of electron transfer. Note that the rate constants are similar for dendrimers **2** and **4** and for **3** and **5**, despite the fact that the G_n of AB_4 dendrimers are of lower molecular weight compared to G_{2n} of AB_2 dendrimers. The percentage difference in molecular weights between compound **2** and **4** and **3** and **5** are 14 and 19%, respectively. Interestingly, the symmetrical dendrimers **7**–**10** exhibit a different behavior. In the case of AB_2 dendrimers, **7** exhibits the redox potential of 500 mV compared to the 496 mV for the control molecule **6**. Then, there is a steep increase in redox potential of 584 mV for the fourth generation dendrimer **8**. The AB_4 dendrimers **9** and **10** exhibit a steady increase in the redox potential of 508 and 528 mV, respectively, compared to the 496 mV for the control molecule **6**. Here also, the heterogeneous electron transfer rate constants are quite similar in the case of **7** and **9** and **8** and **10**. Also, the redox reaction shows significant irreversibility especially at higher scan rates in the case of **8** and **10**. Small differences in the comparison of AB_4 and AB_2 dendrimers are consistent with the differences in molecular weights. Note that the percentage difference in molecular weights between compound **7** and **9** and **8** and **10** are 16 and 20%, respectively.

3. Conclusions

In summary, comparative electrochemical studies of the arylalkyl ether dendrimers based on AB_2 and AB_4 monomer reported here suggest that G_{2n} of AB_2 dendrimers behave similar to G_n of AB_4 dendrimers. This is clear in the comparison of heterogeneous electron transfer rate constants. We suggest that the reason for this behavior might be the three-dimensionally disposed functional groups responsible for dendritic growth present in the AB_4 monomer. Previous studies have suggested that rigidity could result in reduced encapsulation of an electroactive species.[15–19] Since the biaryl AB_4 monomer is more rigid than its AB_2 counterpart and still maintains encapsulation, our studies here show that three-dimensionality of the branching units is an important factor in determining encapsulation.

4. Experimental

^{1}H NMR spectra were recorded on a 400 or 300 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; d of d, doublet of a doublet; m, multiplet; br, broad. ^{13}C NMR spectra were proton decoupled and recorded on a 100 or 75 MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. MALDI-ToF, EI and FAB mass spectra were obtained at the Molecular Weight Characterization Facility at University of Massachusetts. Flash chromatography was performed with 37–75 μm silica

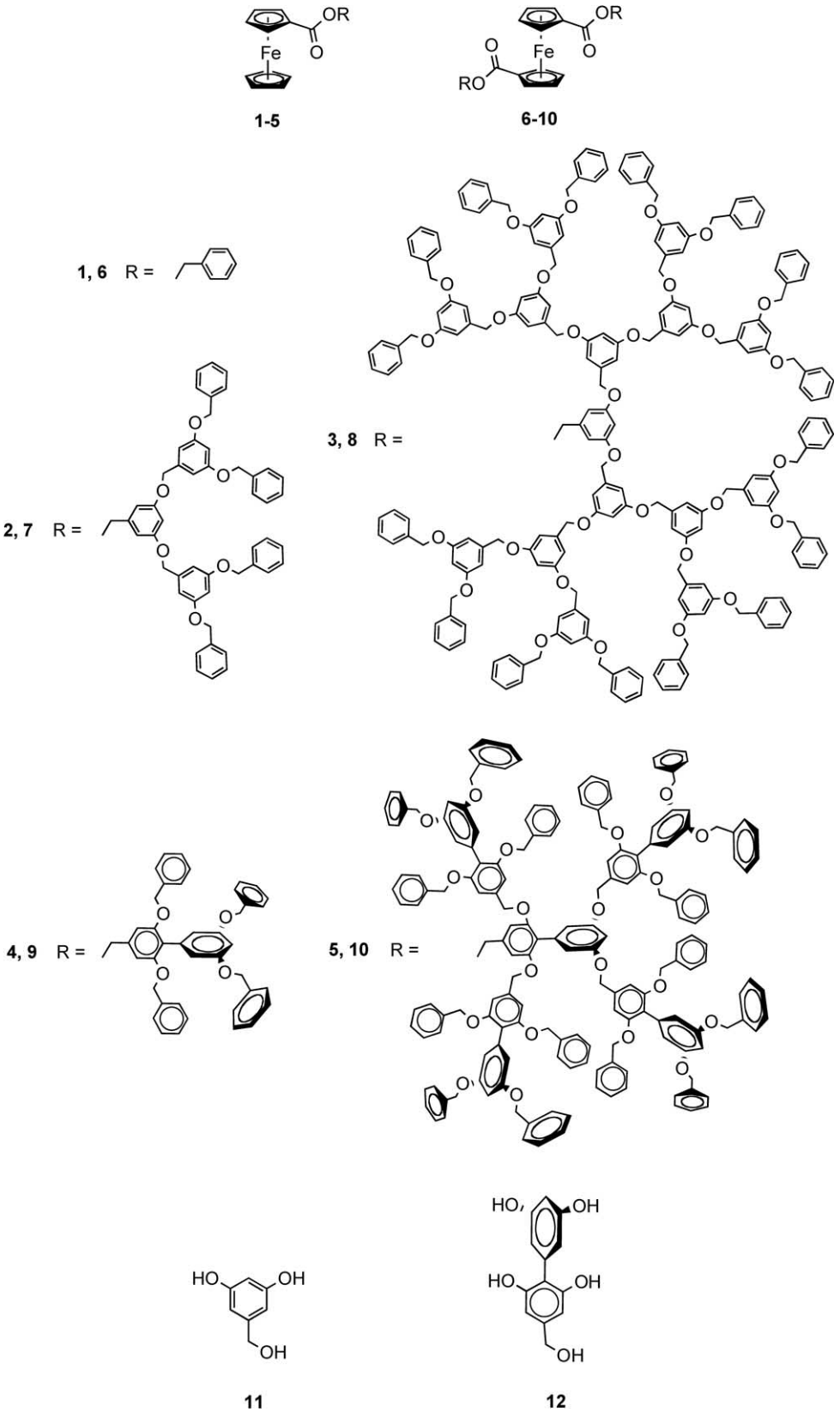
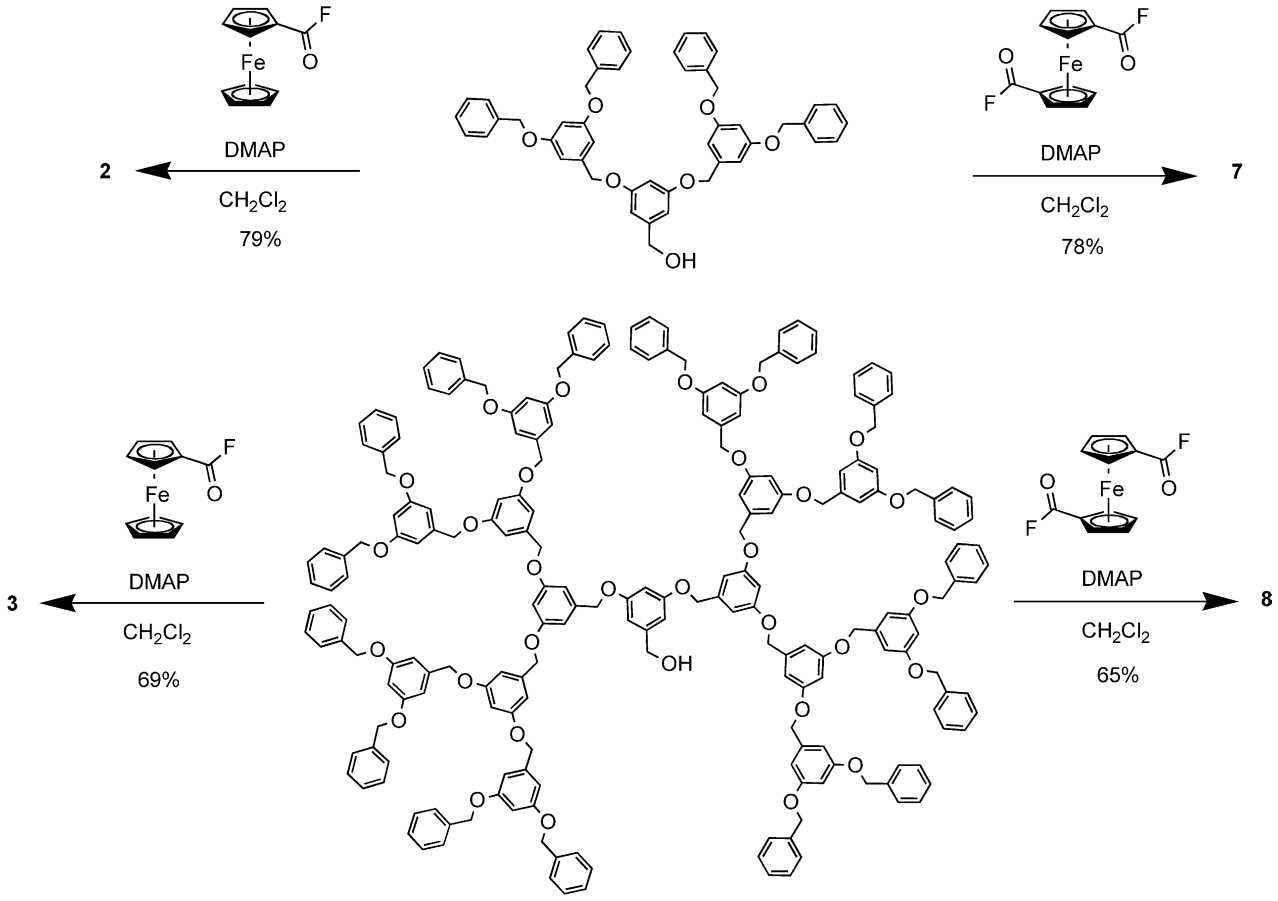


Chart 2. Structures of ferrocene-cored AB_2 and AB_4 dendrimers.

gel. Analytical thin layer chromatography was performed on silica plates with F-254 indicator and the visualization was accomplished by UV lamp or using an iodine chamber. THF was distilled over Na/Ph_2CO ketyl. Dichloromethane was distilled over CaH_2. All other chemicals were obtained from commercial sources and used as received, unless otherwise mentioned. Dendritic alcohols used here were prepared according to previously reported procedure.[20]



Scheme 1. Synthesis of unsymmetric and symmetric ferrocene-cored dendrimers based on AB_2 monomer.

All electrochemical measurements were carried out on Epsilon (BAS) electrochemical analyzer at ambient temperature with a standard three electrode configuration, consisting of platinum wire counter electrode and a glassy carbon working electrode (with a geometric surface area of 0.0707 cm^2) and an Ag/AgCl reference electrode. The electroactive dendrimers (0.001 mol L^{-1}) were dissolved in HPLC grade dichloromethane also containing tetrabutylammonium hexafluorophosphate as the supporting electrolyte (0.2 mol L^{-1}). A nitrogen atmosphere was maintained over the solutions throughout the electrochemical experiments. IR compensation was not applied. Typical scan rate values of 0.010, 0.050, 0.100, 0.200, 0.500, 1.00 and 2.00 V/s were utilized. Square wave voltammetry was used to determine the half wave potential ($E_{1/2}$) values of all compounds relative to F_c/F_c^+. The electrochemical diffusion coefficients of the oxidized and reduced species were calculated by the Randles–Sevcik equation. From the slope obtained in the plot of anodic or cathodic peak current vs the square root of scan rate, the diffusion coefficient can be

Table 1. Electrochemical data for dendrimers[a]

Compound	Molecular weight	$E_{1/2}$[b] (mV)	D_0 (10^{-6} cm^2/s)[c]	hydrodynamic radius[d] (nm)	k^0 (10^{-4} cm/s)[c]
Unsymmetrical dendrimers					
1	320	264	4.5±0.5	1.09±0.12	46±7
2	956	260	1.5±0.1	3.25±0.22	36±8
3	3504	272	0.7±0.0	6.65±0.00	18±4
4	820	264	2.0±0.1	2.44±0.13	31±7
5	2823	268	1.0±0.1	5.18±0.55	21±2
Symmetrical dendrimers					
6	454	496	5.5±2.5	1.12±0.51	45±14
7	1728	500	1.3±0.1	3.76±0.29	31±6
8	6820	584	Irr.	Irr.	2±1[e]
9	1455	508	1.4±0.1	3.49±0.25	28±5
10	5460	528	Irr.	Irr.	7[e,f]

[a] Carried out with 0.2 M $TBA^+PF_6^-$ in CH_2Cl_2 at 25 °C.
[b] Half-wave potentials ($E_{1/2}$) were measured relative to F_c/F_c^+, using square wave voltammetry.
[c] D_0 and k^0 are diffusion coefficients and heterogeneous electron transfer rate constants, respectively, estimated using Digisim.
[d] Determined by using the Stokes–Einstein equation.[22]
[e] k^0 for **8** and **10** was approximated by inputting the D_0 values of **7** and **9**, respectively.
[f] This value is an upper bound value.

calculated:

$$i_p = (2.69 \times 10^{-5})ACD^{1/2}\nu^{1/2}$$

The D_0 and k^0 values were obtained by fitting digital simulations (DigiSim 3.0®) to the experimental voltammograms at the scan rates of 0.100, 0.200, 0.500, 1.00 and 2.00 V/s for all the compounds. The digital simulations at lower scan rates 0.010 and 0.050 V/s were not successful for all the compounds. The hydrodynamic radius was calculated by the Stokes–Einstein equation:

$$D = kT/6\pi\eta r$$

4.1. Synthesis of dendrimers 2–3 and 7–8

Representative procedure for the reaction of fluorocarbonylferrocene or ferrocenyl-1,1′-diacid fluoride with dendritic alcohols. Fluorocarbonylferrocene or ferrocenyl-1,1′-diacid fluoride (1 equiv) was dissolved in anhydrous dichloromethane under nitrogen atmosphere. The dendritic alcohol (1.1 equiv for fluorocarbonylferrocene, 2.3 equiv for ferrocenyl-1,1′-diacid fluoride) and 4-dimethylamino pyridine (1.5 equiv for fluorocarbonylferrocene, 4 equiv for ferrocenyl-1,1′-diacid fluoride) was added at 25 °C and stirred overnight unless otherwise mentioned. The solvent was removed and the residue was purified by silica gel column by elution with appropriate solvent combination to give the ferrocene-cored dendrimers.

4.1.1. Synthesis of dendrimer 2. The crude reaction mixture was purified by elution with EtOAc/hexane (20:80) to give the product 0.15 g (79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 5H), 4.40 (br s, 2H), 4.85 (br s, 2H), 4.99 (s, 4H), 5.01 (s, 4H), 5.18 (s, 2H), 6.55–6.59 (m, 3H), 6.66–6.71 (m, 6H), 7.29–7.44 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.4, 69.7, 69.9, 69.9, 70.1, 70.9, 71.3, 101.4, 101.6, 106.2, 107.0, 127.4, 127.9, 128.5, 136.7, 138.9, 139.1, 159.9, 160.1, 171.3; MALDI-ToF: Calcd for $C_{60}H_{52}FeO_8$: 956.3; Found: 979.34 ($M^+ + Na$).

4.1.2. Synthesis of dendrimer 3. The contents were stirred at 25 °C for 24 h. The crude reaction mixture was purified by starting the elution with CH_2Cl_2/hexane (50:50) and gradually increasing it to 100% CH_2Cl_2 gave the product 0.084 g (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 5H), 4.34 (t, $J=1.9$ Hz, 2H), 4.81 (t, $J=1.9$ Hz, 2H), 4.88–5.03 (m, 60H), 5.17 (s, 2H), 6.53–6.59 (m, 15H), 6.62–6.71 (m, 30H), 7.28–7.43 (m, 80H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.4, 69.7, 69.9, 69.9, 69.9, 70.0, 70.2, 70.9, 71.4, 101.5, 106.3, 106.3, 106.4, 107.1, 127.5, 127.9, 128.4, 128.5, 136.7, 139.2, 139.2, 139.2, 159.9, 159.9, 160.0, 160.0, 160.1, 160.1, 171.1; MALDI-ToF: Calcd for $C_{228}H_{196}FeO_{32}$: 3503.82; Found: 3494.25 (M^+).

4.1.3. Synthesis of dendrimer 7. The crude reaction mixture was purified by elution with EtOAc/hexane (25:75) to give the product 0.24 g (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (t, $J=1.8$ Hz, 4H), 4.80 (t, $J=1.8$ Hz, 4H), 4.85–5.00 (m, 24H), 5.11 (s, 4H), 6.48–6.55 (m, 6H), 6.63 (d, $J=2.0$ Hz, 12H), 7.24–7.38 (m, 40H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.7, 69.7, 69.8, 71.5, 72.6, 72.8, 101.5, 101.5, 106.2, 107.0, 127.3, 127.8, 128.3, 136.6, 138.6, 139.1, 159.9, 160.0, 169.8; MALDI-ToF: Calcd for $C_{110}H_{94}FeO_{16}$: 1727.76; Found: 1727.19 (M^+).

4.1.4. Synthesis of dendrimer 8. The contents were stirred at 25 °C for 2.5 days. The crude reaction mixture was purified by elution with CH_2Cl_2/$CHCl_3$ (60:40) and gradually increasing the polarity to 100% CH_2Cl_2 gave the product 0.12 g (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (br s, 4H), 4.76–5.07 (m, 24H), 5.12 (br s, 4H), 6.45–6.78 (m, 90H), 7.27–7.46 (m, 160H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.8, 69.9,m 69.9, 70.0, 70.1, 71.7, 72.6, 72.8, 101.5, 106.3, 106.4, 127.5, 127.9, 127.9, 128.5, 128.5, 136.7, 139.2, 159.9, 160.0, 160.0, 160.1, 170.0; MALDI-ToF: Calcd for $C_{446}H_{381}FeO_{64}$: 6820.6; Found: 6820.10 (M^+).

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Optimised synthesis and photochemistry of antenna-sensitised 1-acyl-7-nitroindolines☆

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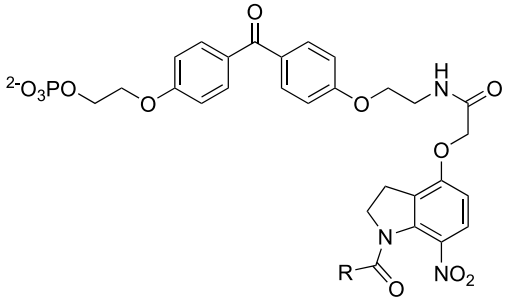
Abstract—Benzophenone antenna-sensitised 1-acyl-7-nitroindolines show a significantly enhanced extent of photochemical cleavage in aqueous solution over their non-sensitised analogues and release the carboxylate derived from their 1-acyl group. The present work investigates length and functional group effects in the linker between the benzophenone sensitiser and the nitroindoline and concurrently establishes a more efficient synthetic route to an effective conjugate than previously described. An incidental finding is that a TBDMS ether is stable during claycop-mediated nitration.

1. Introduction

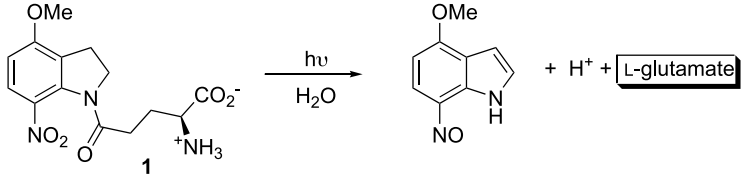
We have previously reported[1] the efficient photochemistry of 1-acyl-7-nitroindolines such as **1**, that release a carboxylate derived from the 1-acyl group upon irradiation by near-UV light in neutral aqueous solution, as shown in Scheme 1. Our interest in this photochemistry arose from a requirement for reagents that could rapidly release neuroactive amino acids by flash photolysis within biological preparations, particularly mammalian brain slices: the L-glutamate conjugate **1** exemplifies a means to achieve one aspect of this goal and has been used in a number of published studies.[2]

Based on mechanistic studies of this photochemistry,[3] we have described triplet-sensitised antenna conjugates of nitroindolines with substantially enhanced photosensitivity,[4] which is desirable as it should enable the photorelease of higher concentrations of the amino acid than from simple, non-sensitised nitroindolines such as **1**. The L-glutamate conjugate **2a** has recently been reported and shown to fulfil the latter requirement.[5]



2a R = $CH_2CH_2CH(NH_3^+)CO_2^-$ (*S*-isomer)
2b R = CH_3

With the general approach and efficacy of the antenna-sensitised methodology established, we wished to optimise



Scheme 1. Overall photocleavage reaction of **1**.

☆ Parts of this work are the subject of UK Patent Application GB03/07231.

Keywords: Photolysis; Nitroindolines; Benzophenones; Triplet sensitisation; Nitration.
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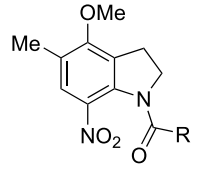
the synthetic chemistry required to assemble conjugates such as **2** and to examine the effects on photolysis efficiency of changes in the link between the benzophenone antenna and the nitroindoline. In particular, two broad aspects relevant to synthesis of the conjugates needed to be addressed. The first was the formation of some 5-nitro isomer during introduction of the nitro group, which required separation either before or after linkage to the benzophenone. The second was a convolution of the relatively cumbersome previous synthesis[4] of the sensitiser moiety of **2** and the more fundamental matter of whether the length of the linker had a significant effect on the photochemistry. Here we report our studies to explore these two issues.

2. Results and discussion

The obvious means to address the first of these issues was to block the 5-position with a suitable substituent. A previous attempt to achieve this in the unsensitised compounds such as **1** used a 5-methyl group, as in **3**, but this caused a significant reduction in photoefficiency that we ascribed to steric inhibition of the resonance interaction between the methoxy group and the aromatic ring.[1b] However we speculated for the sensitised compounds, where light absorption is principally via the sensitiser, that energy transfer might not be adversely affected by the presence of a 5-substituent and therefore set out initially to prepare the conjugate **4**.



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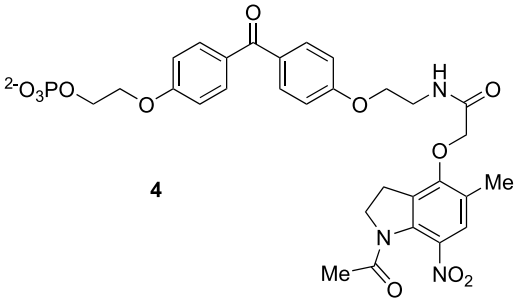

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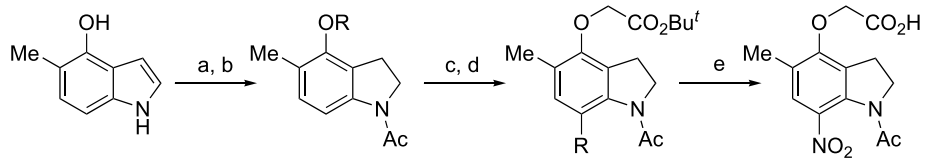
Synthesis of **4**, as outlined in Scheme 2, followed similar lines to that previously used for **2a**,**b**[4,5] but required 4-hydroxy-5-methylindole **5** as the starting material. We had previously prepared this compound by Leimgruber–Batcho synthesis but the overall yield was poor.[1b] In the present work we used an alternative, published method[6] in which 4-hydroxyindole was converted to its 5-(dimethylaminomethyl) derivative with Me_2NH–CH_2O, then hydrogenolysed over Pd–alumina. Details of the procedure in our hands are given in the Supplementary Data. With **5** available, further elaboration to the carboxylic acid **10**, as shown in Scheme 2, followed essentially the route previously used for the 5-nor analogue in our previous work,[4] except for the minor variant of a *tert*-butyl rather than a methyl ester to protect the carboxylic acid side chain. This allowed easy deprotection without the danger of partial hydrolysis of the *N*-acetyl group during saponification of the ester. In both compounds **9** and **10**, the ^{1}H NMR spectrum showed a resolved benzylic coupling (0.5 Hz) between the 5-methyl group and H-6. This was not resolved in other similar compounds within this work, although its presence could be inferred from the broadened line width of the 5-methyl and H-6 signals.

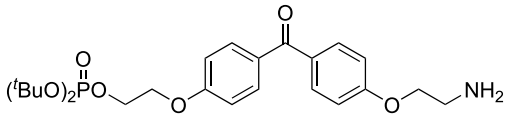
Final assembly of the conjugate **4** was by carbodiimide coupling of **10** with the previously described[4,5] amino-functionalised benzophenone **11**, followed by TFA treatment to remove the *tert*-butyl protecting groups. As described for previous conjugates of this type,[4] the calculated UV–Vis spectrum of **19**, obtained by adding the molar absorption spectra of the individual chromophores, gave an absorption maximum at 300 nm (ε 27,100 M^{-1} cm^{-1}; see Supplementary Data). This value was used to quantify solutions of **4**. Comparative irradiations of separate solutions of **4** and its nor-analogue **2b**, with the disappearance of the starting compounds being monitored by reverse-phase HPLC, showed that photolysis of **4** was ~16% more efficient. Furthermore, progressive irradiation led to very clean changes in the UV–Vis spectra, as previously reported for **2b**,[4] indicating that the photolysis reaction was not altered by the additional substituent. Although the gain in photolysis efficiency was quite modest, it contrasts markedly with the ~2-fold reduction in photoefficiency previously observed for the non-sensitised nitroindolines when a 5-methyl substituent was added.[1b] Furthermore, the presence of the 5-methyl group means that there is no problem of unwanted isomer formation when the nitro group is introduced. In our previous work, it had always been possible to separate the 5 and 7-nitro isomers of several *N*-acetyl compounds, but with a more complex side chain, such as in the precursor of the glutamate conjugate **2a**, it had been necessary to work with a mixture of isomers and to rely upon separation by HPLC of the final, water-soluble conjugate.[4,5] Obviously, avoidance of the isomer



5 **6** R = Ac, **7** R = H; **8** R = H, **9** R = NO_2; **10**

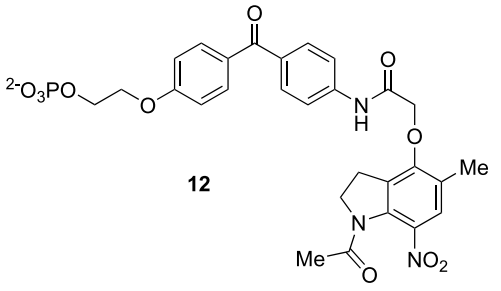
Scheme 2. Synthesis of precursor acid (**10**). Reagents and conditions: (a) $NaBH_3CN$, AcOH, Ac_2O, AcOH, Δ, 73%. (b) aq. NaOH, MeOH, 80%. (c) $BrCH_2CO_2Bu^t$, K_2CO_3, acetone, reflux, 90%. (d) claycop, Ac_2O, CCl_4, 66%. (e) TFA, 75%. Yields are given for recrystallised compounds.

problem is synthetically preferable if, as here, it can be achieved without compromising the photolysis efficiency.



11

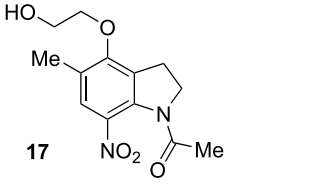
Encouraged by this initial success, we turned our attention to the combined matters of the length of the linker between the benzophenone and the nitroindoline, and establishment of an easier synthesis of a suitably functionalised benzophenone. Although it is possible that conformational relationships between the sensitiser and the nitroindoline could be influential, the more accessible strategy was to investigate shortening the flexible linker. Our first approach aimed at the conjugate **12**. Note that in each of the previous or present conjugates, the phosphate group on the side chain of the benzophenone sensitiser was present only to promote water solubility and is irrelevant to the photochemistry. Synthesis of **16**, a protected precursor of the sensitiser moiety in **12**, is shown in Scheme 3 and was straightforward from known[7] 4-hydroxy-4′-nitrobenzophenone **13**.



12

Carbodiimide-mediated coupling of **10** and **16**, followed by treatment with TFA to remove the *tert*-butyl protecting groups as described above for **4** gave the desired conjugate **12**. Its calculated UV–Vis spectrum had λ_{max} 300 nm (ε 30,500 $M^{-1}\,cm^{-1}$; see Supplementary Data). Disappointingly, irradiation of an aqueous solution of **12** resulted in no changes in the UV–Vis spectrum, even on exposure to the light source for periods up to 8 min. In contrast, irradiation of **2b** for 7 s under the same conditions resulted in ~50% photolysis (see Figure 2 of Ref. 4). We did not attempt to investigate the reasons for the lack of photoreactivity in **12**. However, there is some indication that amidobenzophenones may decay to a lower-energy triplet state than the normal n,π^* benzophenone triplet,[8] and may therefore have an insufficient energy gap to allow triplet transfer to the nitroindoline. Nevertheless, we recognise that the situation must be more complex than this effect alone, since the nitroindoline itself would have been expected to show considerable direct photolysis during such prolonged irradiation.[1] However, in practical terms there seemed little benefit in probing further into this negative result. Experimental details relating to the synthesis of **12** are reported in the Supplementary Data.

Our second approach to the combination of linker length and synthetic practicality was targeted on an ether-linked conjugate, where we envisioned assembly by a Mitsunobu coupling of a suitable ω-hydroxyalkoxy nitroindoline, exemplified by **17**, with the phenolic benzophenone **18**. The expected conjugate, **19**, would have the shortest practicable linker which maintains the principal structural features, i.e. the 4,4′-dialkoxybenzophenone and the 4-alkoxyindoline, that were present in our initial successful conjugate **2b**.



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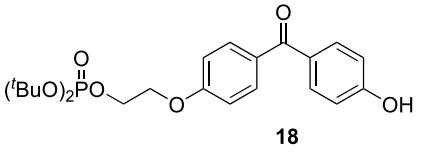

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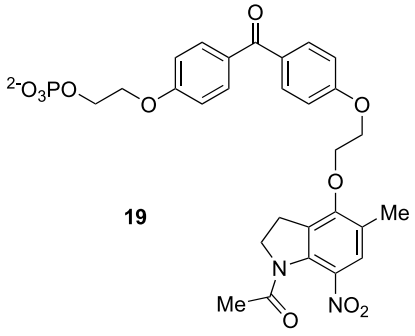

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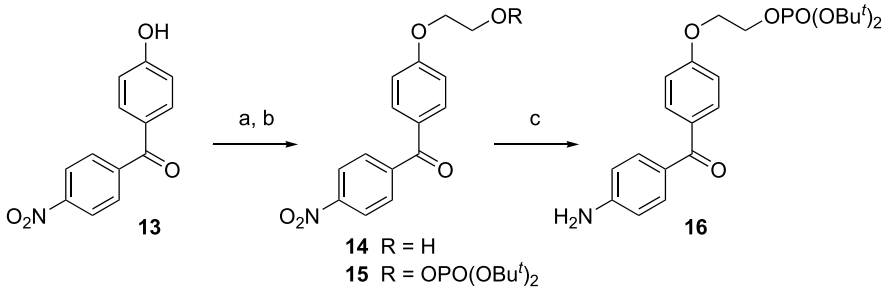
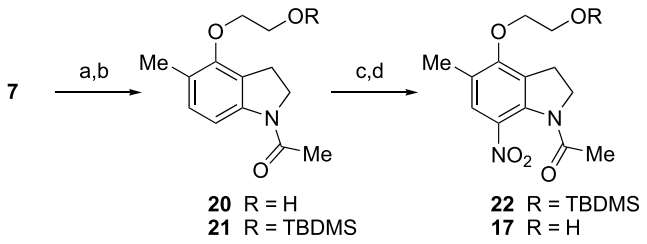
Synthesis of **17**, shown in Scheme 4, was generally straightforward but established a useful point about stability of the TBDMS protecting group (see below). Conversion of



Scheme 3. Synthesis of (**16**). Reagents and conditions: (a) $BrCH_2CH_2OH$, K_2CO_3, NaI, acetone, reflux, 81%. (b) $Et_2NP(OBu^t)_2$, 1*H*-tetrazole, THF, then MCPBA, 81%. (c) H_2, Pd–C, EtOH, ~100%.



Scheme 4. Synthesis of alcohol (**17**). Reagents and conditions: (a) ethylene carbonate, Et_4NBr, DMF, 140 °C, 74%; (b) TBDMSCl, imidazole, CH_2Cl_2, 95%; (c) claycop, Ac_2O, CCl_4, 85%; (d) TBAF, HOAc, THF, 84%.

7 (Scheme 2) to its 2-hydroxyethyl ether **20** was readily achieved by heating with ethylene carbonate in DMF in the presence of catalytic tetraethylammonium bromide.[9] This procedure was much more effective in this case than alkylation with 2-bromoethanol (K_2CO_3-butanone), although the latter method was effective when the phenol was more acidic, as with 4-hydroxybenzophenones, for example in synthesis of **14** (Scheme 3). The next significant step in the synthesis was introduction of the 7-nitro group, for which the previously established use of claycop–Ac_2O as the nitrating reagent[10] was our preferred option. However, it was obviously necessary to protect the primary alcohol to avoid side reaction(s) under the oxidative conditions of this reaction. Protection as a silyl ether was attractive, since its subsequent deprotection was expected to be achievable without perturbing other parts of the molecule but we had some concern as to whether it would survive the conditions: previously we have reported partial loss (presumably acid-catalysed) of a Boc group from a $(Boc)_2N$-moiety during claycop-mediated nitration.[5] However, we were gratified to find that the TBDMS ether **21** underwent claycop nitration to give an 86% yield of purified product **22**, implying that there was no significant cleavage of the silyl ether during the reaction. This useful observation is particularly relevant to proposed future work with more complex acyl groups (such as protected amino acid residues) attached to the indoline nitrogen. Normal TBAF deprotection (buffered with acetic acid) then gave the required alcohol **17**.

Our second required compound was the benzophenone **18**, and a desirable goal was to establish a direct route from a readily available benzophenone precursor. In our previous work, the unsymmetrical benzophenone used as the sensitiser had been prepared from mono-aryl starting materials in order to establish different substituents on the two rings.[4] In the present work (Scheme 5), we started from the symmetrical dipivalate ester **23** of 4,4′-dihydroxybenzophenone. Controlled alkaline hydrolysis gave the monopivalate **24** in purified yield of 73% after simple recrystallisation of the crude hydrolysis mixture. Previous preparations by partial esterification of 4,4′-dihydroxybenzophenone required chromatography for isolation of the pure monoester.[11] Conversion of **24** via **25** to the phosphate ester **26** was uneventful and final alkaline hydrolysis of the pivalate ester gave **18** in excellent yield. The overall yield for the five-stage sequence from commercial 4,4′-dihydroxybenzophenone was 29%.

Mitsunobu coupling of the alcohol **17** and the phenol **18** (Ph_3P, diisopropyl azodicarboxylate)[12] proceeded in high yield and subsequent TFA treatment to remove the *tert*-butyl protecting groups gave conjugate **19**. Solutions of **19** were quantified using the same molar absorbance coefficient (ε_{300} 27,900 $M^{-1}\,cm^{-1}$) calculated for **4**, since the chromophores of the two conjugates are essentially identical. Progressive photolysis of **19** in air-saturated, neutral aqueous solution showed a clean transition between the initial and final UV–Vis spectra (Fig. 1), very similar to that previously reported[4] for photolysis of **2b**. Comparative 300 nm irradiation of separate solutions of **2b** and **19** showed that the two compounds had very similar efficiency of photolysis (Scheme 5).

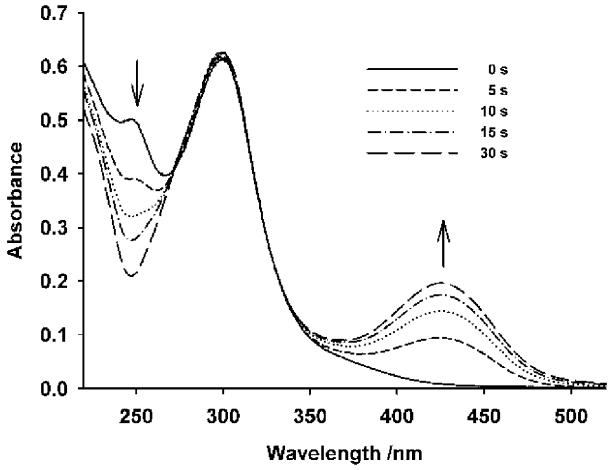
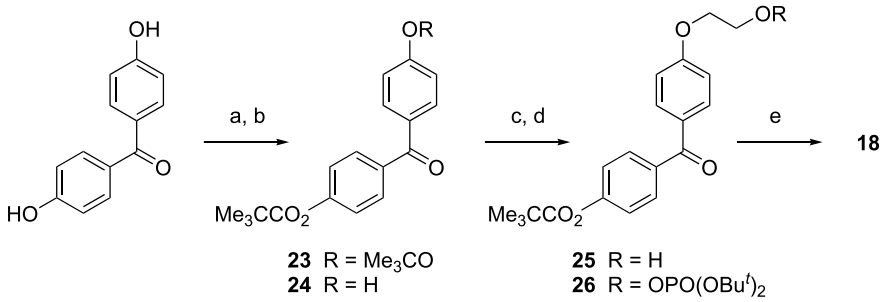


Figure 1. UV–Vis absorption spectra for an aqueous solution of **19** upon 300-nm irradiation for the cumulative time periods indicated. The arrows indicate the direction of absorbance changes with increasing irradiation time.

3. Conclusions

At its outset, a hoped-for outcome this work was to obtain enhanced photolysis efficiency over that of our previous conjugates of general structure **2**. In the event, the improvements have been modest (for **4**) or absent (for **19**), while the amidobenzophenone conjugate **12** was inert. Thus variation in length of the linker between the sensitiser and the nitroindoline, at least over the range explored here, has little effect on the photolysis efficiency. On the other hand, changes in the benzophenone substituents can have major negative consequences. The principal benefit to have emerged is a synthesis of **19** that is more practicable in several respects than that of the initial conjugates **2**. These improvements are (a) in the use of a 5-methyl substituent to block nitration other than at the 7-position of the indoline, (b) a short, effective route to preparation of the sensitiser moiety and (c) efficient chemical coupling of the sensitiser and the nitroindoline. An effective synthesis of conjugates of this general type will be important if the sensitised nitroindoline photochemistry is to become widely adopted. Future work will be to adapt the present synthesis of **19** to an L-glutamate analogue and to perform detailed assessment of the utility of such a conjugate (and perhaps of the corresponding GABA and glycine analogues) in



Scheme 5. Synthesis of benzophenone (**18**). Reagents and conditions: (a) Me_3CCOCl, pyridine, 88%. (b) NaOH (2 equiv), aq. THF, 73%. (c) $BrCH_2CH_2OH$, K_2CO_3, NaI, butanone, reflux, 58%. (d) $Et_2NP(OBu^t)_2$, 1*H*-tetrazole, THF, then MCPBA, 72%. (e) NaOH (1 equiv), aq. MeOH, 91%.

neurophysiological applications. This chemistry and its biological sequelae will be reported in due course.

4. Experimental

4.1. General

^{1}H NMR spectra were determined on Varian Unityplus 500 or JEOL FX90Q spectrometers in $CDCl_3$ solution with TMS as internal reference, unless otherwise specified Elemental analyses were carried out by MEDAC Ltd, Surrey, UK. Merck 9385 silica gel was used for flash chromatography. Analytical HPLC was performed on a 250×4 mm Merck Lichrospher RP8 column at 1.5 mL min^{-1} flow rate. Preparative HPLC was carried out on a 2×30 cm column (Waters C_{18} packing, Cat. No. 20594) at 2 mL min^{-1} flow rate. Details of mobile phases are given at relevant points in the text. Detection for analytical and preparative work was at 254 nm. Organic solvents were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Hexane solvent (bp 40–60 °C) was redistilled before use. Photolysis experiments were performed in a Rayonet RPR-100 photochemical reactor fitted with 16×300 nm lamps.

4.2. Synthesis of 4-{2-[(1-acetyl-5-methyl-7-nitroindolin-4-oxy)acetamido]ethoxy}-4′-[2-(dihydroxyphosphoryloxy) ethoxy]benzophenone (4)

4.2.1. 4-Acetoxy-1-acetyl-5-methylindoline (5). $NaBH_3CN$ (3.58 g, 57 mmol) was added portionwise over 0.5 h to a solution of 5-methylindol-4-ol[6] (2.80 g, 19 mmol) in acetic acid (90 mL), keeping the temperature at ~15 °C by intermittent cooling. The mixture was then stirred at rt for 1 h and water (3 mL) was added and the solvent was evaporated. The residue was dissolved in EtOAc (50 mL) and washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to give 5-methylindolin-4-ol as pale foam (2.83 g, 100%); ^{1}H NMR (90 MHz) δ 6.78 (d, J=8 Hz, 1H), 6.20 (d, J=8 Hz, 1H), 3.98 (s, 2H, exchanges with D_2O), 3.54 (t, J=8 Hz, 2H), 2.93 (t, J=8 Hz, 2H), 2.14 (s, 3H). The crude indoline was dissolved in a mixture of acetic acid (20 mL) and acetic anhydride (20 mL) and heated under reflux for 1 h. The resulting dark solution was diluted with water (5 mL) and the solvents were evaporated. The residue was dissolved in EtOAc (100 mL) and washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to give **6** as pale fawn crystals (3.22 g, 73%), mp 103–104 °C (EtOAc–hexanes); ^{1}H NMR (500 MHz) δ 7.98 (d, J=8.1 Hz, 1H), 7.06 (d, J=8.1 Hz, 1H), 4.08 (t, J=8.5 Hz, 2H), 3.04 (t, J=8.5 Hz, 2H), 2.32 (s, 3H), 2.20 (s, 3H), 2.13 (s, 3H). Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00; found: C, 66.51; H, 6.07; N, 5.97.

4.2.2. 1-Acetyl-5-methylindolin-4-ol (7). A solution of **6** (3.15 g, 13.5 mmol) in MeOH (95 mL) was treated with 1 M aq. NaOH (14.85 mL, 14.85 mmol) and stirred at rt for 0.75 h, then diluted with water (100 mL) and concentrated. The residue was acidified to pH 3 with dilute HCl and the precipitated solid was filtered off, washed with water and dried. The filtrate was washed with EtOAc and the organic phase was washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to give additional solid. The combined solid was recrystallised (MeOH–EtOAc) to give **7** as white crystals (2.06 g, 80%), mp 242 °C; ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6) δ 8.04 (s, 1H), 7.57 (d, J=8.1 Hz, 1H), 6.88 (d, J=8.1 Hz, 1H), 4.05 (t, J=8.5 Hz, 2H), 3.13 (t, J=8.5 Hz, 2H), 2.91 (s, 3H), 2.19 (s, 3H). Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; found: C, 68.93; H, 6.97; N, 7.29.

4.2.3. *tert*-Butyl (1-acetyl-5-methylindolin-4-yloxy)acetate (8). A suspension of anhydrous K_2CO_3 (1.24 g, 9 mmol) in acetone (60 mL) was treated with **7** (1.15 g, 6 mmol). After 15 min, *tert*-butyl bromoacetate (2.34 g, 12 mmol) was added and the mixture was heated under reflux for 4 h. The solid was filtered off, washed with acetone and the filtrate was evaporated. The residue was dissolved in EtOAc (50 mL), washed with brine, dried and evaporated to give **8** as white crystals (1.64 g, 90%), mp 95–96 °C (EtOAc–hexanes); ^{1}H NMR (500 MHz) δ 7.87 (d, J=8.1 Hz, 1H), 7.00 (d, J=8.1 Hz, 1H), 4.38 (s, 2H), 4.05 (t, J=8.4 Hz, 2H), 3.24 (t, J=8.4 Hz, 2H), 2.26 (s, 3H), 2.20 (s, 3H), 1.50 (s, 9H). Anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59; found: C, 67.07; H, 7.64; N, 4.60.

4.2.4. *tert*-Butyl (1-acetyl-5-methyl-7-nitroindolin-4-yloxy)acetate (9). Claycop (3.2 g; prepared as described)[13] was added to a solution of **8** (1.53 g, 5 mmol) in a mixture of CCl_4 (40 mL) and acetic anhydride (20 mL) and the mixture was stirred at rt for 4 h. The solid was filtered off, washed with CCl_4 and the filtrate was evaporated. The residue was dissolved in EtOAc and washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to give **9** as yellow needles (1.15 g, 66%), mp 97.5–98.5 °C (Et_2O–hexanes with charcoal); ^{1}H NMR (500 MHz) δ 7.54 (q, J=0.5 Hz, 1H), 4.47 (s, 2H), 4.22 (t, J=8.0 Hz, 2H), 3.24 (t, J=8.0 Hz, 2H), 2.31 (d, J=0.5 Hz, 3H), 2.24 (s, 3H), 1.49 (s, 9H).

Anal. calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 7.99; found: C, 58.20; H, 6.33; N, 7.96.

4.2.5. (1-Acetyl-5-methyl-7-nitroindolin-4-yloxy)acetic acid (10). A solution of **9** (1.05 g, 3 mmol) in TFA (10 mL) was stirred at rt for 1 h, concentrated and re-evaporated from toluene (2×10 mL) to give **10** as light brown crystals (0.66 g, 75%), mp 188–190 °C (EtOAc); UV: λ_{max} (EtOH)/nm 250 (ε/M^{-1} cm^{-1} 25,400), 287 (9300) 329sh (4000); λ_{max} [EtOH–25 mM Na phosphate, pH 7.0 (1:40)]/nm 247 (ε/M^{-1} cm^{-1} 19,700), 338 (3600); ^{1}H NMR (500 MHz, $CDCl_3$+DMSO-d_6) δ 7.51 (q, J= 0.5 Hz, 1H), 4.57 (s, 2H), 4.23 (t, J=8.0 Hz, 2H), 3.27 (t, J=8.0 Hz, 2H), 2.33 (d, J=0.5 Hz, 3H), 2.24 (s, 3H). Anal. calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52; found: C, 53.16; H, 4.79; N, 9.40.

4.2.6. 4-{2-(1-Acetyl-5-methyl-7-nitroindolin-4-yloxy)acetamido]ethoxy]-4′-[2-(dihydroxyphosphoryloxy)ethoxy]-benzophenone (4). A solution of 4-(2-azidoethoxy)-4′-{2-[di(*tert*-butoxyphosphoryloxy]ethoxy}benzophenone[4] (312 mg, 0.6 mmol) was reduced with Ph_3P in moist THF as previously described,[5] to give the crude amine **11**, which was dissolved in $CHCl_3$ (30 mL), dried and evaporated. The residue was then dissolved in dry MeCN (20 mL) and treated with the acid **10** (206 mg, 0.7 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (161 mg, 0.84 mmol). The mixture was stirred at rt under nitrogen for 18 h, then evaporated and the residue was dissolved in EtOAc and washed successively with 0.5 M aq. HCl, saturated aq. $NaHCO_3$ and brine, dried and evaporated. Flash chromatography [$CHCl_3$–MeOH (95:5)] gave the di-*tert*-butyl ester of **4** (393 mg, 85%) as a yellow viscous oil which was used in the next step without further purification; ^{1}H NMR (90 MHz) δ 7.79 (d, J=8 Hz, 4H), 7.42 (s, 1H), 6.98 (d, J=8 Hz, 4H), 4.42 (s, 2H), 4.04–4.36 (m, 8H), 3.76–3.98 (m, 2H), 3.12 (t, J=8 Hz, 2H), 2.23 (s, 3H), 2.18 (s, 3H), 1.50 (s, 18H). This ester (393 mg, 0.51 mmol) was dissolved in TFA (10 mL), stirred at rt for 1 h and concentrated in vacuo. The residue was dissolved in water (65 mL) and adjusted to pH 7.08 with 1 M aq. NaOH. The solution was washed with ether and analysed by reverse-phase HPLC [mobile phase 25 mM Na phosphate, pH 6.0—MeCN (100:45 v/v), t_R 4.4 min. The solution was lyophilised, dissolved in 25 mM Na phosphate, pH 6.0 (110 mL) and pumped onto the preparative HPLC column. The column was first washed with 25 mM Na phosphate, pH 6.0 for 2 h, then with water for 2 h and finally the product was eluted with water–MeOH (4:1 v/v). Fractions containing the product were analysed by HPLC as above, combined and concentrated in vacuo. The residue was dissolved in water, filtered through a 0.2 μm membrane, lyophilised and the remaining yellow powder was dissolved in water (10.5 mL) and quantified by UV–Vis spectroscopy at 300 nm (see above) to give a solution of **4** (Na^+ salt) (27.5 mM, 289 μmol, 48% from **11**); ^{1}H NMR (500 MHz, D_2O, acetone ref.) δ 7.53 (d, J=8.5 Hz, 4H), 7.10 (s, 1H), 6.97 (d, J=8.5 Hz, 2H), 6.85 (d, J=8.5 Hz, 2H), 4.41 (s, 2H), 4.21–4.24 (m, 2H), 4.12–4.19 (m, 4H), 3.91 (t, J= 7.7 Hz, 2H), 3.68–3.76 (m, 2H), 2.92 (t, J=7.4 Hz, 2H), 2.10 (s, 3H), 1.93 (s, 3H); LRMS (ESI) calcd for $(C_{30}H_{30}N_3O_{12}P+H)^-$: 656.2; found: 656.4.

4.3. Synthesis of 4-[2-(1-acetyl-5-methyl-7-nitroindolin-4-oxy)ethoxy]-4′-[2-(dihydroxyphosphoryloxy)ethoxy] benzophenone (19)

4.3.1. 4-Hydroxy-4′-(trimethylacetoxy)benzophenone (24). A solution of 4,4′-bis(trimethylacetoxy)benzophenone **23** (7.65 g, 20 mmol; see Supplementary Data) in THF (40 mL) was diluted with MeOH (360 mL) and rapidly mixed with 1 M aq. NaOH (40 mL, 40 mmol). The solution was stirred at rt for 1.5 min, then neutralised with 1 M aq. citric acid (40 mL, 40 mmol) and concentrated. The residue was diluted with water and washed with EtOAc and the combined organic phases were washed with brine, dried and evaporated to give **24** as white crystals (4.38 g, 73%), mp 171–173 °C (EtOAc), mp 171–173 °C (lit.[11a] 171–173 °C).

4.3.2. 4-(2-Hydroxyethoxy)-4′-(trimethylacetoxy)benzophenone (25). To a solution of **24** (3.88 g, 13 mmol) in butanone (260 mL) was added anhydrous K_2CO_3 (3.59 g, 26 mmol), NaI (1.3 g) and 2-bromoethanol (8.12 g, 65 mmol), and the mixture was heated under reflux. The progress of the reaction was followed by TLC [EtOAc–hexanes (1:1)]. Further amounts of 2-bromoethanol (8.12 g), NaI (1.3 g) and anhydrous K_2CO_3 (3.59 g,) were added after each of 2 h and 5 h and reflux was continued for a total of 7 h. The solid was filtered off, washed with acetone and the filtrate was evaporated. The residue was taken up in EtOAc (80 mL) and washed with water and brine, dried and evaporated. Flash chromatography [EtOAc–hexanes (1:1)] gave two fractions. The unreacted starting phenol **24** (0.64 g, 16%) eluted first, followed by **25** as white crystals (2.69 g, 60%), mp 115–116 °C (EtOAc–hexanes); ^{1}H NMR (500 MHz) δ 7.82 (dt, J=8.6, 2.0 Hz, 2H), 7.80 (dt, J=8.6, 2.0 Hz, 2H), 7.18 (dt, J=8.6, 2.2 Hz, 2H), 6.99 (dt, J=8.6, 2.2 Hz, 2H), 4.18 (t, J=4.4 Hz, 2H), 4.03 (dt, J=4.4, 6.2 Hz, 2H), 2.00 (t, J=6.2 Hz, 1H, exchanges with D_2O), 1.38 (s, 9H). Anal. calcd for $C_{20}H_{22}O_5$ ¼H_2O: C, 69.25; H, 6.54. Found: C, 69.51; H, 6.33; HRMS (ESI): calcd for $(C_{20}H_{22}O_5+H)^+$: 343.1540. Found: 343.1552.

4.3.3. 4-{2-[Di(*tert*-butoxy)phosphoryloxy]ethoxy}-4′-(trimethylacetoxy)benzophenone (26). A solution of **25** (2.40 g, 7 mmol) in dry THF (50 mL) was treated under nitrogen with 1*H*-tetrazole (1.96 g, 28 mmol) and di-*tert*-butyl *N*,*N*-diethylphosphoramidite (93% purity; 3.75 g, 14 mmol) and the mixture was stirred at rt overnight. The solution was cooled to 0 °C and treated dropwise with a solution of *m*-chloroperbenzoic acid (55% peracid; 6.59 g, 21 mmol) in CH_2Cl_2 (50 mL). The solution was stirred at 4 °C for 1 h, diluted with CH_2Cl_2 (100 mL), washed with 10% aq. $Na_2S_2O_5$ and the organic phase was washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated. Flash chromatography [EtOAc–hexanes (4:1)] gave **26** as white crystals (3.18 g, 85%), mp 80–81 °C (Et_2O–hexanes); ^{1}H NMR (500 MHz) δ 7.81 (dt, J=8.6, 2.0 Hz, 2H), 7.80 (dt, J=8.6, 2.0 Hz, 2H), 7.18 (dt, J=8.6, 2.0 Hz, 2H), 6.97 (dt, J=8.6, 2.0 Hz, 2H), 4.31–4.34 (m, 2H), 4.25–4.28 (t, J=5 Hz, 2H), 1.50 (s, 18H), 1.38 (s, 9H). Anal. calcd for $C_{28}H_{39}O_8P$: C, 62.91; H, 7.35; found: C, 63.00; H, 7.38.

4.3.4. 4-{2-[Di(*tert*-butoxy)phosphoryloxy]ethoxy}-4′-hydroxybenzophenone (18). A solution of **26** (2.94 g, 5.5 mmol) in MeOH (220 mL) was treated with water

(16.5 mL) and 1 M aq. NaOH (5.5 mL, 5.5 mmol) and stirred at rt for 40 min, then neutralised with 1 M aq. citric acid (5.5 mL, 5.5 mmol) and concentrated. The residue was diluted with water and washed with EtOAc and the combined organic phases were washed with brine, dried and evaporated to give **18** as white crystals (2.24 g, 90%), mp 104–106 °C (EtOAc–hexanes); ^{1}H NMR (500 MHz) δ 7.73 (dt, J=8.6, 2.0 Hz, 2H), 7.69 (dt, J=8.6, 2.0 Hz, 2H), 6.95 (dt, J=8.6, 2.0 Hz, 2H), 6.91 (dt, J=8.6, 2.0 Hz, 2H), 4.31–4.34 (m, 2H), 4.23 (t, J=4.7 Hz, 2H), 1.51 (s, 18H). Anal. calcd for $C_{23}H_{31}O_9P$: C, 61.33; H, 6.94; found: C, 61.13; H, 7.05.

4.3.5. 1-Acetyl-4-(2-hydroxyethoxy)-5-methylindoline (20). A solution of **7** (1.53 g, 8 mmol) and ethylene carbonate (1.41 g, 16 mmol) in dry DMF (40 mL) was treated with tetraethylammonium bromide (0.17 g, 0.8 mmol) and the mixture was heated at 140 °C for 20 h. The solvent was then evaporated under reduced pressure and the residue, dissolved in a mixture of EtOAc (50 mL) and MeOH (10 mL), was washed with 1 M aq. NaOH and brine, dried and evaporated to give **20** as white crystals (1.39 g, 74%), mp 112–113 °C (EtOAc–hexanes); ^{1}H NMR (500 MHz) δ 7.87 (d, J=8.2 Hz, 1H), 7.01 (d, J=8.2 Hz, 1H), 4.04 (t, J=8.4 Hz, 2H), 3.97 (t, J=4.4 Hz, 2H), 3.90–3.93 (m, 2H), 3.19 (t, J=8.4 Hz, 2H), 2.24 (s, 3H), 2.20 (s, 3H). Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95; found: C, 66.38; H, 7.38; N, 6.03.

4.3.6. 1-Acetyl-4-[2-(*tert*-butyldimethylsilyloxy)ethoxy]-5-methylindoline (21). To a solution of **20** (1.29 g, 5.5 mmol) in dry CH_2Cl_2 (55 mL) was added imidazole (0.56 g, 8.25 mmol) and *tert*-butyldimethylsilyl chloride (0.99 g, 6.6 mmol) and the mixture was stirred at rt under nitrogen overnight. The precipitated white solid was filtered off, washed with CH_2Cl_2 and the filtrate was washed with 0.5 M aq. HCl, saturated aq. $NaHCO_3$ and brine, dried and evaporated to give **21** as white crystals (1.82 g, 95%), mp 101–102 °C (Et_2O–hexanes); ^{1}H NMR (500 MHz) δ 7.84 (d, J=8.1 Hz, 1H), 6.99 (d, J=8.1 Hz, 1H), 4.05 (t, J=8.4 Hz, 2H), 3.89–3.97 (m, 4H), 3.20 (t, J=8.4 Hz, 2H), 2.24 (s, 3H), 2.20 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H). Anal. calcd for $C_{19}H_{31}NO_3Si$: C, 65.29; H, 8.94; N, 4.01; found: C, 65.27; H, 9.09; N, 3.96.

4.3.7. 1-Acetyl-4-[2-(*tert*-butyldimethylsilyloxy)ethoxy]-5-methyl-7-nitroindoline (22). A solution of **21** (1.75 g, 5 mmol) in a mixture of acetic anhydride (15 mL) and CCl_4 (30 mL) was treated with claycop (3.20 g) and the mixture was stirred at rt for 3 h. The solid was filtered off, washed with CCl_4 and the filtrate was evaporated. The residue was dissolved in EtOAc (50 mL) and washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated. Flash chromatography [EtOAc–hexanes (1:1)] gave **22** as yellow crystals (1.51 g, 86%), mp 79–80 °C (Et_2O–hexanes); ^{1}H NMR (500 MHz) δ 7.54 (s, 1H), 4.21 (t, J=8 Hz, 2H), 4.02 (t, J=4.7 Hz, 2H), 3.91 (t, J=4.7 Hz, 2H), 3.21 (t, J=8 Hz, 2H), 2.28 (s, 3H), 2.23 (s, 3H), 0.90 (s, 9H), 0.09 (s, 6H). Anal. calcd for $C_{19}H_{30}N_2O_5Si$ ¼H_2O: C, 57.19; H, 7.70; N, 7.02; found: C, 57.18; H, 7.79; N, 7.14.

4.3.8. 1-Acetyl-4-(2-hydroxyethoxy)-5-methyl-7-nitroindoline (17). A solution of **22** (1.46 g, 3.7 mmol) and acetic acid (0.45 g, 7.4 mmol) in THF (37 mL) was treated at 0 °C with TBAF (1 M in THF; 7.4 mL, 7.4 mmol) and the mixture was stirred at rt overnight. The solvent was evaporated and the residue was taken up in EtOAc (40 mL) and washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to give **17** as yellow crystals (0.87 g, 84%), mp 171–173 °C (EtOAc–MeOH); ^{1}H NMR (500 MHz; $CDCl_3$+DMSO-d_6) δ 7.50 (s, 1H), 4.30 (t, J=5.5 Hz, 1H, exchanges with D_2O), 4.23 (t, J=8 Hz, 2H), 4.07 (t, J=4.8 Hz, 2H), 3.85–3.88 (m, 2H), 3.26 (t, J=8 Hz, 2H), 2.30 (s, 3H), 2.24 (s, 3H). Anal. calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99; found: C, 55.67; H, 5.78; N, 9.83.

4.3.9. 4-[2-(1-Acetyl-5-methyl-7-nitroindolin-4-oxy)-ethoxy]-4′-[2-(dihydroxy-phosphoryloxy)ethoxy]benzophenone (19). A solution of **17** (0.21 g, 0.75 mmol) in dry THF (14 mL) was treated with **18** (0.38 g, 0.85 mmol) and triphenylphosphine (0.24 g, 0.9 mmol) and cooled to 0 °C under nitrogen. Diisopropyl azodicarboxylate (95% purity; 0.19 g, 0.9 mmol) was added and the mixture was stirred at rt under nitrogen for 24 h. The solvent was evaporated, the residue was dissolved in EtOAc (30 mL) and washed with 0.5 M aq. NaOH, 0.5 M aq. HCl and brine, dried and evaporated. Flash chromatography [EtOAc, then EtOAc–MeOH (95:5)] followed by trituration with ($CHCl_3$–hexanes) gave the di-*tert*-butyl ester of **23** as a pale foam (0.47 g, 88%) which was used in the next step without further purification; ^{1}H NMR (500 MHz) δ 7.80 (dt, J=9.0, 2.0 Hz, 2H), 7.78 (dt, J=9.0, 2.0 Hz, 2H), 7.57 (s, 1H), 6.98 (dt, J=9.0, 2.0 Hz, 2H), 6.97 (dt, J=9.0, 2.0 Hz, 2H), 4.35 (s, 4H), 4.31–4.35 (m, 2H), 4.27 (t, J=4.9 Hz, 2H), 4.22 (t, J=8 Hz, 2H), 3.22 (t, J=8 Hz, 2H), 2.31 (s, 3H), 2.25 (s, 3H), 1.50 (s, 18H). This ester (0.46 g, 0.65 mmol) was dissolved in TFA (10 mL), stirred at rt for 1 h and concentrated in vacuo. The residue was dissolved in water (72 mL) and adjusted to pH 7.1 with 1 M aq. NaOH. The solution was washed with ether and analysed by reverse-phase HPLC [mobile phase 25 mM Na phosphate, pH 6.0—MeCN (100:55 v/v)], t_R 4.6 min. The solution was lyophilised, dissolved in 25 mM Na phosphate, pH 6.0 (100 mL) and pumped onto the preparative HPLC column. The column was first washed with 25 mM Na phosphate, pH 6.0 for 1 h, then with water for 2 h and product was eluted with water–MeOH (3:2 v/v). Fractions containing the product were analysed as above, combined and concentrated in vacuo. The residue was dissolved in water, passed through a 0.2 μm membrane filter, lyophilised and the yellow powder obtained was dissolved in water (15 mL), quantified by UV–Vis spectroscopy at 300 nm (see above), to give **19** (Na^+ salt) (22.1 mM, 331 μmol, 51%); ^{1}H NMR (500 MHz, D_2O, acetone ref.) δ 7.57 (d, J=8.5 Hz, 2H), 7.54 (d, J=8.5 Hz, 2H), 7.24 (s, 1H), 7.00 (d, J=8.9 Hz, 2H), 6.82 (d, J=8.5 Hz, 2H), 4.22–4.28 (m, 6H), 4.12–4.17 (m, 2H), 4.08 (t, J=7.5 Hz, 2H), 3.01 (t, J=7.5 Hz, 2H), 2.17 (s, 3H), 2.01 (s, 3H); LRMS (ESI) calcd for $(C_{28}H_{27}N_2O_{11}P+H)^-$: 599.1; found: 599.2.

4.4. Photolysis experiments

4.4.1. Comparative irradiation of (2b) and (4). Separate solutions of **2b** and **4** (each 0.3 mM in 25 mM Na phosphate, pH 7.0 with 5 mM dithiothreitol) were

simultaneously irradiated in 1 mm path length cells. The solutions were analysed by reverse-phase HPLC with mobile phases of 25 mM Na phosphate, pH 6.0—MeCN (100:40 v/v) for **2b**, t_R 4.6 min and 25 mM Na phosphate, pH 6.0—MeCN (100:45 v/v) for **4**, t_R 5.6 min. The extent of photolysis of each solution was determined by comparison of peak heights with those of unphotolysed controls. After 5 s irradiation, conversions for **2b** and **4** were 39.0% and 45.1%, respectively, indicating that photolysis of **4** was ~1.16-fold more efficient than that for **2b**.

4.4.1.1. Attempted photolysis of (12). A solution of **12** (0.22 mM in 25 mM Na phosphate pH 7.0) was irradiated in a 1 mm path length cell for increasing times up to 8 min and monitored by UV–Vis spectroscopy. No change in the spectrum was observed throughout the irradiation time course.

4.4.1.2. Progressive photolysis of (19). A solution of **19** (0.23 mM in 25 mM Na phosphate, pH 7.0) was irradiated in a 1 mm path length cell for increasing times in the range of 0–35 s. The extent of photolysis was monitored by UV–Vis spectroscopy. Conversion was ~50% after 5.5 s and the spectral evolution was complete after 30 s.

4.4.1.3. Relative photolysis efficiencies of (19) and (2b). Separate solutions of **2b** and **19** (each 0.3 mM in 25 mM Na phosphate, pH 7.0 with 5 mM dithiothreitol) were simultaneously irradiated in 1 mm path length cells. The solutions were analysed by reverse-phase HPLC with mobile phases 25 mM Na phosphate, pH 6.0—MeCN (100:40 v/v) for **2b**, t_R 4.0 min and 25 mM Na phosphate, pH 6.0—MeCN (100:55 v/v) for **19**, t_R 5.1 min. The extent of photolysis of each solution was determined by comparison of peak areas with those of unphotolysed controls and quantification was by measurement of peak heights. After 5 s irradiation, conversions for **2b** and **19** were 49.0% and 49.3%, respectively, indicating that the two compounds photolysed with essentially equal efficiency.

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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.2004.10.094

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First chemical study of anaspidean *Syphonota geographica*: structure of degraded sterols aplykurodinone-1 and -2

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Abstract—Two unprecedented degraded sterols, aplykurodinone-1 (**1**) and -2 (**2**), have been isolated from the skin of the marine anaspidean *Syphonota geographica*, collected along the coasts of Greece. The structures and the relative stereochemistry were established by spectroscopic analysis and confirmed by chemical correlation with related known compounds.

1. Introduction

Opisthobranch molluscs belonging to the order Anaspidea are herbivorous sea slugs in which the shell is retained merely as an internal plate, or lost altogether.[1] Most of them belong to the family Aplysiidae and are commonly called 'sea hares' because of their rabbit-like appearance. Frequently found in shallow waters, the sea hares generally feed on algae from which they sequester secondary metabolites. For this reason, most of the chemicals reported from anaspideans are typical algal metabolites[2,3] even though some peculiar molecules, including degraded sterols,[4–6] oxylipins,[7] and polypropionates,[8] isolated from the skin of anaspidean species have been suggested to be biosynthesised de novo.

Syphonota geographica (Adams and Reeve, 1850) is a sea hare belonging to the family Aplysiidae, the name of which refers to the map-like drawings on its body. The mollusc, listed by Eales (1960) as being circumtropical,[9] was collected off Porto Germeno, along Greek coasts, during December 2002, and its presence in the Mediterranean Sea is probably due to a Lessepsian migration from the Indo-Pacific Ocean through the Suez Canal. A preliminary chemical analysis of secondary metabolites isolated from the ether extract of internal glands of the mollusc showed the presence of a series of polar phenolic and glycosyl components, which are still under investigation as well as their dietaric origin from the invasive sea grass *Halophila stipulacea*, fragment of which were identified in the stomach content of the mollusc. On the other side, the ether extract of the mantle of *S. geographica* was significantly different from that of internal organs, being characterised by the presence of two molecules more polar than sterols, which were absent in the internal extract, along with the usual lipids. We report here the isolation and structure elucidation of these new metabolites.

Seven frozen specimens of *S. geographica* (average size 7 cm) were dissected into mantle and internal organs, that were separately extracted with acetone exhaustively under ultrasound vibration. TLC chromatographic comparison of diethyl ether soluble parts of both extracts showed the presence in the mantle of a spot detected by spraying with $CeSO_4$, less polar than sterols, at R_f 0.60 (light petroleum/diethyl ether, 2:8). The mantle ether extract (66.3 mg) was subsequently submitted to a Silica gel column (light petroleum ether/diethyl ether gradient) and the fraction (10.2 mg) eluted after sterols was further purified on a pasteur-pipette Si-gel column (benzene/diethyl ether gradient) to give, in order of increasing polarity, two related novel compounds, named aplykurodinone-1 (**1**) (2.4 mg) and aplykurodinone-2 (**2**) (3.0 mg) {R_f=0.45 and 0.20 [benzene/diethyl ether, 7:3 (v:v)], respectively}.

A preliminary ^{1}H NMR analysis of compounds **1** and **2** revealed strong structural similarities between the two molecules, both exhibiting an oxygenated terpenoid

Keywords: Marine natural products; Anaspideans; Sterols.
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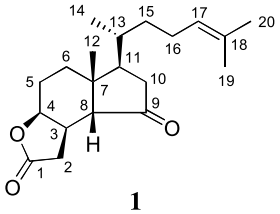
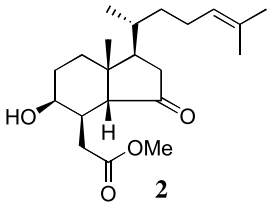
skeleton. In addition, a slow conversion of compound **2** into **1** was observed in $CHCl_3$ solution, further confirming the close structural relationship between them.



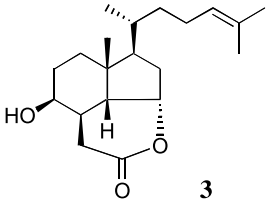
1



2

Compound **1** was considered first. Its molecular formula $C_{20}H_{30}O_3$ was deduced by the sodiated molecular peak in the HRESMS spectrum at *m/z* 341.2083 $(M+Na)^+$, indicating six degrees of unsaturation. The presence of both ketone and ester functional groups was suggested by two intense infrared bands at 1745 and 1782 cm^{-1} and confirmed by two signals in the ^{13}C NMR spectrum at δ 217.7 and 176.1, respectively. In particular, the downshift value of the carbonyl resonance indicated the location of the keto-functionality in a five-membered ring. A trisubstituted terminal double bond bearing two geminal vinyl methyls (δ 5.06, 1.69 and 1.60 in the ^1H NMR spectrum and δ 131.8 (s), 124.2 (d), 25.7 (q) and 17.7 (q) in the ^{13}C NMR spectrum) takes into account another degree of unsaturation, suggesting a tricyclic carbon skeleton. The presence of two additional methyl groups linked to sp^3 carbons was revealed by 3H signals in the ^1H NMR spectrum at δ 1.03 (s, H_3-12) and δ 1.00 (d, $J=7$ Hz, H_3-14). Furthermore, the ^1H NMR spectrum displayed a signal at δ 4.63 (app. q, $J=$ 7 Hz, H-4), which was attributed to an esterified carbinolic proton, showing cross-peaks in ^1H–^1H COSY experiment with both a methylene at δ 2.12 and 1.64 (H_2-5), in turn coupled with another methylene group (δ 1.73 and 1.48, H_2-6), and a methine at δ 2.47 (m, H-3). This latter proton was further correlated with a methylene at δ 2.89 and 2.58, in the α position to the carboxyl ester group, and also with an angular methine at δ 1.73 (H-8). This data suggested the presence of a γ-lactone ring condensed to a six-member cyclic moiety, as depicted in formula **1**. Analysis of ^1H–^1H COSY spectrum led to the assignment of the remaining spin system to a side chain linked to the five-membered ring containing the keto-functional group. ^{13}C NMR spectroscopic data were consistent with the proposed tricyclic structure **1** that could be derived from a sterol skeleton by the loss of seven carbon atoms from rings A and B of the steroid framework. The position of the carbonyl group at C-9 was confirmed by diagnostic correlations of this carbon (δ 217.7) with H-8 (δ 1.73) and H_2-10 (δ 2.50 and 2.10) in the HMBC spectrum. All proton and carbon resonances were assigned by detailed analysis of 2D NMR spectra (^1H–^1H COSY, HMQC and HMBC experiments) as reported in Table 1.

The relative stereochemistry at the chiral centres was determined on the basis of a series of nOe difference and NOESY experiments. In particular, a diagnostic nOe effect was observed between H_3-12 and either H-8 or H-13, indicating the *cis*-geometry of 7,8-ring fusion and also a co-facial orientation between the angular methyl at C-7 and the side chain at C-11. Mutual enhancement of H-3 and H-4 upon irradiation confirmed the expected *cis*-orientation of γ-lactone ring. No special proximity was detected between H-3 and either H-8 or H_3-12, so the γ-lactone moiety was on the same side with respect to 7,8-junction. This relative stereochemistry is the same as that of aplykurodins (e.g. aplykurodin-B, **3**), degraded sterols previously reported from Pacific *Aplysia kurodai*[4] and from both Mediterranean and Atlantic populations of *Aplysia fasciata*.[5,6] Comparison of spectral data of compound **1** with those of derivative **4**, obtained from natural aplykurodins,[5] supported this hypothesis. In fact, strong similarities were observed for the proton signals of γ-lactone and six-member rings of compounds **1** and **4**, with H-4, which resonates as an apparent quartet ($J=7$ Hz) at δ 4.63 in **1** and δ 4.66 in **4**, being particularly diagnostic. However, in order to confirm the structural relationship, a chemical correlation was elaborated starting from a natural sample of aplykurodinone-B (**5**), re-isolated from Mediterranean *A. fasciata*. According to the previous procedure,[5] a sample of aplykurodinone-B (**5**) was reduced by $NaBH_4$ giving, after standard work-up, a mixture of alcohols. In particular, the expected compound **4**, obtained by conversion in acidic conditions of initially formed **3**,[4] was recovered along with alcohol **6** from the reduction mixture. Compound **4** was purified and oxidised by PDC to give a compound that was identical in all respect with **1**, including $[\alpha]_D$ and CD profile. This clearly confirmed the proposed structure and also indicated that the absolute stereochemistry of compound **1** was the same as that of the known aplykurodins.[4–6]



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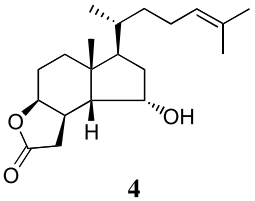

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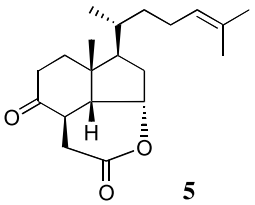

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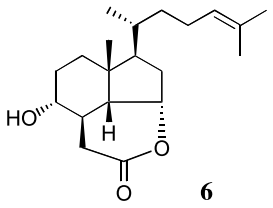
Table 1. NMR data[a,b] for aplykurodinone-1 (**1**) and -2 (**2**)

Position	Aplykurodinone-1					Aplykurodinone-2				
	δ ^{1}H	m, *J*, Hz	δ ^{13}C	m[c]	Long-range connectivities[d]	δ ^{1}H	m, *J*, Hz	δ ^{13}C	m[c]	Long-range connectivities[d]
1			176.1	s	H_2-2, H-3			173.6	s	–OMe, H_2-2
2	2.89	dd, 18, 2	32.9	t	H-3	2.60	dd, 16, 4	33.8	t	H-3, H-8
	2.58	dd, 18, 8				2.49	dd, 16, 9			
3	2.47	m	33.4	d	H_2-2, H-5a	2.08	m	34.9	d	H_2-2, H-8
4	4.63	app.q, 7	78.5	d	H-2a, H-5a, H_2-6, H-8	3.94	bs	66.3	d	H_2-2, H-8
5	2.12	m	24.3	t		1.80	m	27.0	t	H-6a, H_3-12
	1.64	m				1.62	m			
6	1.73	m	31.6	t	H_2-5, H-11, H_3-12	1.82	m	28.0	t	H-8, H-11, H_3-12
	1.48	m				1.72	m			
7			41.3	s	H-3, H_2-10, H-11, H_3-12			41.4	s	H-6a, H-10a, H-11, H_3-12
8	1.73	d, 12	57.1	d	H_2-2, H-4, H_3-12	1.82	d, 12	59.3	d	H_3-12
9			217.7	s	H-8, H_2-10			218.9	s	H-3, H-8, H_2-10
10	2.50	m	41.7	t	H-11	2.55	dd, 19, 9	40.4	t	H-11
	2.10	m				2.05	m			
11	1.87	m	48.2	d	H_2-6, H-8, H-10a, H_3-12, H_3-14	2.23	app.q, 9	42.2	d	H-10b, H_3-12, H_3-14
12	1.03	s	21.4	q	H_2-6, H-11	0.93	s	23.6	q	H-8, H-11
13	1.62	m	34.4	d	H-10a, H-11, H_3-14, H_2-16	1.55	m	34.0	d	H-10b, H-11, H_3-14
14	1.00	d, 7	18.7	q	H-11, H_2-15	1.02	d, 7	19.7	q	H-11, H-15b
15	1.38	m	35.7	t	H-11, H_3-14	1.38	m	35.7	t	H-11, H_3-14, H-16a
	1.10	m				1.10	m			
16	2.05	m	24.8	t		2.10	m	25.1	t	H-17, H_3-19
	1.92	m				1.92	m			
17	5.06	app.t, 7	124.2	d	H_2-16, H_3-19, H_3-20	5.07	m	124.4	d	H_2-15, H_2-16, H_3-19, H_3-20
18			131.8	s	H_2-16, H_3-19, H_3-20			131.7	s	H_2-16, H_3-19, H_3-20
19	1.60	bs	17.7	q	H-17, H_3-20	1.60	bs	17.7	q	H-17, H_3-20
20	1.69	bs	25.7	q	H-17, H_3-19	1.68	bs	25.7	q	H-17, H_3-19
–OMe						3.66	s	51.7	q	

[a] Bruker DPX 300 and AVANCE 400 MHz spectrometers, $CDCl_3$, chemical shifts (ppm) referred to C*H*Cl_3 (δ 7.26) and to *C*DCl_3 (δ 77.0).
[b] Assignments made by ^{1}H–^{1}H COSYand HSQC.
[c] By DEPT sequence.
[d] HMBC experiments ($J = 10$ Hz).



6

Analysis of the ESIMS spectrum of aplykurodinone-2 (**2**) showed a sodiated molecular ion at *m/z* 373 $(M+Na)^+$, which was consistent with a molecular formula $C_{21}H_{34}O_4$ exhibiting 32 additional mass units (CH_4O) with respect to compound **1**. ^1H and ^{13}C NMR spectra indicated that compound **2** differed from **1** in the presence of both a secondary free hydroxyl function at C-4 [δ_H 3.94 (1H, bs), δ_C 66.3 (d)] and a methoxy group esterified with the carboxyl C-1 [δ_H 3.66 (3H, s), δ_C 51.7 (q), 173.6 (s)]. This data clearly suggested that compound **2** was the methyl ester of the hydroxy acid derived by hydrolysis of γ-lactone **1**. Slow conversion of **2** into **1** by elimination of MeOH and intra-molecular *trans*-esterification was observed in $CHCl_3$ solution confirming the structural relationship between aplykurodinones **1** and **2**, including the stereochemical aspects. However, very surprisingly, the carbon value of C-11 (δ 42.2) in aplykurodinone-2 was shifted to high field with respect to the corresponding carbon value (δ 48.2) of aplykurodinone-1, most likely due to a different conformation of the bicyclic compound **2**. Detailed NMR spectroscopic analysis (^1H–^1H COSY, HMQC and HMBC experiments) allowed the assignment of all the proton and the carbon values reported in Table 1.

The role of aplykurodinones in *S. geographica* has not been clarified. They may be involved in the defensive mechanisms of the mollusc since they are selectively localised in the skin of the animal. However, unlike the previously reported aplykurodines which showed strong ichthyotoxic properties, aplykurodinones **1** and **2** were not active in the bioassays against the mosquito fish *Gambusia affinis*. A possible relationship between the hydroxyl function at C-9 and the biological activity of such molecules could be responsible.

Analogously with *Aplysia* metabolites, a biosynthetic origin from a sterol precursor could be ascribed for aplykurodinones in *S. geographica*, but suitable biosynthesis experiments should be conducted to prove this hypothesis. However, the detection of chemical similarities between anaspidean species, collected in different geographic areas and characterised by different alimentary habits, seems to suggest a non-dietary origin of these compounds supporting a biosynthetic hypothesis.

2. Experimental

2.1. General experimental procedures

Silica-gel chromatography was performed using precoated Merck F_{254} plates and Merck Kieselgel 60 powder. HPLC purification was carried out on a Waters liquid chromatograph equipped with a UV detector. Optical rotations were measured on a Jasco DIP 370 digital polarimeter. The IR spectra were taken on a Bio-Rad FTS 7 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on an AVANCE 400 and a DPX 300 MHz Bruker spectrometers in $CDCl_3$; chemical shifts are reported in ppm referred to $CHCl_3$ as internal standard (7.26 for proton and 77.0 for carbon). EIMS were determined at 70 eV on a HP-GC 5890 series II mass spectometer. Low and high resolution ESIMS were performed on a Micromass Q-TOF Micro™.

2.2. Biological material

Seven specimens of *S. geographica* (average size 7 cm) were collected off Porto Germeno, along Greek coasts (Corinthian Gulf), at a depth of 12 m, in December 2002, were immediately frozen and transferred to ICB. One specimen of *A. fasciata* (size 15 cm) was collected in the intertidal zone of the lake Fusaro (Naples), in September 2003 and was frozen at −20 °C. The molluscs were stored at −20 °C till the extraction.

2.3. Extraction and isolation of *S. geographica*

Each specimen of *S. geographica* was carefully dissected into mantle and internal organs, which were separately extracted by acetone (3×20 mL) at room temperature. The filtered acetone solutions were concentrated and the residual H_2O was extracted with Et_2O (3×50 mL) and with *n*-BuOH (2×50 mL) successively. The Et_2O phases of both mantle and internal organs sections were concentrated under reduced pressure to give 66.0 and 589.0 mg of crude material, respectively. The composition of both Et_2O extracts was analysed by TLC chromatography (light petroleum ether/Et_2O in several ratios) using $CeSO_4$ to detect the spots.

The mantle Et_2O extract (66.0 mg) was submitted to silica-gel column using light petroleum ether with increasing amounts of Et_2O as eluent. The degraded sterols containing fraction (10.2 mg), eluted after sterols, was further purified on a pipette-pasteur silica-gel column (benzene/diethyl ether gradient) affording **1** (2.4 mg) and **2** (3.0 mg) [R_f (30% Et_2O/benzene) 0.45 and 0.20 respectively].

2.3.1. Aplykurodinone-1 (1). Amorphous white solid. $[\alpha]_D^{25}$ +51.2° (*c* 0.30, $CHCl_3$); CD (*n*-hexane), θ_{315} +1610; ν_{max} (liquid film) 1782, 1745 cm^{-1}; ^1H and ^{13}C NMR in Table 1; *m/z* 318 (48, M^+), 300 (9, $M-H_2O$), 247 (26, $M-C_5H_{11}$), 229 (13, $M-C_5H_{11}-H_2O$), 207 (56, M-side chain), 189 (100, M-side chain-CH_3), 147 (17), 109 (26), 95 (30%); HRMS (ESI): $(M+Na)^+$, found 341.2083. ($C_{20}H_{30}O_3+Na)^+$ requires 341.2093.

2.3.2. Aplykurodinone-2 (2). Amorphous white solid. $[\alpha]_D^{25}$ +9.1° (*c* 0.24, $CHCl_3$); CD (*n*-hexane), θ_{218} −840; ν_{max} (liquid film) 1735 cm^{-1}; ^1H and ^{13}C NMR in Table 1; *m/z* 318 (71), 300 (8), 285 (4), 247 (13), 229 (12), 207 (67), 189 (100), 161 (12), 147 (17), 109 (12), 95 (17%); HRMS (ESI): $(M+Na)^+$, found 373.2362. ($C_{21}H_{34}O_4+Na)^+$ requires 373.2355.

2.4. Extraction of *A. fasciata* and isolation of aplykurodinone B (5)

One specimen of *A. fasciata* was dissected into mantle and internal organs, which were separately extracted by acetone (3×35 mL). The mantle acetone extract was partitioned between Et_2O and H_2O to give 256 mg of ether crude extract. An aliquot of this extract (85 mg) was purified on preparative TLC (30% Et_2O/light petroleum ether) affording compound **5** (11 mg): $[\alpha]_D^{25}$ −46.9° (*c* 0.5, $CHCl_3$), $[\alpha]_D^{20}$ lit.[5] −198.0° (*c* 0.73, $CHCl_3$).

2.5. $NaBH_4$ reduction of compound 5

To a solution containing **5** (11.0 mg, 0.035 mmol) dissolved in EtOH (1 mL), $NaBH_4$ (1.5 mg, 0,039 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. Excess $NaBH_4$ was eliminated adding a drop of AcOH, and usual work-up gave 11 mg of crude product. This product was purified on TLC using 20% Et_2O/light petroleum ether as eluent, affording 3.0 mg of **4** and 2.4 mg of **6**. The two compounds were identified by comparison of spectral data (^1H NMR, ^{13}C NMR) with those reported in the literature.[5]

2.6. PDC oxidation of compound 4

To a solution containing **4** (3.0 mg, 0.009 mmol) dissolved in anhydrous THF (1.5 mL), PDC (3.0 mg, 0.008 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. After neutralization of pH, the usual work-up gave 2.4 mg of crude product, which was purified by *n*-phase HPLC (Kromasil 5μ 100A silica 250× 10.00 mm, *n*-hexano/isopropanol, 99:1; flow rate 2.5 mL/min) affording a compound (1.0 mg) that was identical in all respect with **1** (^1H NMR, ^{13}C NMR and MS): $[\alpha]_D^{25}$ +38.2° (*c* 0.1, $CHCl_3$); CD (*n*-hexane), θ_{315}+1580.

Acknowledgements

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Regioselective synthesis of optically active (pyrazolyl)pyridines with adjacent quaternary carbon stereocenter: chiral *N,N*-donating ligands

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Abstract—Novel optically active 2-(pyrazol-1-yl)pyridines have been prepared using resolved the *O*-methyl ether of atrolactic acid as a source of the adjacent quaternary carbon stereocenter. Different regioisomers were formed selectively in the reaction of 2-hydrazinopyridines with the chiral 1,3-diketone and in the nucleophilic substitution of 2-chloropyridines with the potassium salt of the chiral pyrazole. The second route gave 2-(pyrazol-1-yl)pyridines with the stereogenic center neighboring the coordinating nitrogen in the pyrazole ring. Also, new C_2-symmetric chiral ligands based on 2,6-bis(pyrazolyl)pyridine and 6,6′-bis(pirazolyl)-2,2′-bipyridine structures were obtained.

1. Introduction

Chiral chelating ligands are considered as important for transition-metal catalyzed enantioselective reactions.[1] Usually, the most successful are C_2 symmetric catalysts.[2] However, in some prominent cases, lack of C_2 symmetry leads to additional stereoelectronic effects that improve enantioselectivity.[2] This effect can be attained using heterodonatig ligands, for example, N, S-[3] or ligands with donating atoms of the same element but differing in electronic character. A plethora of chiral *N,N*-donating ligands have already been described,[4] but only a few of them combine pyrazole (π-excessive, weaker basicity) and pyridine (π-deficient, higher basicity) systems.[5] The most prepared chiral pyrazoles are those derived from the natural monoterpenes. On the other hand, achiral ligands of this type are well known and their complexes were studied.[6] As well as the complexing property, another feature essential for enantioselectivity in catalysis is a stereocontrolling element. In order to gain high chiral discrimination it is usually located closely to the catalytically active metal center. For all these reasons, we decided to develop the synthesis of 2-(pyrazol-1-yl)pyridines bearing a chiral quaternary carbon center derived from enantiomeric the *O*-methyl ether of atrolactic acid. This nonracemizing acid is an analogue of the *O*-methyl ether of mandelic acid, well known for its high stereodiscriminating properties.[7] In spite of that fact, its synthetic use has not been explored up to now.

2. Results and discussion

A multi-gram synthesis of racemic *O*-methyl ether of atrolactic acid (**2**) was carried out in three steps from inexpensive *rac*-mandelic acid. The racemic product was resolved by the crystallization of its brucine salt[8a] and subsequently both enantiomeric acids were esterified. The methyl ester **1** (90% e.e., ^{1}H NMR spectroscopy with Eu(hfc)$_3$) and acetone underwent the Claisen condensation using sodium hydride to give the corresponding chiral 1,3-diketone **3** in good yield (Scheme 1).

Both enantiomeric diketones were submitted to the reaction with hydrazine to give the respective chiral pyrazole **4**. 2-Hydrazinopyridine and 2-chloro-6-hydrazinopyridine were treated with the diketone **3** analogously and the optically active 2-(pyrazol-1-yl)pyridines **5a** and **5b** resulted in each case as a single product, respectively (Scheme 2).

When the potassium salt of chiral pyrazole **4** was used in a nucleophilic substitution with 2,6-dichloropyridine, depending upon the ratio of reagents, the other (pyrazolyl)pyridine **6** or **7** was formed (Scheme 3).

Keywords: Cyclization; Pirazolylpyridines; Quaternary carbon stereocenter; Nitrogen chiral ligands.
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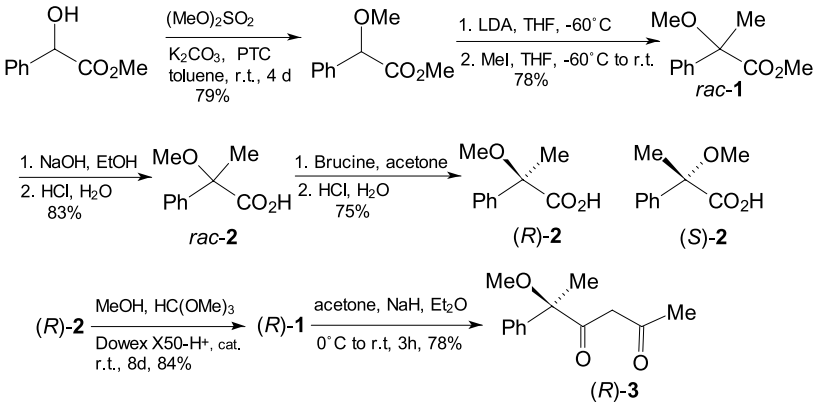
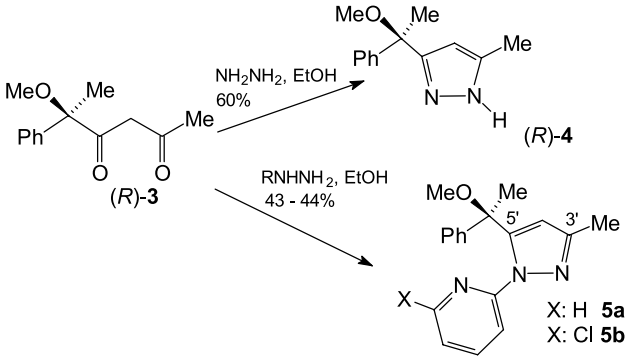
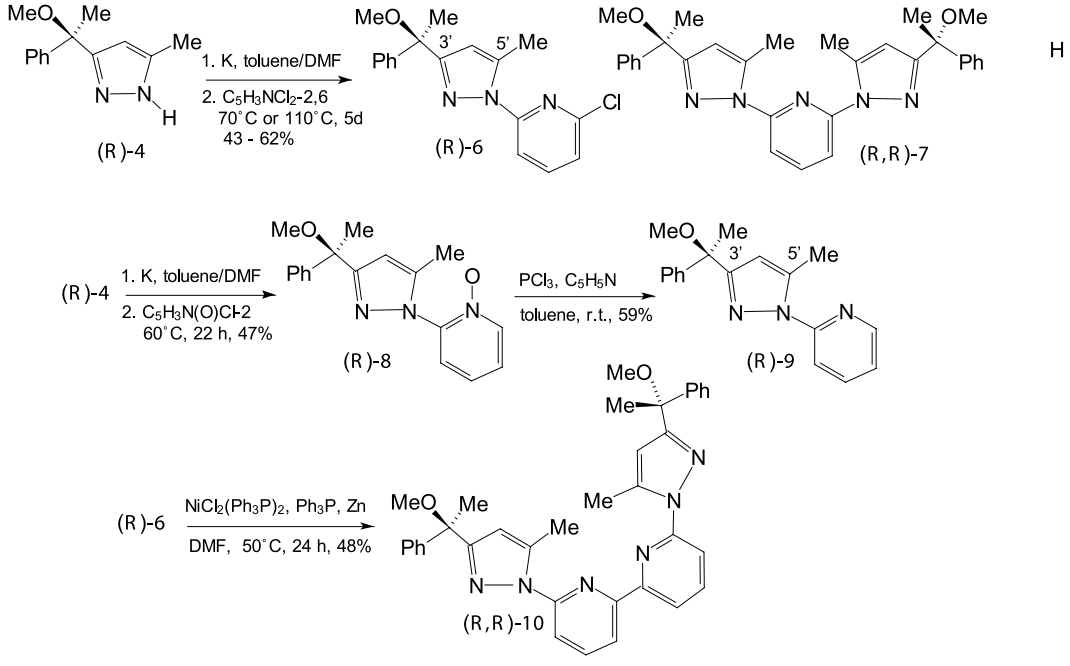


Scheme 1.



Scheme 2.

The products **5b** and **6** are regioisomers and both types of compounds have already been reported. Generally, the reaction of arylhydrazines with unsymmetrical 1,3-diketones leads to mixtures of both regioisomers.[9] On the other hand, the pyrazoles bearing bulky substituents give main products of N-arylation at the nitrogen furthest from the bulky group.[10] Here, both reactions were regioselective and the structures of the products were unambiguously established by ^{1}H NMR spectroscopy. Thus, the cyclization products **5** showed the presence of a 3′-methyl group $\delta=$ 2.2–2.3 ppm, while the substitution products **6** and **9** showed the 5′-methyl deshielded by the pyridine moiety to $\delta=2.5$–2.7 ppm. This interpretation has already been proposed for similar compounds.[11] Moreover, 2,6-bis(pyrazol-1-yl)pyridine derivative **7** formed in the substitution of 2,6-dichloropyridine with four equivalents of the potassium salt of chiral pyrazole was a regio- and diastereomerically pure product of C_2-symmetry with both pyrazole 5′-methyl groups appearing as a single resonance at $\delta=2.55$ ppm. Additionally, inspection of a molecular model for the prevailing *trans*,*trans*-conformation of 5′-methyl derivative **7** suggests that the *O*-methyl group should be deshielded by the pyrazole nitrogen lone pair (observed $\delta=3.26$ ppm). A similar chemical shift was found for **9** ($\delta=3.27$ ppm). This effect is not expected for **5a** (observed $\delta=3.06$ ppm). This explanation is in accord with nuclear Overhauser effects that



Scheme 3.

we observed in the respective NOESY spectra, namely for **5a**: OMe gave a strong cross-peak with 3-H and for **7**: no such NOE enhancement was detected between OMe and 3-H.

An attempted direct nucleophilic substitution with 2-chloropyridine failed, so we activated this derivative by its oxidation to the respective *N*-oxide. In this case we obtained the corresponding 2-(pyrazol-1-yl)pyridine-1-oxide **8** as a single product. Finally, the deoxygenation of **8** with phosphorus trichloride in the presence of excess pyridine gave the required *N*,*N*-complexing ligand **9** (Scheme 3).

An interesting C_2-symmetric tetradentate ligand **10** was obtained by the reductive homocoupling of the 2-chloro-6-(pyrazol-1-yl)pyridine **6** with $Ni(Ph_3P)_2Cl_2/Zn/Ph_3P$.[12] Even though the starting material was of 90% e.e., both C_2-symetric derivatives, **7** and **10** were obtained as enantiopure products and no *meso*-diastereomers could be detected.

It is noteworthy that the nucleophilic substitution products **7**, **9** and **10** with 5′-methyl groups contain a potentially highly stereodiscriminating center at 3′-positions, in close proximity to the complexed metal. This makes them very promising chiral ligands. However, preliminarily examination of their catalytic use in the Pd-catalyzed allylic alkylation of dimethyl malonate with *rac*-1,3-diphenyl-2-propenyl acetate[3b] gave ca 30% e.e. as the best result. Further work on the catalytic use of the new ligands with other transition metals is currently underway in our laboratory.

3. Experimental

3.1. General

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker CPX (^{1}H, 300 MHz) or a Bruker Avance (^{1}H, 500 MHz) spectrometer using TMS as an internal standard. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. GC/MS analyses were determined on a Hewlett-Packard 5890 II gas chromatograph (25 m capillary column) with a Hewlett Packard mass spectrometer 5971 A operating on the electron impact mode (70 eV). High resolution mass spectra were recorded on a Finnigan MAT 95 spectrometer operating on the same mode (EI, 70 eV). Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck. Thin layer chromatography analyses were performed using silica gel 60 precoated plates (Merck).

3.2. α-Methoxy-α-phenylacetic acid methyl ester

To the mechanically stirred mixture of methyl mandelate (61 g, 0.37 mol), K_2CO_3 (300 g, 2.2 mol) and Adogen® (6.9 g) in toluene (230 mL), at room temperature was added dropwise for 2 h $(CH_3O)_2SO_2$ (52 mL, 0.55 mol). The mixture was left for 2 days and after this time another portion of $(CH_3O)_2SO_2$ (7 mL) was added and the stirred mixture was heated at 90 °C for 12 h. After cooling the mixture was treated slowly with water until the layers were separated. The aqueous phase was saturated with NaCl and extracted with toluene (100 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4). Concentration by distilling off toluene afforded 73 g of the crude product (71.5% by GC/MS, 79% yield), that was directly submitted to the next reaction.

3.2.1. 2-Methoxy-2-phenylpropionic acid (2). To a solution of LDA in THF (4.55 M, 75 mL, 0.34 mol) stirred under argon atmosphere at −60 °C was added for 1 h, by a syringe, a solution of crude α-methoxy-α-phenylacetic acid methyl ester (52.2 g, 0.29 mol) in dry THF (100 mL). The mixture was allowed to warm to 0 °C and it was further stirred for 60 min. After cooling again to −60 °C, a solution of methyl iodide (23 mL, 0.37 mol) in THF (25 mL) was added for 45 min, the mixture was left for 30 min at this temperature and allowed to warm to 20 °C. After 18 h, the reaction mixture was quenched by the addition of HCl (100 mL, 10% aq) and ether (100 mL). The separated organic layer was washed with HCl (100 mL, 1 M, aq), water (100 mL), $NaHCO_3$ (50 mL, sat. aq), brine (50 mL) and dried (Na_2SO_4). Concentration in vacuo gave brown oil (45.5 g), which was treated with solution of NaOH pallets (12.06 g, 0.30 mol) in the mixture of C_2H_5OH–H_2O (150 mL, 11:4, v/v) and allowed to crystallize for 2 days at rt. The filtered crystals were washed with cold C_2H_5OH, recrystallized from C_2H_5OH–H_2O (11:2, v/v) giving pure sodium salt of *O*-methyl atrolactic acid (45.6 g, 96%) as a white solid.

To the solution of sodium salt of **2** (40.2 g, 225 mmol) in water (100 mL) was added in 5 portions HCl (23 mL, 12 M, aq). The resulted emulsion was extracted successively with toluene (10×20 mL). The combined organic extract was washed with water (60 mL) and filtered through a paper filter to give a clear and colorless liquid which was evaporated leaving of *title compound rac*-**2** (28.7 g, 87% yield) as a light yellow oil.

Resolution of the diastereomeric salts of *rac*-**2** (24.7 g) with brucine was carried out according to the literature procedure[8a] and gave 11.37 g (46%) of *R*-(−)-2-methoxy-2-phenyl-propionic acid, *R*-(−)-**2**: $[\alpha]_D=-25.5$ (*c* 1, MeOH), lit[8a]: −26 (*c* 1, MeOH) and free *S*-(+)-**2**: 7.22 g (29%), $[\alpha]_D=+24$ (*c* 1.2, MeOH), lit[8a]: +25 (*c* 1, MeOH), lit[8b]: +37.6 (*c* 8.8, MeOH) for 97% e.e.; *m*/*z* (EI, 70 eV) 180 (0.02, M^+), 135 (100), 105 (11), 77 (17), 43 (38%). IR and ^{1}H NMR spectroscopic data identical to that reported in the literature.[13]

3.2.2. *R*-(−)-2-Methoxy-2-phenylpropionic acid methyl ester (*R*-(−)-1). A solution of *R*-(−)-**2** (9.70 g, 53.8 mmol) in methanol (100 mL) with DOWEX 50Wx4 resin, H^+-form (2.7 g) was left for 4 days. Then, after the addition of methyl orthoformate (6 mL), the mixture was refluxed for 10 h. After evaporation the crude product was dissolved in CH_2Cl_2 (100 mL) and left overnight over anhd. K_2CO_3. Solvent evaporation gave pure (GC) *title product R*-(+)-**1** (8.8 g, 84%) as a yellowish oil; $[\alpha]_D=-12.9$ (*c* 0.92, MeOH); Lit.[8a] $[\alpha]_D=-12$, (*c* 1, MeOH). The enantiomeric excess of 90% was determined by ^{1}H NMR in CCl_4 in the

presence of 10 mol% of Eu(hfc)$_3$; $\Delta\delta=0.055$ ppm for the ester methyl singlet was observed with the signal for the major levoratory enantiomer shifted downfield. *S*-(+)-**1**, (90% yield); $[\alpha]_D=+11.9$ (*c* 0.9, MeOH); lit.[8c] for 44% e.e. $[\alpha]_D=+6.4$ (MeOH); *m/z* (EI, 70 eV) 194 (0.2, M^+), 135 (100), 105 (12), 77 (17), 43 (23%). IR and ^{1}H NMR spectroscopic data identical to that reported in the literature.[13]

3.2.3. *R*-5-Methoxy-5-phenyl-hexane-2,4-dione (*R*-(+)-3). To a sodium hydride (1.56 g, 32.5 mmol, 50% dispersion in oil) at 25 °C were added a solutions of *R*-(+)-**1** (2.99 g, 15.4 mmol) in dry ether (8 mL) and, under inert atmosphere by a syringe for 1.5 h, acetone (1.82 g, 31.4 mmol) in dry ether (8 mL). After 45 min the reaction flask was placed on a sonic bath and the addition was continued for the next 40 min. Then the mixture was poured into ether (20 mL), quenched by the addition of water and acidified to pH=2.5 with HCl (1 M). The layers were separated and the aqueous layer was extracted with ether (6×8 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated in vacuo giving 3.40 g of oiled mixture containing 78% (GC/MS) of the *title compound* (2.65 g, 78% yield). This crude product was submitted to the following step without purification. An analytical sample of *R*-(+)-**3** was isolated using column chromatography on silica gel (10% ethyl acetate/*n*-hexane) as a yellow oil; R_f 0.45 (10% ethyl acetate/*n*-hexane); $[\alpha]_D=+91$ (*c* 0.4, MeOH); ν_{max} (liquid film) 3089, 3060, 3026, 2987, 2937, 2831, 1729, 1712, 1599, 1447, 1246, 1173, 1134, 1072, 1047 cm^{-1}; δ_H (300 MHz, $CDCl_3$), for the main (81%) tautomer 15.05 (1H, bs, –O*H*), 7.28–7.46 (5H, m, Ph), 5.96 (1H, s, –C*H*=), 3.25 (3H, s, O–*Me*), 2.07 (3H, s, *Me*), 1.70 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 202.1, 187.5, 141.5, 128.2, 127.7, 126.2, 96.3, 86.2, 51.8, 23.8, 20.3; *m/z* (EI, 70 eV) 220 (0.14, M^+), 135 (100), 105 (7.5), 77 (10), 43 (22%); HRMS (EI): M^+ found 220.1104. $C_{13}H_{16}O_3$ requires 220.1099.

S-(−)-**3** $[\alpha]_D=-96$ (*c* 0.45, MeOH), 79% of the main tautomer by NMR.

3.2.4. *R*-3(5)-(1-Methoxy-1-phenyl-ethyl)-5(3)-methyl-1*H*-pyrazole (*R*-(+)-4). A solution of the crude diketone *R*-(+)-**3** (2.99 g, 12 mmol) and hydrazine monohydrate (2 mL, 41.2 mmol) in absolute ethanol (5 mL) was refluxed for 0.5 h and left overnight at room temperature. Ethanol was evaporated and the residue was partitioned between water (10 mL) and Et_2O (10 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), and the solvent evaporated in vacuo. Purification of the crude product by column chromatography (silica gel, $CHCl_3$/ethyl acetate/EtOH 2:1:0.05, v/v/v) gave the *title compound R*-(+)-**4** (1.55 g, 60% yield) as a yellow oil; R_f 0.34 ($CHCl_3$/ethyl acetate/EtOH 2:1:0.05); $[\alpha]_D=+36$ (*c* 0.86, MeOH); ν_{max} (liquid film) 3396, 3190, 3104, 2936, 2871, 1582, 1493, 1464, 1367, 1185, 1104 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24–7.41 (5H, m, Ph), 5.99–6.12 (1H, bs, N*H*), 5.86 (1H, s, H-4, pyrazole), 3.19 (3H, s, O*Me*), 2.27 (3H, s, *Me*), 1.85 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 151.9, 145.3, 144.5, 128.1, 126.1, 112.6, 103.9, 77.7, 51.0, 25.2, 12.4; *m/z* (EI, 70 eV) 216 (16, M^+), 201 (100), 185 (51), 139 (16), 105 (30), 77 (27%); HRMS (EI): M^+ found 216.1261. $C_{13}H_{16}ON_2$ requires 216.1263.

S-(−)-**4**; $[\alpha]_D=-35.7$ (*c* 0.98, MeOH).

3.2.5. *R*-2-[5-(1-Methoxy-1-phenylethyl)-3-methylpyrazol-1-yl]pyridine (*R*-5a). A solution of *R*-(+)-**3** (100 mg, 0.46 mmol), 2-hydrazinopyridine (50 mg, 0.46 mmol) and TsOH (catalytic amount) in ethanol (1.5 mL) was refluxed for 5 h and then left at room temperature for 2 days. Solvent was removed in vacuo and the residue was treated with water (10 mL) and extracted with CH_2Cl_2 (5×10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel ($CHCl_3$/ethyl acetate/EtOH 2:1:0.025, v/v/v) gave the *title compound* (58 mg, 43% yield) as a brown oil; R_f 0.34 ($CHCl_3$/ethyl acetate/EtOH 2:1:0.025); $[\alpha]_D=+28$ (*c* 0.84, MeOH); ν_{max} (liquid film) 3086, 3058, 3025, 2983, 2935, 2827, 1590, 1575, 1477, 1446, 1364, 1103, 1066 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.24 (1H, dd, $J=4.8$, 1.5 Hz), 7.33 (1H, dt, $J=7.9$, 1.5 Hz), 6.97–7.11 (6H, m), 6.72 (1H, d, $J=7.9$ Hz), 6.29 (1H, s), 3.06 (3H, s), 2.30 (3H, s), 1.76 (3H, s); δ_C (75 MHz, $CDCl_3$) 152.8, 148.8, 148.1, 147.2, 145.2, 136.9, 127.7, 126.9, 125.8, 122.7, 121.0, 108.9, 77.5, 51.0, 26.8, 13.7; *m/z* (EI, 70 eV) 293 (6.7, M^+), 278 (100), 78 (21), 77 (12%); HRMS (EI): M^+ found 293.1533. $C_{18}H_{19}ON_3$ requires 293.1528.

3.2.6. *R*-2-Chloro-6-[5-(1-methoxy-1-phenylethyl)-3-methylpyrazol-1-yl] pyridine (*R*-5b). A solution of *R*-(+)-**3** (129 mg, 0.58 mmol) and 2-chloro-6-hydrazinopyridine (84 mg, 0.58 mmol) in ethanol (6 mL) was refluxed for 3 h, then stirred at room temperature for 17 h and finally concentrated in vacuo. Purification of the residue by column chromatography (silica gel, 10% ethyl acetate/*n*-hexane) gave the *title compound* (84 mg, 44%) as a red oil; R_f 0.33 (10% ethyl acetate/*n*-hexane); $[\alpha]_D=+32$ (*c* 0.74, MeOH); ν_{max} (liquid film) 3087, 3060, 3027, 2983, 2935, 2826, 1581, 1550, 1455, 1411, 1364, 1133, 1100, 1068 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35 (1H, t, $J=7.8$ Hz), 7.13–7.04 (5H, m), 7.01 (1H, dd, $J=7.8$, 0.7 Hz), 6.80 (1H, dd, $J=7.8$, 0.7 Hz), 6.31 (1H, s), 3.06 (3H, s), 2.28 (3H, s), 1.86 (3H, s); δ_C (75 MHz, $CDCl_3$) 152.3, 149.3, 148.9, 148.3, 139.4, 127.7, 127.5, 127.0, 126.1, 122.9, 118.7, 109.3, 76.7, 50.6, 26.1, 13.7; *m/z* (EI, 70 eV) 329 (2, M^+ +2), 327 (7, M^+), 312 (100), 297 (32), 210 (14), 105 (13), 77 (13%); HRMS (EI): M^+ found 327.1145. $C_{18}H_{18}O^{35}ClN_3$ requires 327.1138.

3.2.7. *R*-2-Chloro-6-[3-(1-methoxy-1-phenyl-ethyl)-5-methylpyrazol-1-yl]pyridine (*R*-6). To a solution of *R*-(+)-**4** (380 mg, 1.76 mmol) in toluene (15 mL) pieces of potassium (70 mg, 1.79 mmol) were added followed by the addition of two drops of abs. EtOH. The mixture was stirred at 90 °C until the metal was dissolved. Most of toluene was removed under the reduced pressure and the remaining suspension was treated with a solution of 2,6-dichloropyridine (260 mg, 1.76 mmol) in DMF (5 mL) and kept for 5 days at 67 °C. The mixture was concentrated in vacuo, treated with water (10 mL) and extracted with CH_2Cl_2 (5× 10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel (10% ethyl acetate/*n*-hexane) gave the *title compound* (352 mg, 62%) as a colourless oil; R_f 0.50 (10% ethyl acetate/*n*-hexane); $[\alpha]_D=+76$ (*c* 0.5, MeOH); ν_{max} (liquid film) 3088, 3059,

3026, 2985, 2934, 2826, 1577, 1557, 1472, 1434, 1375, 1131, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.84 (1H, d, J= 8.0 Hz), 7.65 (1H, dd, J=8.0, 7.8 Hz), 7.41 (2H, d, J= 7.9 Hz), 7.25 (2H, dd, J=7.9, 7.0 Hz), 7.17 (1H, t, J=7.0 Hz), 7.09 (1H, d, J=7.8 Hz), 5.97 (1H, s), 3.20 (3H, s), 2.57 (3H, s), 1.86 (3H, s); δ_C (75 MHz, $CDCl_3$) 157.5, 153.3, 148.7, 145.9, 142.3, 140.5, 128.0, 126.9, 126.0, 120.6, 113.8, 108.5, 78.5, 51.2, 24.6, 14.9; *m/z* (EI, 70 eV) 329 (0.2, M^+ +2), 327 (0.8, M^+), 312 (81), 297 (100), 112 (50), 103 (30), 77 (56), 51 (20%); HRMS (EI): M^+ found 327.1139. $C_{18}H_{18}O^{35}ClN_3$ requires 327.1138.

3.2.8. *R,R*-2,6-Bis[3-(1-methoxy-1-phenylethyl)-5-methylpyrazol-1-yl]pyridine (*R,R*-7). To a solution of *R*-(+)-**4** (746 mg, 3.45 mmol) in toluene (15 mL) was added potassium (144 mg, 3.68 mmol) and the reaction mixture was heated to 90 °C under neutral atmosphere until whole metal was dissolved. The mixture was concentrated in vacuo, treated with DMF (6 mL) and 2,6-dichloropyridine (127 mg, 0.86 mmol) and heated for 5 days in 110 °C. Cooled mixture was concentrated, poured into water (10 mL) and extracted with ether (5×8 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and evaporated in vacuo. Purification of the crude product by column chromatography on silica gel (*n*-hexane/$CHCl_3$/ethyl acetate, 6:1:1, v/v/v) gave the *title compound* (*R,R*)-**7** (186 mg, 43%) as a colourless oil; R_f 0.42 (*n*-hexane/$CHCl_3$/ethyl acetate, 6:1:1); $[\alpha]_D^{20}$ +88 (*c* 2.48, MeOH); ν_{max} (liquid film) 3088, 3058, 3026, 2984, 2935, 2826, 1598, 1584, 1471, 1435, 1359, 1145, 1123, 1075 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.87 (1H, t, J=8.1 Hz), 7.76 (2H, d, J=8.1 Hz), 7.66 (4H, d, J=7.9 Hz), 7.27–7.32 (4H, m), 7.20–7.23 (2H, m), 5.98 (2H, s), 3.26 (6H, s), 2.55 (6H, s), 1.92 (6H, s); δ_C (125 MHz, $CDCl_3$) 157.7, 152.0, 146.3, 141.6, 140.8, 128.4, 127.3, 126.5, 114.7, 108.2, 78.9, 51.6, 24.9, 14.8; *m/z* (EI, 70 eV) 507 (1.2, M^+), 445 (13), 43 (100), 39 (13%); HRMS (EI): M^+ found 507.2632. $C_{31}H_{33}O_2N_5$ requires 507.2634.

3.2.9. *R*-2-[3-(1-Methoxy-1-phenylethyl)-5-methyl-pyrazol-1-yl]pyridine-1-oxide (*R*-8). To the stirred solution of *R*-(+)-**4** (220 mg, 1.0 mmol) in toluene (3 mL) pieces of potassium were added (46 mg, 1.1 mmol) and the resulted suspension was heated in 80 °C under argon until whole metal was dissolved. After cooling, a solution of 2-chloropyridine N-oxide (200 mg, 1.5 mmol) in DMF (3 mL) was added dropwise from syringe for 35 min, stirred at this temperature for the next 30 min, and then at 60 °C for 22 h. Most of the solvents were evaporated and remaining DMF was removed in a desiccator. Purification of the crude product by column chromatography (gradient chloroform/chloroform–ethanol 2:0.07, v/v) gave 70 mg of recovered **4** (32%) and the *title compound R*-**8** (149 mg, 47%) as a colourless solid, mp 203–205 °C (EtOH); $[\alpha]_D$ = +80 (*c* 0.22, MeOH); ν_{max} (KBr) 3128, 3100, 3046, 2980, 1557, 1511, 1431, 1370, 1257, 1118, 1030 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.30–8.32 (1H, m), 7.53–7.57 (1H, m), 7.48 (2H, d, J=7.3 Hz), 7.20–7.34 (5H, m), 6.05 (1H, s), 3.27 (3H, s), 2.26 (3H, s), 1.88 (3H, s); δ_C (75 MHz, $CDCl_3$) 159.2, 145.8, 145.5, 144.1, 140.3, 128.0, 126.9, 126.4, 126.1, 125.45, 125.40, 106.1, 78.4, 51.2, 24.7, 11.6; *m/z* (EI, 70 eV) 277 (12), 260 (100), 249 (18), 78 (54), 51 (22%).

3.2.10. *R*-2-[3-(1-Methoxy-1-phenylethyl)-5-methyl-pyrazol-1-yl]pyridine (*R*-9). To a vigorously stirred suspension of *R*-**8** (87 mg, 0.3 mmol) in toluene (1.2 mL) and pyridine (0.8 mL) at 0 °C was added dropwise, by a syringe, phosphorus trichloride (0.1 mL, 1.2 mmol). The mixture was warmed to room temperature for 25 min and sonicated for further 30 min. Then, it was quenched with ice in $NaHCO_3$ (sat. aq), made alkaline (pH≅9), and extracted with ether (5×5 mL). The combined organic layers were washed with brine (5 mL), dried (K_2CO_3), evaporated in vacuo and dried overnight in a vacuum desiccator over H_2SO_4 giving the *title compound R*-**9** (50 mg, 59%, >97% pure, GC/MS) as a colourless oil; R_f 0.59 (3.5% EtOH/$CHCl_3$); $[\alpha]_D$ = +90 (*c* 0.96, MeOH); ν_{max} (liquid film) 3086, 3060, 2984, 2934, 2826, 1591, 1579, 1557, 1475, 1429, 1370, 1144, 1089 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.41–8.42 (1H, m), 7.93 (1H, d, J=8.1 Hz), 7.78 (1H, dt, J=8.1, 1.5 Hz), 7.49 (2H, d, J=7.4 Hz), 7.21–7.34 (3H, m), 7.15 (1H, dd, J=6.8, 1.5 Hz), 6.02 (1H, s), 3.27 (3H, s), 2.63 (3H, s), 1.93 (3H, s); δ_C (75 MHz, $CDCl_3$) 156.8, 153.9, 147.4, 146.2, 141.6, 138.2, 128.1, 126.8, 126.1, 120.9, 116.3, 107.9, 78.5, 51.2, 25.0, 14.6; *m/z* (EI, 70 ev) 293 (1.5, M^+), 278 (69), 263 (100), 216 (10), 105 (17), 78 (38), 77 (21), 51 (13%); HRMS (EI): M^+ found 293.1527. $C_{18}H_{19}ON_3$ requires 293.1528.

3.2.11. *R,R*-6,6′-Bis[3-(1-methoxy-1-phenylethyl)-5-methylpyrazol-1-yl]-[2,2′]bipyridine (*R,R*-10). A suspension of [$NiCl_2(PPh_3)_2$] (441 mg, 0.67 mmol), PPh_3 (353 mg, 1.34 mmol), and zinc dust (48 mg, 0.73 mmol), in DMF (3 mL) was vigorously stirred in argon atmosphere at 50 °C changing color from dark blue to brown-deep red. Then, a solution of *R*-**6** (221 mg, 0.67 mmol) and slight amount of NaI in DMF (2 mL) was added, by a syringe, and the whole mixture was stirred at 50 °C for 24 h. Cooled mixture was quenched by addition of NH_3 (10 mL, 25% aq) and brine (5 mL) and extracted with CH_2Cl_2 (5×8 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and evaporated in vacuo. The crude product, dried from DMF in a desiccator over sulfuric acid, was purified by column chromatography (silica gel, 2.5% EtOH/$CHCl_3$) and gave the *title compound* (*R,R*)-**10** (95 mg, 48%) as a white solid, mp 116–118 °C; $[\alpha]_D$ = +137, (*c* 0.7, CH_2Cl_2); ν_{max} (KBr) 3109, 3085, 3058, 2985, 2931, 2824, 1589, 1569, 1466, 1430, 1370, 1090 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.15 (2H, d, J=7.7 Hz), 7.97 (2H, d, J=8.0 Hz), 7.85 (2H, dd, J=8.0, 7.7 Hz), 7.44 (4H, d, J=7.1 Hz), 7.26 (4H, dd, J=7.7, 7.1 Hz), 7.15–7.19 (2H, m), 6.01 (2H, s), 3.27 (6H, s), 2.75 (6H, s), 1.88 (6H, s); δ_C (75 MHz, $CDCl_3$) 157.0, 153.7, 153.3, 146.1, 141.4, 139.3, 128.0, 126.8, 126.1, 117.9, 116.2, 108.2, 78.6, 51.2, 24.7, 15.5; *m/z* (EI, 70 eV) 584 (12, M^+), 569 (37), 552 (79), 522 (100), 277 (14), 269 (13), 105 (11%); HRMS (EI): M^+ found 584,2922. $C_{36}H_{36}O_2N_6$ requires 584.2900.

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Solid-phase synthesis of imidazoquinazolinone derivatives with three-point diversity ☆

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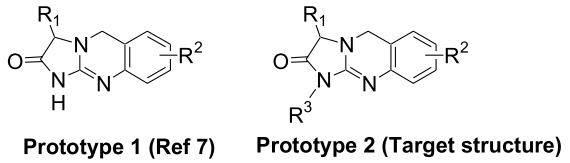
Abstract—A novel imidazoquinazolinone-based tricyclic structure with three-point diversity has been synthesized using solid-phase methodology. The compounds were obtained by treating the amino group of polymer-linked amino acids with 2-nitrobenzaldehyde followed by reduction of the nitro group to an amine. Derivatization of amine with isothiocyanates and cyclization of the resulting thioureas with DIC followed by acidolytic cleavage yielded the desired imidazoquinazolinone based compounds in high purity and moderate to high yield.

1. Introduction

In recent years, the design and synthesis of structurally diverse multifunctional libraries of small organic molecules on solid supports has been the central claim of combinatorial chemistry. Among small molecules, heterocyclic structures have received special attention in combinatorial synthesis, as they belong to a class of compound with proven utility in medicinal chemistry.[1–3] Small heterocycles, in particular, are used as rigid, highly functionalized molecular scaffolds, and are of significant biological interest.

As part of our continuing effort to develop new solid phase reactions for synthesizing heterocyclic molecules of medicinal importance,[4–6] we recently reported solid-phase synthesis of imidazoquinazolinones (**1**; Fig. 1) while exploring the chemistry for 3-substituted-3,4-dihydroquinazoline-2-amine.[7] However, prototypes **1** described by us had only two sites for introducing chemical diversity. Since two of the imidazoquinazolinone derived drugs: Anagrelide[8] and Quazinone[9] based on **1** are used clinically as antithrombotic and cardiotonic agents respectively, we envisaged that analogues with three-point diversity based on **2** (Fig. 1) will offer a novel prototype for evaluation against a variety of biological targets. A careful survey of the literature revealed one paper[10] dealing with the synthesis of this class of compounds in solution-phase. They were found to be strong inhibitors of blood platelet aggregation. Our efforts to introduce an additional third diversity at the NH present in the 5- membered ring, with the view to generate imidazoquinazolinones with three-point diversity (**2**; Fig. 1) led to a novel synthetic strategy distinctly different from our earlier strategy for **1**. The earlier strategy for the synthesis of **1** involved formation of 2-aminoquinazolines using BrCN followed by intramolecular cyclization between the resulting amine and resin bound carboxyl ester. Attempts to synthesize **2** by alkylating the amine functionality (as a possibility for introducing the third point of diversity) in the 2-aminoquinazolines followed by intramolecular cyclization of the resulting 2-amino substituted quinazoline was not satisfactory (Scheme 1). In fact, reductive alkylation of the amine using aldehydes led to complex mixtures probably due to its presence in conjugation with a double bond. This prompted us to develop an alternate solid-phase strategy for the synthesis of title compounds **2**. In this paper, we report a facile and efficient method for the solid phase synthesis of novel imidazoquinazolinone derivatives with three-point diversity derived from amino acids R^1, 2-nitrobenzaldehydes R^2 and



Prototype 1 (Ref 7) **Prototype 2 (Target structure)**

Fig. 1. Imidazoquinazolinone based compounds.

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Keywords: Imidazoquinazolinone; Solid-phase methodology; Isothiocyanates.
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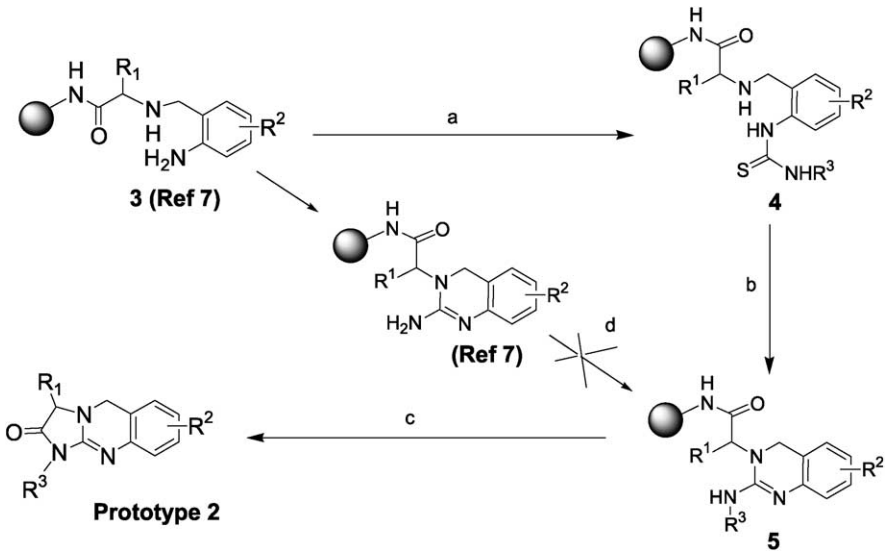


Scheme 1. Reagents and conditions: (a) isothiocyanates (3 equiv), 16 h, rt; (b) 1 M DIC in DCM, 12 h; (c) 10% AcOH/DCM, 16 h rt; (d) aldehydes, $NaCNBH_3$, 1% AcOH/TMOf, 3 h, rt.

isothiocyanates R^3 as versatile building blocks. To the best of our knowledge this is the first report of the synthesis of imidazoquinazolinones **2** with three-point diversity on solid-phase.

2. Results and discussion

The synthetic strategy for imidazoquinazolinones **2** with three point diversity is depicted in Scheme 1. The synthesis was carried out on RAM resin instead of Wang resin, as the later resulted in products in extremely low yields and purities, probably due to premature cyclization during the guanylation step. This is in contrast to our previous strategy for **1**, wherein synthesis on Wang resin produced compounds in $>90\%$ yields and purities. Our strategy for prototype **2** commenced with the synthesis of resin **3** from the resin bound amino acids by the method described earlier for **1**.[7] The resin thus obtained was then treated with aryl isothiocyanates to give resin bound thioureas **4**. This was followed by two sequential cyclizations. The first cyclization involved the treatment of resin **4** with 1 M DIC in DCM to give resin bound quinazoline **5**. Though formation of **5** can be achieved simply by heating resin **4** in DCM, without any addition of DIC, complete intramolecular cyclization leading to **5** from **4** could not be affected. Guanylation involving secondary amines and thioureas in the presence of 1 M DIC on solid-phase has been reported earlier by us[4] and others.[11–14] Alkyl isothiocyanates did not successfully undergo the carbodiimide mediated cyclization.

This is in accordance with the hypothesis that carbodiimide mediated cyclization proceeds via a carbodiimide intermediate generated in situ after the desulfurisation[15,16] of the thiourea intermediate, because the desulfurization efficiency of alkyl thioureas is on the lower.[15–17]

The second cyclization involved a cyclative cleavage step, wherein resin **5** was treated with 10% AcOH to obtain the desired imidazoquinazolinones **2**.

The crude product was purified on high throughput LC-MS (LaChrom MS 8000) and characterized by ^1H NMR. Using the synthetic method outlined above, a library containing fifteen single compounds based on prototype **2** (I-XV) was synthesized. The library was generated using an Advanced Chemtech multiple organic synthesizer MOS 496 Ω. Structural diversity in *o*-nitrobenzaldehydes and isothiocyanates did not have any negative effect on the yields and purities of these compounds. The crude products obtained after cleavage were found to have high yields (70–90%) with purities ranging from 69–96% (Table 1). The compounds were purified by high throughput HPLC-MS and obtained in moderate to good isolated yields (Table 1). Representative LC-MS for a compound [**2**(XIV)] is presented in Fig. 2(a) and (b).

3. Conclusions

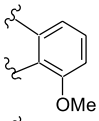
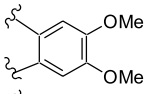
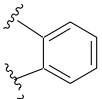
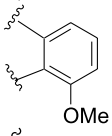
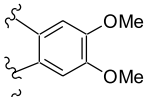
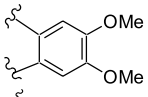
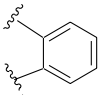
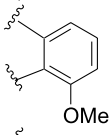
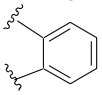
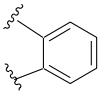
In summary, we have developed a versatile approach using mild reaction conditions for the solid-phase synthesis of imidazoquinazolinones with three-point diversity in high purity and moderate to high yield. The strategy is amenable to automation and can be successfully used for the generation of large libraries of imidazoquinazolinones.

4. Experimental

4.1. General

Rink amide AM resin (1% divinylbenzene, 100–200 mesh, 0.63 mmol/g substitution) and amino acids were purchased from Novabiochem, Switzerland. *N*-Hydroxy-benzotriazole was purchased from Jansen Chemica, Belgium. *N*,*N*′-diisopropylcarbodiimide, piperidine and trifluoroacetic acid were purchased from Aldrich. Anhydrous solvents were used for reactions. All other reagents were obtained from commercial sources and were used without further purification. The reactions on solid phase were optimized using polypropylene syringes of 5 mL capacity with frit,

Table 1. Purity and ESMS of compounds based on prototype **2**

Products no.	R^1	R^2	R^3	Purity# (%)	ESMS (M+H)+	Yield crude/ isolated (%)
2(I)	-Benzyl		-Benzyl	90	368.93	86/55
2(II)	-Benzyl		-Phenyl	69	354.93	79/48
2(III)	-Benzyl		-2-EthylPh	81	382.80	70/39
2(IV)	-Benzyl		-Phenyl	93	384.93	89/57
2(V)	-Benzyl		-Phenyl	77	414.93	74/42
2(VI)	-Methyl		-Benzyl	80	292.87	78/48
2(VII)	-Methyl		-2-EthylPh	80	306.93	72/41
2(VIII)	-Methyl		-Phenyl	96	278.80	88/55
2(IX)	-Methyl		-Benzyl	89	322.53	90/62
2(X)	-Methyl		-Phenyl	80	338	90/65
2(XI)	-Methyl		-2-EthylPh	81	366.92.	70/45
2(XII)	-Propyl		-Phenyl	85	306.93.	77/48
2(XIII)	-Propyl		-Tolyl	91	350.93	87/56
2(XIV)	-Isopropyl		-Benzyl	89	320.47	88/57
2(XV)	-Isopropyl		-Phenyl	93	306.80	77/46

Crude purity obtained from the relative peak areas(%) of HPLC chromatogram at $\lambda = 220$ nm. Crude yields with respect to initial loading on the resin, isolated yield obtained after purification.

which were shaken on an orbital shaker IKA-Vibrax-VXR. Libraries were generated on a multiple organic synthesizer (Advanced Chemtech, MOS 496 Ω). The ^{1}H NMR spectra were obtained on a Bruker Avance DRX-300 spectrometer and chemical shifts were reported in ppm (δ) relative to TMS. Because of solubility properties, the solvents used were DMSO-d_6, and $CDCl_3$. RP-HPLC analysis of crude products was carried out on Agilent liquid chromatograph using a 5 μm, 4.8×150 mm^2 C-18 reverse-phase column with a linear gradient of 0–100% acetonitrile in water (v/v) having 0.05% TFA over 25 min. The flow rate was 1.0 mL/min, and UV detection was observed at 220/254 nm. The compounds were purified by high throughput HPLC-MS (Lachrom MS 8000) using a 5 μm, 10×50 mm C-18 reverse-phase column with a linear gradient 10–100% MeOH–water (v/v) over 12 min with a flow rate 6 mL/min. Mass spectra were recorded using electron spray ionization (ESI) technique.

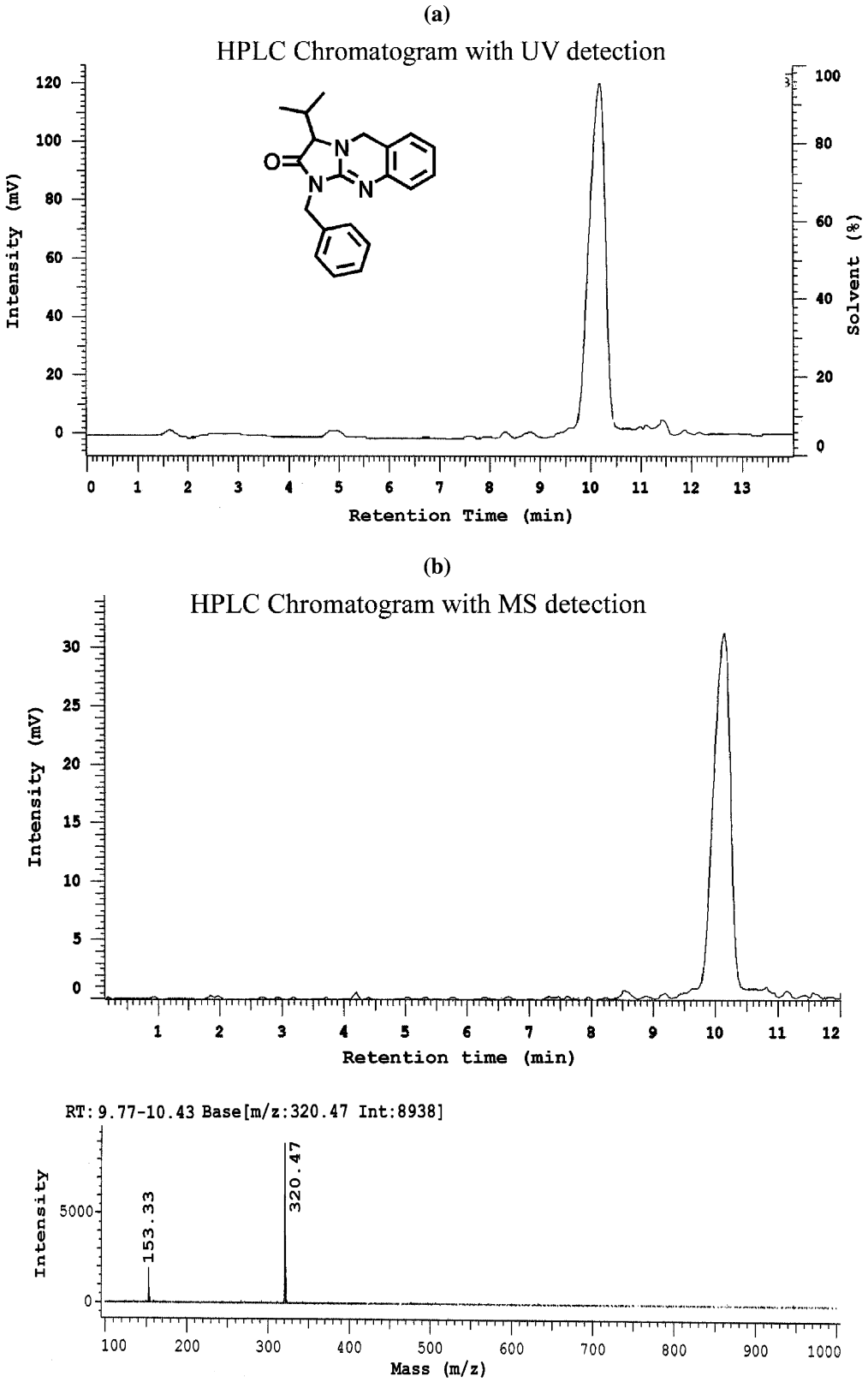


Fig. 2. (a) HPLC chromatogram with UV detection on LC-MS (10×50 mm^2; C18 column) of 1-benzyl-3-isopropyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [**2**(XIV)]. (b) HPLC chromatogram with MS detection on LC-MS (10×50 mm^2; C18 column) of 1-benzyl-3-isopropyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [**2**(XIV)].

4.2. General procedure for the synthesis of prototype 2

(A) Loading of amino acids. The Fmoc groups of the Rink Amide AM resin were removed by treating with 25% piperidine in DMF (1 ml) twice for 5 and 25 min. The resin was filtered and washed with DMF (9×5 ml). The resin so obtained was coupled with Fmoc protected amino acids (3 equiv) by using HOBt (3 equiv), TBTU (3 equiv), DIPEA

(6 equiv) and DMF (1 ml) as solvent for 16 h at room temperature. The resin was filtered and washed successively with DMF (3×2 ml), MeOH (3×2 ml), DCM (3×2 ml) and ether (3×2 ml) and finally dried in vacuo. Completion of the reaction was confirmed by a negative Kaiser test.

(B) Reductive alkylation with o-*nitrobenzaldehydes*. The Fmoc groups of the resulting resin were removed by treating with 25% piperidine in DMF (1 ml) twice for 5 and 25 min. The resin was filtered and washed with DMF (9×5 ml). The resin so obtained was treated with *o*-nitrobenzaldehydes (5 fold) in trimethylorthoformate for 3 h at room temperature. The resin was then filtered and treated with 1% AcOH solution of trimethylorthoformate and $NaCNBH_3$ (10 equiv) for 2 h at room temperature. The resin was filtered and washed successively with MeOH (3×2 ml), DMF (3×2 ml), DCM (3×2 ml) and ether (3×2 ml) and finally dried in vacuo. Completion of the reaction was confirmed by a negative Kaiser test and positive chloranil test.

(C) Reduction of nitro group to amine. The nitro group of the resin so obtained was reduced to amine with 2 M $SnCl_2 \cdot 2H_2O$ in DMF (1 ml) for 5 h at room temperature. Thereupon the resin was washed successively with DMF (3×2 ml), MeOH (3×2 ml), DCM (3×2 ml) and ether (3×2 ml) and finally dried in vacuo to give **3**.

(D) Treatment of amines with isothiocyanates. Next, the resin **1** was treated with isothiocyanates (3 equiv) in DCM for 16 h at room temperature. The resin was successively washed with DMF (3×2 ml), EtOH (3×2 ml), MeOH (3×2 ml), DCM (3×2 ml) and ether (3×2 ml) and dried in vacuo to give **4**.

(E) Formation of 2-amino substituted quinazolines. The resin bound thiourea **4** so obtained was treated with 1 M DIC in DCM (1 ml) for 12 h. Thereafter the resin was successfully washed with DMF (3×2 ml), EtOH (3×2 ml), MeOH (3×2 ml), DCM (3×2 ml) and ether (3×2 ml) and dried in vacuo to give quinazoline **5**.

(F) Cyclative cleavage. The resulting resin **5** was subjected to acidolytic cyclative cleavage with a mixture of 10% AcOH in DCM (1 ml) for 16 h at room temperature. The resulting mixture was filtered and filtrate was evaporated to dryness in vacuo. The residue was freeze dried after dissolving in ^{t}BuOH/water (4:1) to give the desired compounds based on prototype **2**.

4.2.1. 1,3-Dibenzyl-1,5-dihydro-imidazo[2,1-b]quinazoline-2-one [2(I)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ= 3.07 (dd, 1H, J=14.6, 3.2 Hz, $CHCH_{2a}Ph$), 3.26 (dd, 1H, J=14.6, 3.2 Hz, $CHCH_{2b}Ph$), 4.40 (t, 1H, J=5.0 Hz, COCHN), 4.43 (d, 1H, J=13.2 Hz, $NCH_{2a}Ph$), 4.68 (d, 1H, J=13.2 Hz, $CH_{2b}Ph$), 4.58 (d, 1H, J=8.8 Hz, NCH_{2a}-Ph), 4.63 (d, 1H, J=8.8 Hz, $NCH_{2b}Ph$), 6.82 (d, 1H, J= 8.5 Hz, ArH), 6.86 (m(o), 1H, ArH), 6.95 (t, 1H, J=7.3 Hz, ArH), 7.02 (d, 1H, J=7.3 Hz, ArH), 7.11 (t(o), 1H, J= 7.3 Hz, ArH), 7.14–7.33 (m(o), 9H, ArH). Anal. calcd for $C_{24}H_{21}N_3O$: C, 78.45; H, 5.76; N, 11.44; Found C, 78.43; H, 5.77; N, 11.40%.

4.2.2. 3-Benzyl-1-phenyl-1,5-dihydro-imidazo[2,1-b]quinazoline-2-one [2(II)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.20 (dd, 1H, J=14.0, 6.4 Hz, $CHCH_{2a}Ph$), 3.41 (dd, 1H, J=14.0, 4.1 Hz, $CHCH_{2b}Ph$), 4.26 (dd, 1H, J=5.9, 4.1 Hz, COCHN), 4.47 (s, 2H, NCH_2Ph), 6.93 (d, 1H, J= 7.9 Hz, ArH), 7.02 (t, 1H, J=7.9 Hz, ArH), 7.11–7.51 (m(o), 12H, ArH). Anal. calcd for $C_{23}H_{19}N_3O$: C, 78.16; H, 5.42; N, 11.89; Found C, 78.10; H, 5.48; N, 11.87%.

4.2.3. 3-Benzyl-1-(2-ethyl-phenyl)-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(III)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, 3H, J=7.6 Hz, CH_2CH_3), 2.57 (q, 2H, J=7.9 Hz, CH_2CH_3), 3.21 (dd, 1H, J=7.9, 5.2 Hz, $CH_{2a}Ph$), 3.37 (dd, 1H, J=7.9, 5.2 Hz, $CH_{2b}Ph$), 4.24 (t, 1H, J=4.3 Hz, COCHN), 4.48 (d, 1H, J=12.6 Hz, $NCH_{2a}Ph$), 4.56 (d, 1H, J=12.6 Hz, $NCH_{2b}Ph$), 6.84–7.54 (m(o), 13H, ArH). Anal. calcd for $C_{25}H_{23}N_3O$: C, 78.71; H, 6.08; N, 11.02; Found C, 78.67; H, 6.09; N, 10.99%.

4.2.4. 3-Benzyl-9-methoxy-1-phenyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(IV)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.18 (dd, 1H, J=14.3, 5.5 Hz, $CH_{2a}Ph$), 3.38 (dd, 1H, J=14.3, 3.7 Hz, $CH_{2b}Ph$), 3.74 (s, 3H, OCH_3), 4.21(t, 1H, J=4.8 Hz, COCHN), 4.41 (s, 2H, NCH_2Ph), 6.54 (d, 1H, J=7.7 Hz, ArH), 6.74 (d, 1H, J=7.7 Hz, ArH), 6.96 (t, 1H, J=7.7 Hz, ArH), 7.17–7.48 (m(o), 10H, ArH). Anal. calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96; Found C, 75.24; H, 5.50; N, 10.89%.

4.2.5. 3-Benzyl-7,8-dimethoxy-1-phenyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(V)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.27 (d, 1H, J=4.2 Hz, $CH_{2a}Ph$), 3.32 (d(o), 1H, J=4.2 Hz, $CH_{2b}Ph$), 3.63 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.42 (d, 1H, J=12.3 Hz, $NCH_{2a}Ph$), 4.44 (t(o), 1H, COCHN), 4.60 (d, 1H, J=12.3 Hz, $NCH_{2b}Ph$), 6.37 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.06 (d, J=7.2 Hz, 2H, ArH), 7.17–7.51 (m(o), 8H, ArH). Anal. calcd for $C_{25}H_{23}N_3O_3$: C, 72.62; H, 5.61; N, 10.16; Found C, 72.67; H, 5.63; N, 10.11%.

4.2.6. 1-Benzyl-3-methyl-1,5-dihydro-imidazo[2,1-b]quinazoline-2-one [2(VI)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.34 (d, 3H, J=6.6 Hz, CH_3), 4.10 (q, 1H, J=6.6 Hz, COCHN), 4.41 (d, 1H, J=12.8 Hz, $CH_{2a}Ph$), 4.60 (d, 1H, J=12.8 Hz, $CH_{2b}Ph$), 4.74 (s, 2H, NCH_2Ph), 6.95 (d(o), 1H, J=8.1 Hz, ArH), 6.96 (t(o), 1H, J=7.7 Hz, ArH), 7.10 (d, 1H, J=7.7 Hz, ArH), 7.14 (t, 1H, J=8.1 Hz, ArH), 7.19–7.48 (m(o), 5H, ArH). Anal. calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42; Found C, 74.17; H, 5.90; N, 14.41%.

4.2.7. 1-(2-Ethyl-phenyl)-3-methyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(VII)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.18 (t(o), 3H, J=7.6 Hz, CH_2CH_3), 1.58 (d, 3H, J=6.6 Hz, $CHCH_3$), 2.52(q, 2H, J=7.6 Hz, CH_2CH_3), 4.03 (q, 1H, J=7.3 Hz, COCHN), 4.52 (d, 1H, J=12.2 Hz, $NCH_{2a}Ph$), 4.68 (d, 1H, J=12.2 Hz, $NCH_{2b}Ph$), 6.87–7.51 (m(o), 8H, ArH). Anal. calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76; Found C, 74.76; H, 6.23; N, 13.81%.

4.2.8. 3-Methyl-1-phenyl-1,5-dihydro-imidazo[2,1-b] quinazolin-2-one [2(VIII)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.42 (d, 3H, J=7.0 Hz, CH_3), 4.24 (q, 1H, J=7.0 Hz, COCHN), 4.71 (d, 1H, J=15.5 Hz, $CH_{2a}Ph$), 5.20 (d, 1H, J=

15.5 Hz, CH_{2b}Ph), 6.58 (t, 1H, J=7.3 Hz, ArH), 6.99 (d, 1H, J=7.3 Hz, ArH), 7.04 (t, 1H, J=7.3 Hz, ArH), 7.14 (d, 1H, J=7.3 Hz, ArH), 7.36 (d, 2H, J=7.3 Hz, ArH), 7.48 (d(o), 3H, J=7.3 Hz, ArH). Anal. calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15; Found C, 73.64; H, 5.43; N, 15.17%.

4.2.9. 1-Benzyl-9-methoxy-3-methyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(IX)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.43 (d, 3H, J=6.9 Hz, CH_3), 3.81 (q, 1H, J=7.3 Hz, COCHN), 3.89 (s, 3H, OCH_3), 4.38 (d, 1H, J=12.2 Hz, NCH_{2a}Ph), 4.56 (d, 1H, J=12.2 Hz, NCH_{2b}Ph), 4.89 (s, 2H, CH_2Ph), 6.61 (d, 1H, J=7.3 Hz, ArH), 6.82 (d, 1H, J=7.3 Hz, ArH), 6.97 (t, 1H, J=7.3 Hz, ArH), 7.30 (t(o), 3H, J=7.3 Hz, ArH), 7.53 (d, 2H, J=7.3 Hz, ArH). Anal. calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08; Found C, 71.06; H, 5.99; N, 13.03%.

4.2.10. 7,8-Dimethoxy-3-methyl-1-phenyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(X)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.60 (d, 3H, J=7.0 Hz, CH_3), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.12 (q, 1H, J=6.7 Hz, COCHN), 4.53 (d, 1H, J=12.3 Hz, NCH_{2a}Ph), 4.67 (d, 1H, J=12.0 Hz, NCH_{2b}Ph), 6.53 (s, 1H, ArH), 6.71 (s, 1H, ArH), 7.37–7.57 (m(o), 5H, ArH). Anal. calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.46; Found C, 67.61; H, 5.64; N, 12.51%.

4.2.11. 1-(2-Ethyl-phenyl)-7,8-dimethoxy-3-methyl 1,5-dihydro-imidazo[2,1-b]quinazoline-2-one [2(XI)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.06 (t, 3H, J=7.0 Hz, CH_2CH_3), 1.42 (d, 3H, J=6.5 Hz,$CHCH_3$), 2.41 (q, 2H, J=7.0 Hz, $PhCH_2CH_3$), 3.63 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.16 (q, 1H, J=6.6 Hz, COCHN), 4.38 (d, 1H, J=13.2 Hz, NCH_{2a}Ph), 4.58 (d, 1H, J=13.2 Hz, NCH_{2b}Ph), 6.42 (s, 1H, ArH), 6.68 (s, 1H, ArH), 7.14–7.55 (m(o), 4H, ArH). Anal. calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50; Found C, 69.07; H, 6.37; N, 11.44%.

4.2.12. 1-Phenyl-3-propyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(XII)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.01 (t, 3H, J=7.7 Hz, CH_3), 1.44 (m, 1H, $CH_2CH_{2a}CH_3$), 1.55 (m, 1H, $CH_2CH_{2b}CH_3$), 2.01(m, 2H, $CH_2CH_2CH_3$), 4.02 (t, 1H, J=4.4 Hz, COCHN), 4.54 (d, 1H, J=12.4 Hz, NCH_{2a}Ph), 4.66 (d, 1H, J=12.4 Hz, NCH_{2b}Ph), 7.03 ((o), 2H, ArH), 7.08 (d, 1H, J=8.1 Hz, ArH), 7.19 (m, 1H, ArH), 7.36–7.54 (m(o), 5H, ArH). Anal. calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76; Found C, 74.77; H, 6.32; N, 13.79%.

4.2.13. 9-Methoxy-3-propyl-1-o-tolyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(XIII)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.99 (t, 3H, J=7.3 Hz, CH_3), 1.55 (m, 2H, $CH_2CH_2CH_3$), 1.98 (m, 2H, $CH_2CH_2CH_3$), 2.21 (s, 3H, $PhCH_3$), 3.73 (s, 3H, OCH_3), 4.00 (t, 1H, J=4.3 Hz, COCHN), 4.49 (d, 1H, J=12.3 Hz, NCH_{2a}Ph), 4.60 (d, 1H, J=12.3 Hz, NCH_{2b}Ph), 6.63 (d, 1H, J=7.3 Hz, ArH), 6.75 (d, 1H, J=7.3 Hz, ArH), 6.97 (t, 1H, J=7.3 Hz, ArH), 7.19–7.37 (m(o), 4H, ArH). Anal. calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03; Found C, 72.19; H, 6.67; N, 12.04%.

4.2.14. 1-Benzyl-3-isopropyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(XIV)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.02 (d, 3H, J=7.3 Hz, CH_3), 1.09 (d, 3H, J=7.3 Hz, CH_3), 2.33 (m, 1H, $CH(CH_3)_2$), 4.08 (d, 1H, J=2.6 Hz, COCHN), 4.46 (d, 1H, J=13.2 Hz, NCH_{2a}Ph), 4.59 (d, 1H, J=13.2 Hz, NCH_{2b}Ph), 4.76 (s, 2H, CH_2Ph), 6.94 (d(o), 1H, J=8.1 Hz, ArH), 6.98(t(o), 1H, J=7.7 Hz, ArH), 7.07 (d, 1H, J=7.7 Hz, ArH), 7.15 (t, 1H, J=8.1 Hz, ArH), 7.22–7.38 (m(o), 5H, ArH). Anal. calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16; Found C, 75.27; H, 6.64; N, 13.13%.

4.2.15. 3-Isopropyl-1-phenyl-1,5-dihydro-imidazo[2,1-b]quinazolin-2-one [2(XV)]. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.02 (d, 3H, J=7.3 Hz, CH_3), 1.09 (d, 3H, J=7.3 Hz, CH_3), 2.33 (m, 1H, $CH(CH_3)_2$), 4.08 (d, 1H, J=3.0 Hz, COCHN), 4.50 (d, 1H, J=13.2 Hz, NCH_{2a}Ph), 4.63 (d, 1H, J=13.2 Hz, NCH_{2b}Ph), 6.81 (d, 1H, J=7.7 Hz, ArH), 6.96 (t, 1H, J=7.3 Hz, ArH), 7.07 (d(o), 1H, J=7.3 Hz, ArH), 7.11 (t, 1H, J=7.7 Hz, ArH), 7.35–7.55 (m, 5H, ArH). Anal. calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76; Found C, 74.74; H, 6.30; N, 13.79%. (o)=overlapped.

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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.2004.10.090

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Stereoselective synthesis of (*E*)-β-arylvinyl bromides by microwave-induced reaction of *anti*-3-aryl-2,3-dibromopropanoic acids using an AgOAc–AcOH system

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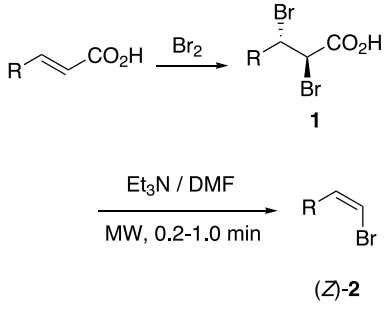
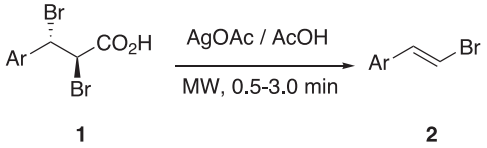
Abstract—(*E*)-β-Arylvinyl bromides were stereoselectively prepared in high yields by microwave irradiation of the corresponding *anti*-3-aryl-2,3-dibromopropanoic acids in AcOH in the presence of AgOAc for 0.5–3.0 min.

1. Introduction

(*E*)-Vinyl bromides are very useful synthetic intermediates in organic synthesis.[1] The classical Hunsdiecker reaction[2] and its modified reactions[3] and Takai procedure[4] have been frequently used for synthesis of (*E*)-β-arylvinyl bromides. Although most of these methods are useful for the synthesis of (*E*)-vinyl halides, a more convenient and efficient method for synthesis is needed to overcome the problems in these methods which involve the use of complex reagents and large amounts of solvent, long reaction times and low yields, especially in the case of cinnamic acids carrying electron-withdrawing groups or *ortho*-substituents.[3f,h–j] We recently reported that microwave irradiation of *anti*-2,3-dibromoalkanoic acids (**1**) in DMF in the presence of triethylamine for 0.2–1.0 min stereoselectively afforded (*Z*)-vinyl bromides ((*Z*)-**2**) in high yields (Scheme 1).[5] This method is very convenient and useful since the starting dibromides **1** are readily obtained by bromination of the corresponding *trans*-2-alkenoic acids. On the other hand, conventional thermal reaction of **1** under a variety of conditions also gives the corresponding (*Z*)-β-arylvinyl bromides as a major product.[6] (*E*)-β-Arylvinyl bromides are only obtained in the case of *anti*-3-aryl-2,3-dibromoalkanoic acids carrying a strongly electron-donating group at their aryl group.[7] We recently found that microwave irradiation of *anti*-3-aryl-2,3-dibromopropanoic acids (**1**, R = aryl) stereoselectively gave the corresponding (*E*)-β-arylvinyl bromides ((*E*)-**2**) by simply modifying the solvent and additive(Scheme 2). Here we report the first general method for a stereoselective synthesis of (*E*)-β-arylvinyl bromides from *anti*-3-aryl-2,3-dibromopropanoic acids by using microwave irradiation.



Scheme 1.



Scheme 2.

Microwave-induced efficient and rate accelerate technology is becoming a powerful tool in organic synthesis.[8] We have successfully used a microwave irradiation method for the synthesis of (*E*)-vinyl halides by Hunsdiecker-type reaction of 3-arylpropenoic acids[9a] and by the reaction of

Keywords: (*E*)-β-Arylvinyl bromides; *anti*-3-Aryl-2,3-dibromopropanoic acids; Silver acetate; Microwave irradiation.
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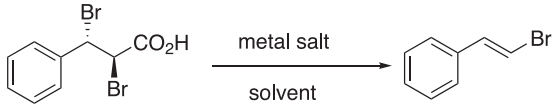
Table 1. Transformation of *anti*-2,3-dibromo-3-phenylpropanoic acid (**1a**) into (*E*)-β-bromostyrene (**2a**) under various conditions



1a **2a**

Entry	Metal salt (1.2 equiv)	Solvent (5 ml)	Conditions	Yield (%)[a]	*E*/*Z*[b]
1	AgOAc	AcOH	Room temperature, 1 min	40[c]	>98/2
2	AgOAc	AcOH	Room temperature, 6 h	82	98/2
3	AgOAc	AcOH	80 °C, 30 min	84	98/2
4	AgOAc	AcOH	MW 1 min	86	>98/2
5	AgOAc	DMF	MW 1 min	60	73/27
6	AgOAc	MeCN	MW 1 min	70	73/27
7	AgOAc	THF	MW 1 min	50	95/5
8	AgOTf	AcOH	MW 1 min	70	95/5
9	Ag_2O	AcOH	MW 1 min	80	92/8
10	$AgNO_2$	AcOH	MW 1 min	20	92/8
11	$AgNO_3$	AcOH	MW 1 min	0	
12	TiOAc	AcOH	MW 1 min	72	94/6
13	$Hg(OAc)_2$	AcOH	MW 1 min	0	
14	$Pb(OAc)_4$	AcOH	MW 1 min	0	

[a] Determined by ^{1}H NMR analysis.
[b] Isomer ratios were determined by ^{1}H NMR analysis.
[c] A formation of β-lactone was also observed.

1,1-dibromoalkenes with diethyl phosphonate and sodium ethoxide.[9b]

2. Results and discussion

Microwave irradiation of *anti*-3-aryl-2,3-dibromopropanoic acids carrying electron-donating or electron-withdrawing groups (**1**) in acetic acid in the presence of AgOAc gave the corresponding (*E*)-β-aryl-vinyl bromides (**2**) (Scheme 2). For example, microwave irradiation of *anti*-2,3-dibromo-3-phenylpropanoic acid (**1a**) in AcOH (5 ml) in the presence of 1.2 equiv of AgOAc for 1 min gave (*E*)-β-bromostyrene (**2a**) in 86% yield (*E*/*Z*>98/2). Various conditions were examined to optimize the yield and stereoselectivity of **2a**. The results are summarized in Table 1. The reaction of **1a** with AgOAc in acetic acid was found to give **2a** even without microwave irradiation (Table 1, entries 1–3). When microwave irradiation was applied to the reaction mixture for 1 min by using a conventional microwave oven, the reaction proceeded very rapidly and **2a** was obtained in 86% yield (entry 4). Table 1 shows that metal salts such as $AgNO_2$, $AgNO_3$, $Hg(OAc)_2$ and $Pb(OAc)_4$ were not effective in this reaction and that DMF, MeCN and THF were less satisfactory as solvents than was AcOH. At this stage, an AgOAc/AcOH system appears to be the best system for the reaction (entry 4).

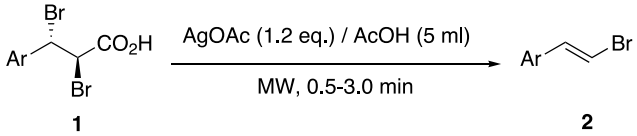
Microwave irradiation of various *anti*-3-aryl-2,3-dibromopropanoic acids **1** under the optimum conditions gave the corresponding (*E*)-β-arylvinyl bromides **2** in the yields and stereoselectivities shown in Table 2. These results indicate that *anti*-3-aryl-2,3-dibromopropanoic acids carrying electron-donating or electron-withdrawing groups at the *ortho*, *meta*, or *para* position could be converted into the corresponding (*E*)-vinyl bromides in excellent yields with high stereoselectivities by the use of a microwave irradiation method (entries 2–4 and 7–12). It is noteworthy that (*E*)-vinyl bromides carrying bromo, chloro, fluoro or methoxycarbonyl groups were obtained in 80–96% isolated yields by the present method (entries 7–12). In addition, (*E*)-β-bromostyrene carrying *ortho* chloro substituent was also obtained stereoselectively in 88% yield (entry 9). (*E*)-β-Arylvinyl bromides having 1- or 2-naphthyl groups were also obtained in high yields with high stereoselectivities (entries 5 and 6).

We applied this transformation to a one-pot synthesis of (*E*)-vinyl bromides from substituted *trans*-cinnamic acids. For example, bromination of *trans*-4-bromocinnamic acid in AcOH at 55 °C for 2 h and subsequent microwave irradiation of the mixture in the presence of AgOAc gave the desired product **2g** in 91% yield (Scheme 3).

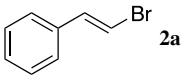
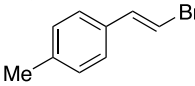
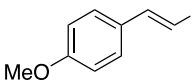
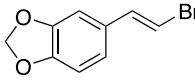
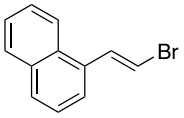
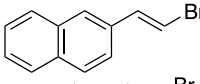
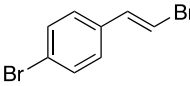
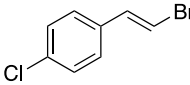
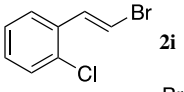
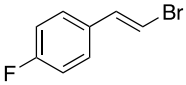
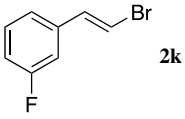
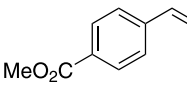
We found that microwave irradiation for only a short time of a mixture of *anti*-3-aryl-2,3-dibromopropanoic acids carrying an electron-withdrawing group and AgOAc in AcOH gave a mixture of (*E*)-β-arylvinyl bromide and β-lactone. For example, microwave irradiation of 2,3-dibromo-3-(4-methoxycarbonylphenyl)propanoic acid **1l** (1 mmol) and AgOAc in 5 ml of AcOH for only 5 s gave a mixture of methyl (*E*)-4-(β-bromovinyl)benzoate (**2l**) and *trans*-α-bromo-β-lactone (**3**) (**2l/3**=78/22) (Scheme 4). Lactone **3** could be separated by chromatography. On the other hand, in the microwave reaction of *anti*-3-aryl-2,3-dibromopropanoic acids having an electron-rich 4-methoxyl or methylenedioxyl substituent (**1c** or **1d**), no signal indicating the formation of a β-lactone intermediate was detected. The rate of decarboxylation is highly dependent on a substituent of β-lactone.[10] An electron-donating group at the aryl ring facilitates the decarboxylation, while an electron-withdrawing group retards the rate of the decarboxylation reaction.[10]

Probable reaction pathways are shown in Scheme 5. Two pathways, that is, a zwitterionic route or decarboxylation of

Table 2. Stereoselective synthesis of (*E*)-β-arylvinyl bromides **2**

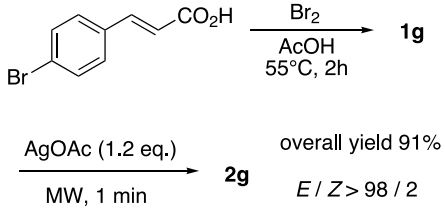


1 **2**

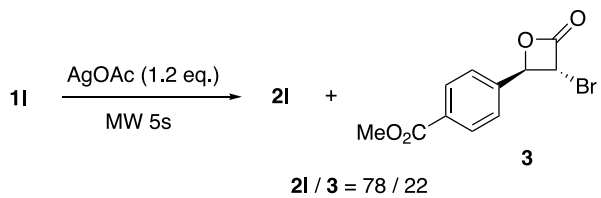
Entry	Dibromide	Product	MW (min)	Yield (%)[a]	*E*/*Z*[b]
1	**1a**	 **2a**	1.0	86	>98/2
2	**1b**	 **2b**	1.0	87	>98/2
3	**1c**	 **2c**	0.5	85	>98/2
4	**1d**	 **2d**	0.5	88	>98/2
5	**1e**	 **2e**	1.0	92	>98/2
6	**1f**	 **2f**	1.0	93	>97/3
7	**1g**	 **2g**	1.0	95	>98/2
8	**1h**	 **2h**	1.0	96	>98/2
9	**1i**	 **2i**	2.0	88	>98/2
10	**1j**	 **2j**	2.0	92	>98/2
11	**1k**	 **2k**	2.0	90	>97/3
12	**1l**	 **2l**	3.0	80	>97/3

[a] Isolated yields.
[b] Isomer ratios were determined by ^{1}H NMR analysis.

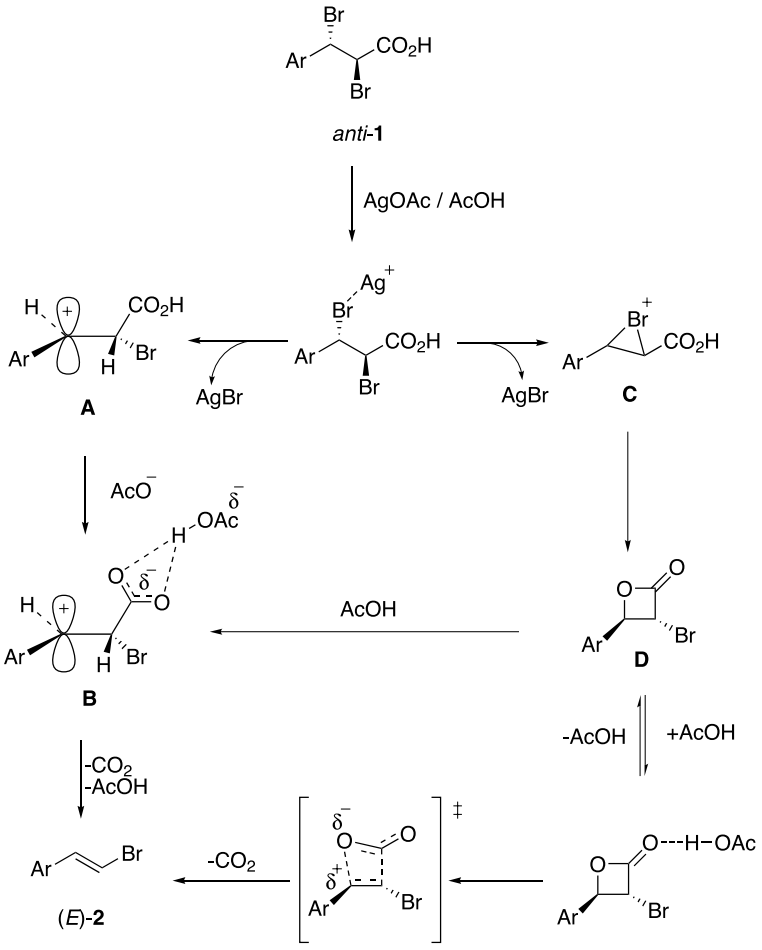
α-bromo-β-lactone, might depend on the nature of the aryl-substituent. Some of the reactions probably proceed via an electrophilic attack of Ag^+ on a bromine atom of **1** to give the zwitterionic intermediate **B**,[10c,e] which would eliminate carbon dioxide to give (*E*)-β-arylvinyl bromide ((*E*)-**2**). The reactions of *anti*-3-aryl-2,3-dibromopropanoic acids (**1c** and **1d**) undergo this mechanism. On the other hand, in some reactions, α-bromo-β-lactone (**D**) would be formed via bromonium ion (**C**), and an elimination of carbon dioxide from the lactone (**D**) would occur with a retention of



Scheme 3.



Scheme 4.



Scheme 5.

configuration to give (*E*)-**2**. In most cases, two pathways coexist; one pathway takes precedence over the other one on the basis of the electron character of the substituent. *anti*-3-Aryl-2,3-dibromopropanoic acids **1a**, **1b**,**1e** and **1f** might mainly proceed in zwitterionic route, whereas **1g**, **1h**, **1i**, **1j**, **1k** and **1l** mainly undergo α-bromo-β-lactone route. The possibility that α-bromo-β-lactone **D** can be converted to zwitterionic intermediate **B** also exists, it depends on the stability of α-bromo-β-lactone (**D**) varying from the substituents.

3. Conclusion

In summary, we have developed a new and efficient method for stereoselective synthesis of (*E*)-β-arylvinyl bromides from the corresponding *anti*-3-aryl-2,3-dibromopropanoic acids using an AgOAc/AcOH system, in which the use of microwave irradiation enables preparation of (*E*)-β-arylvinyl bromides in high yields and high stereoselectivities within 0.5–3.0 min of reaction time. In addition, we applied this transformation to a one-pot synthesis of (*E*)-arylvinyl bromides in high yields and high stereosectivities from substituted *trans*-cinnamic acids carrying electron-withdrawing groups. Moreover, we proved that the debrominative decarboxylation pathways including zwitterionic route and decarboxylation of α-bromo-β-lactones might depend on a nature of aryl-substituent.

4. Experimental

4.1. General

Melting points were recorded using a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were recorded using a JASCO IR-810 infrared spectrometer (between NaCl plates). ^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-EX270 FT NMR spectrometer at 270 MHz (^{1}H) and at 67.8 MHz (^{13}C) in $CDCl_3$ with $SiMe_4$ as an internal standard. High- and low- resolution mass spectra were determined using a JEOL JMS-FABmate or JEOL JMS-700TZ spectrometer. Column chromatography was carried out on a Silica Gel 60 N (100–210 μm, Kanto Chemical Co. Ltd). New compound was further characterized by elemental analysis.

4.2. General procedure for the synthesis of (*E*)-β-arylvinyl bromides (2)

anti-2,3-Dibromo-3-arylpropanoic acid (**1a**–**l**) were prepared according to the previously described procedures.[6g,h,7a]

A mixture of *anti*-2,3-dibromo-3-arylpropanoic acid (**1**, 1 mmol), AgOAc (1.2 mmol), and AcOH (5 ml) in a 100 ml Erlenmeyer flask was kept in a microwave oven operated at 2450 MHz (TOSHIBA, ER-V11, 200 W) and was irradiated

for 0.5–3.0 min. The reaction mixture was then removed from the oven and cooled to room temperature. Water and ether were added to the reaction mixture and the organic layer was separated. Aqueous layer was extracted with ether. The combined organic layers were washed with water and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude product, which was subjected to column chromatography (silica gel, hexane–ether) to afford (*E*)-β-arylvinyl bromides **2**.

4.2.1. (*E*)-β-Bromostyrene (2a).[3d,11] Column chromatography was carried out with hexane as an eluent; colorless oil; IR (neat) 1609, 1575, 941 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.77 (1H, d, $J=13.9$ Hz), 7.11 (1H, d, $J=13.9$ Hz), 7.27–7.32 (5H, m).

4.2.2. (*E*)-β-Bromo-4-methylstyrene (2b).[3d,11] Column chromatography was carried out with hexane as an eluent; mp 46.0–46.5 °C (EtOH) (lit.[6g] 46.0–46.5 °C); IR (nujol) 1605, 1511, 931 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (3H, s), 6.70 (1H, d, $J=13.9$ Hz), 7.06 (1H, d, $J=13.9$ Hz), 7.12 (2H, d, $J=8.3$ Hz), 7.19 (2H, d, $J=8.3$ Hz).

4.2.3. (*E*)-β-Bromo-4-methoxystyrene (2c).[3d,12] Column chromatography was carried out with 10% ether in hexane as an eluent; mp 58–59 °C (EtOH) (lit.[12] 58–59 °C); IR (nujol) 1607, 1513, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (3H, s), 6.61 (1H, d, $J=13.9$ Hz), 6.85 (2H, d, $J=8.9$ Hz), 7.04 (1H, d, $J=13.9$ Hz), 7.23 (2H, d, $J=8.9$ Hz).

4.2.4. (*E*)-β-Bromo-3,4-methylenedioxystyrene (2d).[3h] Column chromatography was carried out with 10% ether in hexane as an eluent; mp 52.5–53.0 °C (hexane); IR (nujol) 1505, 1250, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.96 (2H, s), 6.59 (1H, d, $J=13.7$ Hz), 6.77 (2H, m), 6.81 (1H, s), 6.99 (1H, d, $J=13.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 101.27, 104.51, 105.39, 108.44, 120.93, 130.27, 136.67, 147.76, 148.13; EIMS *m/z* 228 ($(M+2)^{\cdot+}$, 38), 226 (M^+, 40), 175 (100); HRMS calcd for $C_9H_7^{79}Br\,O_2$. *m/z* 225.9629. Found *m/z* 225.9635.

4.2.5. (*E*)-1-(β-Bromovinyl)naphthalene (2e).[13] The crude product was purified by silica gel column chromatography eluted with 5% ether in hexane; colorless oil; IR (neat) 1603, 1590, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.76 (1H, d, $J=13.9$ Hz), 7.38–7.56 (4H, m), 7.79–7.86 (3H, m), 8.02 (1H, d, $J=8.9$ Hz).

4.2.6. (*E*)-2-(β-Bromovinyl)naphthalene (2f).[14] The crude product was purified by silica gel column chromatography eluted with 5% ether in hexane; mp 84–85 °C (EtOH); IR (nujol) 1611, 1594, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.90 (1H, d, $J=13.9$ Hz), 7.26 (1H, d, $J=13.9$ Hz), 7.44–7.49 (3H, m), 7.69 (1H, d, $J=1.0$ Hz), 7.77–7.83 (3H, m).

4.2.7. (*E*)-β-Bromo-4-bromostyrene (2g).[15,16] The crude product was purified by silica gel column chromatography eluted with 10% ether in hexane; mp 67–68 °C (lit.[15] 67–68 °C); IR (nujol) 1610, 1589, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (1H, d, $J=14.2$ Hz), 7.04 (1H, d, $J=14.2$ Hz), 7.15 (2H, d, $J=8.3$ Hz), 7.44 (2H, d, $J=8.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 107.33, 122.17, 127.55, 131.93, 134.77, 136.03; EIMS *m/z* 264 ($(M+2)^{\cdot+}$, 90), 262 (M^+, 100), 181 (78), 102 (70); HRMS calcd for $C_8H_6^{79}Br^{81}Br$. *m/z* 261.8816. Found *m/z* 261.8825.

4.2.8. (*E*)-β-Bromo-4-chlorostyrene (2h).[3d,17] The crude product was purified by silica gel column chromatography eluted with 10% ether in hexane; mp 47–48 °C (MeOH) (lit.[17] 47–48 °C); IR (nujol) 1604, 1586, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.75 (1H, d, $J=13.9$ Hz), 7.05 (1H, d, $J=13.9$ Hz), 7.21 (2H, d, $J=8.6$ Hz), 7.29 (2H, d, $J=8.6$ Hz).

4.2.9. (*E*)-β-Bromo-2-chlorostyrene (2i).[3i] The crude product was purified by silica gel column chromatography eluted with 20% ether in hexane; colorless oil; IR (neat) 1605, 1470, 1440, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (1H, d, $J=13.9$ Hz), 7.21–7.25 (2H, m), 7.3–7.4 (2H, m), 7.47 (1H, d, $J=13.9$ Hz).

4.2.10. (*E*)-β-Bromo-4-fluorostyrene (2j).[16] The crude product was purified by silica gel column chromatography eluted with 5% ether in hexane; colorless oil; IR (neat) 1602, 1589, 946 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (1H, d, $J=13.9$ Hz), 6.95–7.03 (2H, m), 7.04 (1H, d, $J=13.9$ Hz), 7.21–7.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 106.07 (d, $J=2.5$ Hz), 115.76 (d, $J=20.7$ Hz), 127.68 (d, $J=8.5$ Hz), 132.10 (d, $J=3.7$ Hz), 135.93, 162.56 (d, $J=247.8$ Hz); EIMS *m/z* 202 ($(M+2)^{\cdot+}$, 28), 200 (M^+, 27), 202 (28), 149 (100); HRMS calcd for $C_8H_6^{79}BrF$. *m/z* 199.9637. Found *m/z* 199.9629.

4.2.11. (*E*)-β-Bromo-3-fluorostyrene (2k).[16] The crude product was purified by silica gel column chromatography eluted with 5% ether in hexane; colorless oil; IR (neat) 1611, 1582, 937 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.77 (1H, d, $J=13.9$ Hz), 6.93–7.06 (4H, m), 7.10–7.30 (1H, m); ^{13}C NMR ($CDCl_3$) δ 108.03, 112.64 (d, $J=23.2$ Hz), 115.11 (d, $J=22.0$ Hz), 167.45 (d, $J=2.5$ Hz), 130.26 (d, $J=8.5$ Hz), 136.06 (d, $J=2.4$ Hz), 137.96 (d, $J=7.3$ Hz), 162.98 (d, $J=246.6$ Hz); EIMS *m/z* 202 ($(M+2)^{\cdot+}$, 28), 200 (M^+, 27), 202 (28), 149 (100); HRMS calcd for $C_8H_6^{79}BrF$. *m/z* 199.9637. Found *m/z* 199.9642.

4.2.12. (*E*)-4-(β-Bromovinyl)benzoic acid methyl ester (2l).[16] The crude product was purified by silica gel column chromatography eluted with 25% ether in hexane; mp 60–61 °C (hexane); IR (nujol) 1732, 1607, 1584, 936 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (3H, s), 6.92 (1H, d, $J=14.0$ Hz), 7.13 (1H, d, $J=14.0$ Hz), 7.36 (2H, d, $J=8.3$ Hz), 7.98 (2H, d, $J=8.3$ Hz); ^{13}C NMR ($CDCl_3$) δ 52.17, 109.38, 125.95, 129.63, 130.10, 136.32, 140.05, 166.61; EIMS *m/z* 242 ($(M+2)^{\cdot+}$, 100), 240 (M^+, 100), 211 (100), 181 (75), 102 (70); HRMS calcd for $C_{10}H_9^{81}BrO_2$. *m/z* 241.9765. Found *m/z* 241.9774.

4.2.13. 4-(3-Bromo-4-oxo-oxetan-2-yl)-benzoic acid methyl ester (3). The crude product was purified by silica gel column chromatography eluted with 50% ether in hexane; Yield: 20%; mp 85–86 °C (hexane/ether=6/4); IR (nujol) 1850 (γ CO), 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (3H, s), 4.99 (1H, d, $J=3.96$ Hz), 5.64 (1H, d, $J=3.96$ Hz), 7.50 (2H, d, $J=8.4$ Hz), 8.12 (2H, d, $J=8.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 46.72, 52.45, 80.29, 125.31, 130.45, 131.68, 139.20, 163.57, 166.15; EIMS *m/z* 286 ($(M+2)^{\cdot+}$, 47), 284 (M^+, 46), 255 (25), 240 (M^+-CO_2, 46), 209 (80), 122

(100); HRMS calcd for $C_{11}H_9^{79}BrO_4$. *m/z* 283.9657. Found *m/z* 283.9684. Anal. Calcd for $C_{11}H_9BrO_4$: C, 46.34, H, 3.18, Br, 28.03. Found: C, 46.48, H, 3.23, Br, 27.76.

Acknowledgements

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Stereoselective synthesis of swainsonines from pyridines

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Abstract—An efficient synthesis of (−)-swainsonine and (−)-2,8a-di-*epi*-swainsonine was developed starting from readily available 2-pyridinecarbaldehyde and 3-hydroxypyridine. In particular, it was demonstrated that the mixture of simple indolizidines, i.e. lentiginosine and *epi*-lentiginosine, being readily available by a number of different synthetic routes, can be directly converted to swainsonine.

1. Introduction

Indolizidines belong to an important class of alkaloids that have received broad attention due to their biological properties such as antimetastatic, antitumor-proliferative, anticancer or immunoregulating activity.[1] Most prominent, (−)-swainsonine (**1b**) is a very potent α-mannosidase inhibitor, being currently under clinical evaluation.[2] Despite their relative simple structure, the synthesis of indolizidines has remained challenging, although a number of elegant routes towards them have been reported[3] (Fig. 1).

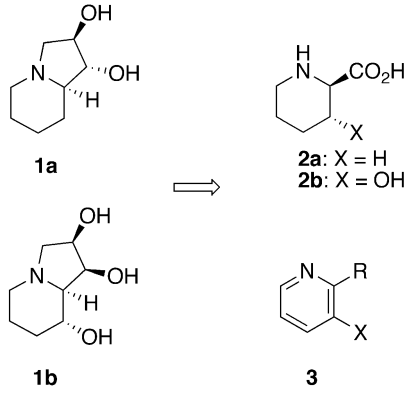

Figure 1. Retrosynthetic analysis of indolizidines.

One obvious approach towards indolizidines would be construction of the five-membered ring by appropriate functionalization of (hydroxylated) pipecolic acids, and indeed, this approach was successfully developed for the synthesis of (−)-lentiginosine (**1a**) and also of (−)-swainsonine (**1b**).[4]

However, even the parent pipecolic acid (**2a**) is not readily available in enantiomerically pure form since it is not available from the chiral pool, and—despite contrary announcements[5]—an efficient chemical large scale process is yet to be developed.

An alternate approach towards indolizidines can be envisioned from pyridines, requiring the efficient transformation of the pyridine into a piperidine ring at some point in the synthesis.[6] Following our interest to use heteroaromatic starting materials such as pyrrols,[7] furans[8] or pyridines[9] for the synthesis of natural products and analogs, we report here such a strategy that leads stereoselectively to (−)-swainsonine (**1b**) and to the epimer (−)-2,8a-di-*epi*-swainsonine.

We have reported that acrylates of pyridines cannot be used as substrates in the Sharpless asymmetric aminohydroxylation (AA) due to poisoning of the osmium catalyst by the pyridine nitrogen.[10] However, we demonstrated that the corresponding pyridine *N*-oxides **7** readily underwent this transformation, which was applied to the enantioselective synthesis of pyridine analogous side chains of paclitaxel. Recently, this strategy was taken up for the synthesis of (−)-lentiginosine (**1a**), using an asymmetric dihydroxylation of **7a** as the key step,[11] which prompts us to report our own results for the synthesis of swainsonine epimers.

2. Results and discussion

Asymmetric dihydroxylations of pyridine *N*-oxides **7a–e**, which were readily prepared from pyridines **3** and **8**

Keywords: Indolizidines; Swainsonine; 2,8a-Di-*epi*-swainsonine; Pyridine-*N*-oxides; Asymmetric dihydroxylation.
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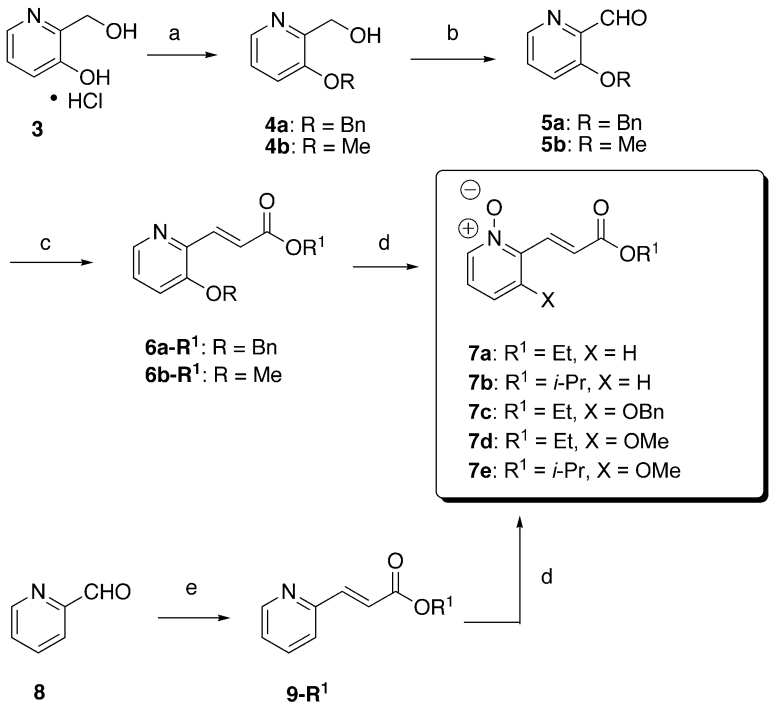
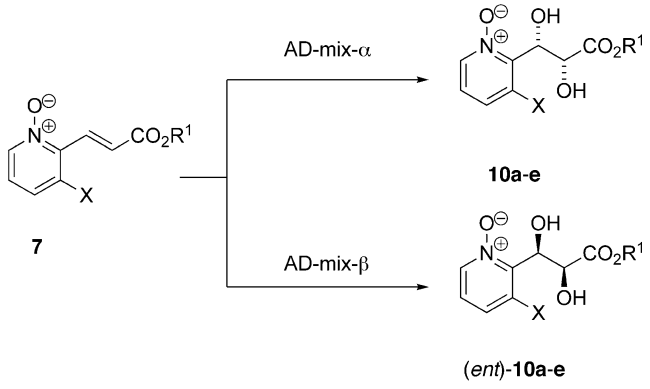


Scheme 1. Reagents and conditions: (a) (i) NaOEt, ethanol; (ii) DMSO, (**4a**: benzyl chloride; **4b**: methyl iodide), 28–39%. (b) SeO_2, dioxane, reflux, 83–84%. (c) LiBr, acetonitrile, NEt_3, $(R^1O)_2POCH_2COOR^1$, 62–84%. (d) Glacial acetic acid, hydrogen peroxide (30%), 60 °C, 77–97%. (e) LiBr, acetonitrile, NEt_3, $(R^1O)_2POCH_2COOR^1$, 62–86%.

(Scheme 1), were investigated using commercially available AD-mix.

7a gave the desired dihydroxylated products **10a**, as recently reported,[11] or (*ent*)-**10a**, respectively, with high enantioselectivity, either by employing AD-mix-α or AD-mix-β (Table 1). Likewise, the alkoxy substituted *N*-oxides **7c** and **7d** could be converted to the corresponding diols with respectable yields, however, the enantioselectivity of the reaction was distinctively dependent on the protecting group at the hydroxyl group in the 3-position on the pyridine ring: while the benzyloxy derivative **7c** gave the diols **10c** or (*ent*)-**10c** with only 53–66% ee, **7d**, substituted with the smaller methoxy group gave rise to the diols **10d** or (*ent*)-**10d** with excellent enantioselectivity. Switching from the ethyl to the isopropyl esters **7b** and **7e** considerably improved the yields by retaining the high selectivities (93–98% ee) of the dihydroxylation reaction due to the increased hydrolytic stability of the starting materials and products.

Table 1. Asymmetric dihydroxylation of **7** to **10a–e** (AD-mix-α) or (*ent*)-**10a–e** (AD-mix-β)[a]



	AD-mix-α		AD-mix-β	
	% ee	Yield (%)	% ee	Yield (%)
7a	97	39	96	36
7b	97	66	98	65
7c	53	55	66	59
7d	97	52	98	54
7e	97	93	93	72

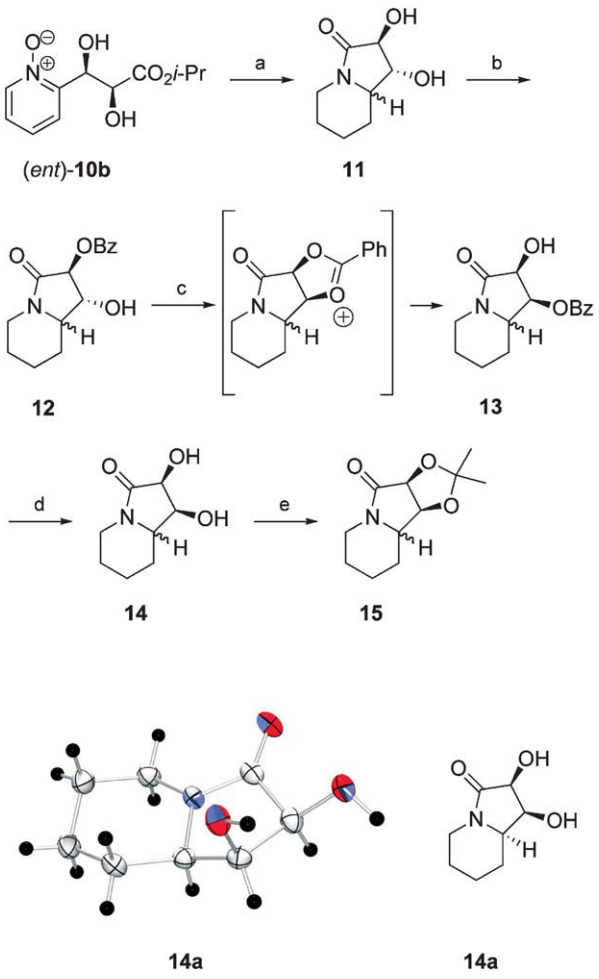
[a] Reagents and conditions: AD-Mix, $MeSO_2NH_2$, *t*-BuOH/H_2O, room temperature, 24–72 h.

2.1. Synthesis of (−)-Swainsonine

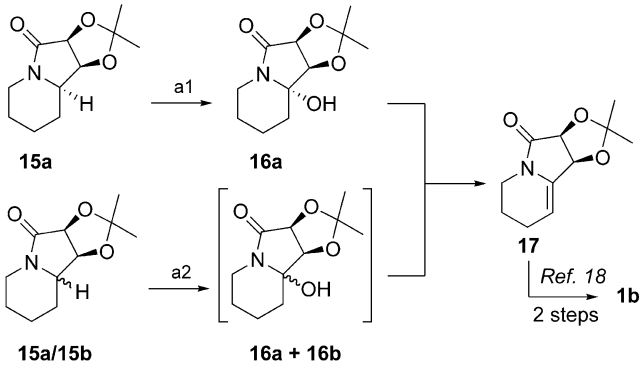
Hydrogenation of (*ent*)-**10b** was achieved at ambient pressure in methanol using platinum dioxide as catalyst. Under these conditions, reduction of the pyridine *N*-oxide to the piperidine with concurrent ring closure takes place, giving rise directly to the bicyclic derivative **11**. If palladium on charcoal was used as the catalyst instead, selective reduction of the pyridine-*N*-oxides to the corresponding pyridines takes place in quantitative yield. Compound **11** was obtained from (*ent*)-**10b** as an inseparable mixture of epimers (60:40) with respect to the stereocenter at C-2 (Scheme 2).[12] In order to invert the stereocenter[13] at C-1, this mixture was selectively benzoylated at C-2 to yield **12**, followed by treatment with triflic anhydride. The resulting **13** was debenzoylated to **14**[14] and subsequently converted to the acetonide **15**. If desired, the major epimer **14a** can be obtained in pure form by recrystallization, and its X-ray structure[15] analysis confirmed the successful establishment of the *syn*-stereochemistry of the two hydroxy groups.

The α-oxidation of *N*-acylated piperidines by ruthenium-(VIII)-catalyzed hydroxylation[16] or electrochemical alkoxylation[17] has ample precedent. As a general rule it was shown that bicyclic derivatives could be selectively oxidized at the ring junction, while acyclic substituted piperidines will be oxidized at the less substituted α-carbon.

Treatment of the mixture of epimers **15** with ruthenium-tetroxide, being generated in situ from rutheniumdioxide and sodium hypochlorite, indeed resulted in a regioselective oxidation to form **16** (Scheme 3). However, the two epimers **15** differ largely in their reactivity as well as in their stereospecifity as could be shown by carrying out the oxidation with the individual isomers: While **15a**, having the hydrogen to be oxidized oriented on the convex face of the tricyclic ring system readily formed exclusively **16a** with retention of configuration, **15b** reacted much more sluggishly and unspecifically to a mixture of **16a** and **16b**, which upon elimination gave rise to the known compound **17**.[18] Thus, when the epimeric mixture **15a/15b** (60:40) is used in this oxidation/elimination sequence, **17** is obtained (50% yield) along with unreacted **15b** (29%) which can readily be separated and recovered by chromatography. Compound **17** was subsequently converted to (−)-swainsonine (**1b**) as previously described in the literature.[18]



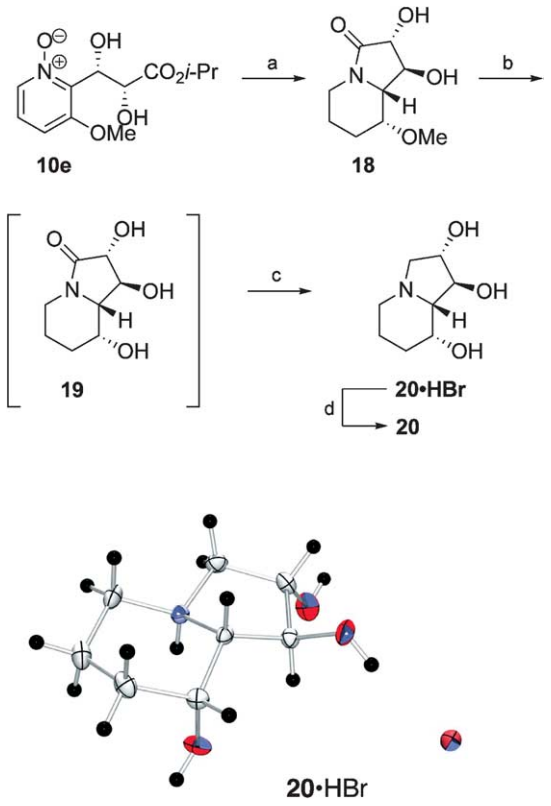
Scheme 2. Reagents and conditions: (a) $PtO_2 \cdot H_2O$, MeOH, H_2, 89%. (b) Benzoyl chloride, DMAP, pyridine, −30 °C, 84%. (c) Triflic anhydride, pyridine, CH_2Cl_2, 53%. (d) NaOMe, MeOH, 78%. (e) 2,2-Dimethoxypropane, *p*-TsOH, CH_2Cl_2, 98%.



Scheme 3. Reagents and conditions: (a1) (i) $RuO_2 \cdot H_2O$, 12% aqueous NaOCl, ethyl acetate, 0 °C→10 °C; (ii) HOAc, $CHCl_3$, 79% (2 steps). (a2) (i) $RuO_2 \cdot H_2O$, 12% aqueous NaOCl solution, ethyl acetate, 0 °C; (ii) HOAc, $CHCl_3$, 50% (2 steps) **17** + 29% recovered **15b**.

2.2. Synthesis of (−)-2,8a-di-*epi*-Swainsonine

Hydrogenation of **10e** could be analogously carried out under conditions as described for (*ent*)-**10b**. From the possible four diastereomers, **18** was formed as the major one (7:1:1:0.5) which could be obtained pure after recrystallization (Scheme 4). The configuration of **18** was confirmed by X-ray crystal analysis (not shown) as well as by subsequent chemical transformation to the known (−)-2,8a-di-*epi*-swainsonine (**20**).[19] Thus, **18** was demethylated using concentrated HBr, and the resulting crude **19** which contained ammonium bromide as a byproduct was directly reduced without purification to give rise to **20**·**HBr**. Recrystallization of **20**·**HBr** gave suitable crystals for X-ray structure analysis[15] which confirmed the relative and absolute (Flack parameter = 0.00(1)) stereochemical assignment of the product. These crystals were converted to the salt-free (−)-2,8a-di-*epi*-swainsonine (**20**) by ion exchange chromatography, showing identical melting point and NMR



Scheme 4. Reagents and conditions: (a) Pt/C (5%), HOAc, H_2, 47%. (b) HBr (48%), 140 °C, 88%. (c) $BH_3 \cdot DMS$, THF, 0 °C, 59%. (d) (i) Recrystallization ethyl acetate/MeOH 1:1, 55%; (ii) Dowex 1×8, 100–200 mesh, 100%.

data, but a different value of optical rotation (−8.8) as previously reported (−24.0) in literature.[19]

The greatly improved diastereoselectivity in the hydrogenation of **10e** compared to (*ent*)-**10b** clearly must be attributable to the alkoxy substituent in the pyridine moiety. The preferred formation of **18** from **10e** can therefore be rationalized by chelation of platinum by that group and a side chain hydroxy group as depicted in Figure 2. Restriction of the conformation in **10e** by a hydrogen bond of the second hydroxy group in the side chain with the *N*-oxide might very well be an additional control factor in this hydrogenation.

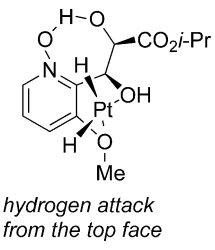


Figure 2. Model for the stereoselective hydrogenation of **10e**.

In conclusion, we have demonstrated that readily available pyridines provide a convenient access to swainsonines in diastereo- and enantiopure form.

3. Experimental

3.1. General

Reactions with moisture-sensitive chemicals were performed under nitrogen in a flame-dried reaction flask. Solvents were dried by standard methods.

Chromatography: Macherey–Nagel silica gel (0.03–0.06 mm). Enantiomeric excesses were determined by analytical HPLC using a Chiracel OD-H column (flow: 1 ml/min) and a UV detector at 254 nm. Diastereomeric ratios were determined by integration of the respective diastereomeric peaks in ^{1}H NMR. TLC: commercially precoated aluminum sheets 60 F 254 (Merck). Uncorrected melting point: Büchi SMP 20. IR: Mattson Genesis series FT-IR, Perkin–Elmer 298, Bruker IFS 66, ν in cm^{-1}. ^{1}H NMR and ^{13}C NMR: Bruker Avance 600, ARX 400, Avance 300, AC 250 F, δ in ppm, J in Hz. Multiplicities were determined by DEPT (distortionless enhancement by polarization transfer) measurements, + signifies a positive signal (CH, CH_3), − signifies a negative signal (CH_2) in DEPT 135. MS: Finnigan MAT 95, Varian MAT 311A. Elemental analysis: Heraeus CHN-Rapid. XRD: Stoe Imaging Plate System, Siemens Stoe AED2. Optical rotation: Perkin–Elmer polarimeter PE 241.

3.1.1. 3-Benzyloxy-2-hydroxymethylpyridine (4a). Sodium (4.60 g, 0.20 mol, 2.0 equiv) was added to ethanol (80 ml). After 2 h of stirring 3-hydroxy-2-(hydroxymethyl)-pyridine hydrochloride (16.2 g, 0.10 mol, 1.0 equiv) was added and the solution was stirred further for 1 h at room temperature. After addition of DMSO (125 ml), ethanol was removed under reduced pressure. Benzyl chloride (12.55 g, 11.5 ml, 0.10 mol, 1.0 equiv) was added and stirred for 12 h at room temperature. After addition of H_2O (1.5 l), the aqueous layer was extracted with $CHCl_3$ (4×100 ml). The combined organic layers were dried over $MgSO_4$, and the solution was concentrated under reduced pressure. The crude product was extracted with hot hexane (3×250 ml), and after removal of the solvent recrystallized from hexane (500 ml) to give **4a** (8.39 g, 0.04 mmol, 39%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 4.39 (br s, 1H), 4.82 (s, 2H), 5.11 (s, 2H), 7.16–7.17 (m, 2H), 7.34–7.40 (m, 5H), 8.15–8.17 (m, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 60.1 (−, CH_2), 69.9 (−, CH_2), 118.0 (+, Aryl-C), 122.2 (+, Aryl-C), 127.2 (+, 2C, Aryl-C), 128.3 (+, Aryl-C), 128.7 (+, 2C, Aryl-C), 136.0 (quat C), 139.8 (+, Aryl-C), 148.8 (quat C), 151.4 (quat C).

3.1.2. 3-Methoxy-2-hydroxymethylpyridine (4b). Sodium (11.5 g, 0.50 mol, 2.0 equiv) was added to ethanol (200 ml). After 3 h of stirring, DMSO (300 ml) and 3-hydroxy-2-(hydroxymethyl)-pyridine hydrochloride (40.4 g, 0.25 mol, 1.0 equiv) were added. Ethanol was removed under reduced pressure. The mixture was cooled to 0 °C, methyl iodide (35.5 g, 15.6 ml, 0.25 mol, 1.0 equiv) was added and stirred for 12 h at room temperature. After addition of H_2O (1.0 l) the aqueous layer was extracted with CH_2Cl_2 (5×100 ml). The combined organic layers were washed with brine (300 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica to yield **4b** (9.75 g, 0.07 mol,

28%) as colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82 (s, 3H, OCH_3), 4.72 (s, 2H, CH_2), 7.10 (dd, J=8, 1 Hz, 1H, Aryl-H), 7.18 (dd, J=8, 4 Hz, 1H, Aryl-H), 8.12 (dd, J=4, 1 Hz, 1H, Aryl-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.1 (+, CH_3), 60.0 (−, CH_2), 116.4 (+, Aryl-C), 122.6 (+, Aryl-C), 139.3 (+, Aryl-C), 148.3 (quat C), 152.3 (quat C).

3.1.3. 3-Benzyloxypyridine-2-carbaldehyde (5a).[20] Compound **4a** (3.86 g, 17.9 mmol, 1.0 equiv) and SeO_2 (1.99 g, 17.9 mmol, 1.0 equiv) were dissolved in 50 ml of dioxane. The solution was refluxed, filtrated and concentrated. The crude product was purified by chromatography on silica to yield **5a** (3.21 g, 15.1 mmol, 84%); R_f 0.26 (hexanes/ethyl acetate 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 5.25 (s, 2H, CH_2Ph), 7.30–7.50 (m, 7H, Aryl-H), 8.40 (dd, J=3.6 Hz, 2.0 Hz, 1H, Aryl-H), 10.44 (s, 1H, CHO).

3.1.4. 3-Methoxypyridine-2-carbaldehyde (5b). Compound **4b** (9.00 g, 64.7 mmol, 1.0 equiv) and SeO_2 (7.17 g, 64.7 mmol, 1.0 equiv) were dissolved in dioxane (180 ml). The solution was refluxed (4 h), filtrated and concentrated. The crude product was purified by chromatography on silica to yield **5b** (7.33 g, 53.5 mmol, 83%). R_f 0.32 (ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 3.98 (s, 3H, OCH_3), 7.43 (dd, J=8.6 Hz, 1.4 Hz, 1H, Aryl-H), 7.50 (dd, J=8.6 Hz, 4.3 Hz, 1H, Aryl-H), 8.41 (dd, J=4.3 Hz, 1.4 Hz, 1H, Aryl-H), 10.35 (s, 1H, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.8 (+, OCH_3), 120.2 (+, Aryl-C), 128.8 (+, Aryl-C), 141.0 (C quat), 142.0 (+, Aryl-C), 157.9 (C quat), 190.3 (C quat).

3.1.5. (*E*)-Ethyl 3-(3-(benzyloxy)pyridin-2-yl)acrylate (6a-Et). To a stirred suspension of LiBr (1.04 g, 12.0 mmol, 1.2 equiv) in dry acetonitrile (50 ml) was added triethylamine (1.11 g, 1.5 ml, 11 mmol, 1.1 equiv), triethyl phosphonoacetate (1.24 g, 10 mmol, 1.0 equiv) and finally 3-benzyloxy-pyridine-2-carboxaldehyde (2.13 g, 10 mmol, 1.0 equiv). The solution was stirred 72 h at room temperature. H_2O (40 ml) was added and the aqueous layer was extracted with ethyl acetate (3×30 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica (ethyl acetate/hexanes 1:3) to yield **6a-Et** (2.39 g, 8.4 mmol, 84%, *E*/*Z*=99:1) as yellow solid. R_f 0.48 (hexanes/ethyl acetate 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.32 (t, J=7.1 Hz, 3H, CH_2CH_3), 4.26 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 5.15 (s, 2H, CH_2Ph), 7.04 (d, J=15.8 Hz, 1H, CH=CHCO$_2$Et), 7.15–7.45 (m, 7H, Aryl-H), 8.16 (dd, J=15.8 Hz, J=0.45 Hz, 1H, CH=CHCO$_2$Et), 8.22 (ddd, J=4.1 Hz, J=1.6 Hz, J=0.45 Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 60.5 (−, CH_2CH_3), 70.4 (−, CH_2Ph), 120.0 (+, Aryl-C), 122.4 (+, Aryl-C), 125.1 (+, Aryl-C), 127.2 (+, 2C, Aryl-C), 128.3 (+, CH=CHCO$_2$Et), 128.8 (+, 2C, Aryl-C), 135.8 (quat, Aryl-C), 137.8 (+, CH=CHCO$_2$Et), 141.9 (+, Aryl-C), 142.9 (quat, Aryl-C), 153.7 (quat, Aryl-C), 167.2 (quat, CO_2Et). IR (KBr) ν: 3056, 2982, 2937, 2877, 1684, 1573, 1444, 1391, 1365, 1297, 1274, 1245, 1169, 1108, 1048, 981, 927, 880, 859, 793, 773, 750, 705, 626, 598, 556 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 283.3 (3.7, M^+), 210.1 (28.9), 146.9 (1.1), 118.9 (2.7), 90.9 (100), 65.0 (7.6). Anal. Calcd for $C_{17}H_{17}NO_3$ (283.32) C 72.07, H 6.05, N 4.94. Found C 72.05, H 6.09, N 4.85.

3.1.6. (*E*)- and (*Z*)-Ethyl 3-(3-methoxypyridin-2-yl)acrylate (6b-Et). To a stirred suspension of LiBr (3.72 g, 42.7 mmol, 1.5 equiv) in dry acetonitrile (100 ml) was added triethylamine (3.18 g, 4.4 ml, 31.4 mmol, 1.1 equiv), triethyl phosphonoacetate (6.40 g, 28.5 mmol, 1.0 equiv) and finally 3-methoxypyridine-2-carbaldehyde (3.92 g, 28.5 mmol, 1.0 equiv). The solution was stirred 18 h at room temperature. H_2O (40 ml) was added and the aqueous layer was extracted with ethyl acetate (3×100 ml). The combined organic layers were washed with brine (100 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product (*E*/*Z*=93:7) was purified by chromatography on silica (ethyl acetate/hexanes 1:2) to yield (*E*)-**6b-Et** (4.81 g, 23.2 mmol, 81%) as colorless solid and (*Z*)-**6b-Et** (382 mg, 1.8 mmol, 6.5%) as yellow oil. (*E*)-**6b-Et**: R_f 44 (hexanes/ethyl acetate 1:1). Mp 63 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.33 (t, J=7.1 Hz, 3H, CH_2CH_3), 3.87 (s, 3H, OCH_3), 4.27 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 7.01 (d, J=15.8 Hz, 1H, CH=CHCO$_2$Et), 7.18–7.29 (m, 2H, Aryl-H), 8.07 (dd, J=15.8, 0.46 Hz, 1H, CH=CHCO$_2$Et), 8.21 (ddd, J=3.9, 1.9, 0.42 Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.2 (+, CH_2CH_3), 55.4 (+, OCH_3), 60.3 (−, CH_2CH_3), 118.3 (+, Aryl-C), 122.1 (+, Aryl-C), 125.2 (+, CH=CHCO$_2$Et), 137.8 (+, Aryl-C), 141.4 (+, CH=CHCO$_2$Et), 142.3 (quat, Aryl-C), 154.6 (quat, Aryl-C), 167.1 (quat, CO_2Et). IR (KBr) ν: 3016, 2990, 2940, 2904, 1707, 1635, 1573, 1464, 1440, 1423, 1365, 1303, 1276, 1259, 1235, 1166, 1108, 1069, 1035, 1012, 980, 895, 876, 799, 774, 595, 574 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 207.0 (39.2 M^+), 177.9 (30.4), 161.9 (100.0), 133.9 (50.2), 119.9 (28.1), 105.9 (19.0), 90.9 (11.5). Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23) C 63.76, H 6.32, N 6.76. Found C 63.64, H 6.29, N 6.81. (*Z*)-**6b-Et**: R_f 0.30 (hexanes/ethyl acetate 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.20 (t, J=7.2 Hz, 3H, CH_2CH_3), 3.82 (s, 3H, OCH_3), 4.18 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 6.13 (d, J=12.1 Hz, 1H, CH=CHCO$_2$Et), 7.09 (d, J=12.1 Hz, 1H, CH=CHCO$_2$Et), 7.12–7.22 (m, 2H, Aryl-H), 8.15 (ddd, J=3.9, 2.1, 0.27 Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.0 (+, CH_2CH_3), 55.4 (+, OCH_3), 60.3 (−, CH_2CH_3), 117.5 (+, Aryl-C), 123.90 (+, Aryl-C), 123.96 (+, CH=CHCO$_2$Et), 132.8 (+, CH=CHCO$_2$Et), 140.7 (+, Aryl-C), 143.9 (quat, Aryl-C), 153.4 (quat, Aryl-C), 167.6 (quat, CO_2Et). IR (Film) ν: 3059, 2982, 2941, 2840, 1724, 1637, 1580, 1462, 1432, 1398, 1277, 1189, 1118, 1069, 1029, 948, 858, 830, 798, 749 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 207.1 (34.2, M^+), 178.0 (32.1), 162.0 (100.0), 148.0 (14.4), 134.0 (44.4), 119.9 (26.4), 106.0 (17.8), 91.0 (11.5). Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23) C 63.76, H 6.32, N 6.76. Found C 63.36, H 6.36, N 6.76.

3.1.7. (*E*)- and (*Z*)-Isopropyl 3-(3-methoxypyridin-2-yl)acrylate (6b-*i*Pr). To a stirred suspension of LiBr (4.51 g, 51.9 mmol, 1.5 equiv) in dry acetonitrile (100 ml) under nitrogen atmosphere was added at room temperature triethylamine (3.85 g, 5.3 ml, 38.1 mmol, 1.1 equiv), triisopropyl phosphonoacetate (9.23 g, 34.6 mmol, 1.0 equiv) and finally 3-methoxypyridine-2-carbaldehyde (4.75 g, 34.6 mmol, 1.0 equiv). The solution was stirred for 120 h at room temperature. H_2O (100 ml) was added and the aqueous layer was extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with H_2O (100 ml) and brine (100 ml), dried over $MgSO_4$ and

concentrated under reduced pressure. The crude product (*E*/*Z*=86:14) was purified by chromatography on silica (ethyl acetate/hexanes 1:2) to yield (*E*)-**6b**-***i*Pr** (4.76 g, 21.5 mmol, 62%) and (*Z*)-**6b**-***i*Pr** (567 mg, 2.6 mmol, 7%) as colorless oils. (*E*)-**6b**-***i*Pr**: R_f 0.30 (ethyl acetate/hexanes 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (d, J=6.2 Hz, 6H, CH(CH_3)$_2$), 3.90 (s, 3H, OCH_3), 5.14 (hept, J=6.2 Hz, 1H, CH(CH_3)$_2$), 6.99 (d, J=15.8 Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.23 (d, J=1.7 Hz, 1H, Aryl-H), 7.24 (d, J=4.2 Hz, 1H, Aryl-H), 8.05 (d, J=15.8 Hz, 1H, CH=CHCO$_2$*i*-Pr), 8.22 (dd, J=4.2, 1.7 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.9 (+, 2C, CH(CH_3)$_2$), 55.4 (+, OCH_3), 67.7 (+, CH(CH_3)$_2$), 118.3 (+, CH=CHCO$_2$*i*-Pr), 122.9 (+, Aryl-C), 125.1 (+, Aryl-C), 137.7 (+, CH=CHCO$_2$*i*-Pr), 141.5 (+, Aryl-C), 142.6 (quat, Aryl-C), 154.6 (quat, Aryl-C), 166.7 (quat, CO$_2$*i*-Pr). MS (DCI, NH_3) *m*/*z* (%): 222.3 (100, MH^+). IR (film) ν: 3061, 2979, 2940, 2839, 1712, 1638, 1576, 1466, 1429, 1301, 1271, 1235, 1179, 1109, 1069, 1017, 986, 917, 879, 834, 799, 772 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25) C 65.14, H 6.83, N 6.33. Found C 64.75, H 6.76, N 6.30. (*E*)-**6b**-***i*Pr**: R_f 0.22 (ethyl acetate/hexanes 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (d, J=6.2 Hz, 6H, CH(CH_3)$_2$), 3.84 (s, 3H, OCH_3), 5.09 (hept, J=6.2 Hz, 1H, CH(CH_3)$_2$), 6.12 (d, J=12.1 Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.07 (d, J=12.1 Hz, 1H, CH=CHCO$_2$-*i*-Pr), 7.17 (d, J=1.9 Hz, 1H, Aryl-H), 7.18 (d, J=4.4 Hz, 1H, Aryl-H), 8.15 (dd, J=4.2 Hz, 1.7 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.7 (+, 2C, CH(CH_3)$_2$), 55.3 (+, OCH_3), 67.9 (+, CH(CH_3)$_2$), 117.4 (+, CH=CHCO$_2$-*i*-Pr), 123.8 (+, Aryl-C), 124.5 (+, Aryl-C), 132.1 (+, CH=CHCO$_2$*i*-Pr), 140.6 (+, Aryl-C), 144.0 (quat, Aryl-C), 153.3 (quat, Aryl-C), 167.2 (quat, CO$_2$*i*-Pr). MS (DCI, NH_3) *m*/*z* (%): 266.3 (13.2), 222.3 (100, MH^+). IR (film) ν: 3057, 2980, 2938, 2838, 1718, 1637, 1579, 1454, 1431, 1395, 1275, 1179, 1115, 1069, 961, 859, 828, 799, 782, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_3$ (221.25) C 65.14, H 6.83, N 6.33. Found C 64.65, H 6.81, N 6.33.

3.1.8. (*E*)-Ethyl 3-(*N*-oxypyridin-2-yl)acrylate (7a). To a cooled solution (0 °C) of 70% *m*-chlorperbenzoic acid (1.45 g, 7.9 mmol, 1.1 equiv) in CH_2Cl_2 (50 ml) was added a solution of (*E*)-**9**-**Et** (1.43 g, 8.1 mmol, 1.0 equiv) in CH_2Cl_2 (10 ml). After 30 min the solution was refluxed for 20 h, cooled to room temperature and concentrated. The crude product was purified by chromatography on neutral aluminium oxide ($CHCl_3$/MeOH 19:1) to give **7a** (1.54 g, 8.0 mmol, 97%) as a yellow solid. Mp 71 °C. R_f 0.41 ($CHCl_3$/MeOH 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, J=7.2 Hz, 3H, CH_2CH_3), 4.29 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 6.98 (d, J=16.3 Hz, 1H, CH=CHCO$_2$Et), 7.23–7.29 (m, 2H, Aryl-H), 7.53–7.57 (m, 1H, Aryl-H), 8.07 (d, J=16.3 Hz, 1H, CH=CHCO$_2$Et), 8.25–8.28 (m, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 61.0 (−, CH$_2$CH$_3$), 124.9 (+, CH=CHHCO$_2$-Et), 125.1 (+, Aryl-C), 125.7 (+, Aryl-C), 125.8 (+, Aryl-C), 133.9 (+, Aryl-C), 140.4 (+, CH=CHCO$_2$Et), 145.2 (quat, Aryl-C), 166.3 (quat, CO$_2$Et). IR (KBr) ν: 3090, 3042, 2980, 2440, 1700, 1625, 1480, 1425, 1365, 1305, 1230, 1180, 1020, 985, 875, 860, 832, 808, 740, 727, 580, 540 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 193.1 (6.1), 177.1 (5.7), 148.0 (21.3), 132.1 (19.9), 120.1 (100), 104.1 (7.7), 92.0 (74.8). Anal. Calcd for $C_{10}H_{11}NO_3$ (193.20) C 62.17, H 5.74, N 7.25. Found C 61.97, H 5.65, N 7.18.

3.1.9. (*E*)-Isopropyl 3-(*N*-oxypyridin-2-yl)acrylate (7b). To a solution of (*E*)-**9**-***i*Pr** (4.39 g, 28.2 mmol, 1.0 equiv) in glacial acid (10.9 g, 10.3 ml, 181 mmol, 6.4 equiv) was added hydrogen peroxide (30%, 10.3 ml, 102 mmol, 3.6 equiv), and the mixture was heated for 12 h at 60 °C. The resulting solution was concentrated under reduced pressure to give a yellow oil, which was purified by chromatography on silica (ethyl acetate) to give **7b** (4.59 g, 22.1 mmol, 79%) as a yellow solid. Mp 98 °C. R_f 0.42 ($CHCl_3$/MeOH 19:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.32 (d, J=6.3 Hz, 6H, CH(CH_3)$_2$), 5.15 (hept, J=6.3 Hz, 1H, CH(CH_3)$_2$), 6.95 (d, J=16.3 Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.26–7.34 (m, 2H, Aryl-H), 7.56–7.61 (m, 1H, Aryl-H), 8.07 (d, J=16.3 Hz, 1H, CH=CHCO$_2$*i*-Pr), 8.26–8.31 (m, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.8 (+, 2C, CH(CH_3)$_2$), 68.4 (+, CH(CH_3)$_2$), 125.2 (+, Aryl-C), 125.4 (+, Aryl-C), 125.7 (+, Aryl-C), 125.8 (+, CH=CHCO$_2$*i*-Pr), 133.6 (+, CH=CHCO$_2$*i*-Pr), 140.4 (+, Aryl-C), 145.3 (quat, Aryl-C), 165.6 (quat, CO$_2$*i*-Pr). MS (EI, 70 eV) *m*/*z* (%): 207.0 (3.4, MH^+), 191.0 (5.36), 147.9 (23.3), 131.9 (23.2), 119.9 (100), 104.9 (11.9), 103.9 (10.4), 91.9 (84.4), 77.9 (16.7), 65.0 (23.9). IR (film) ν: 3076, 2989, 1701, 1491, 1473, 1435, 1377, 1350, 1317, 1279, 1240, 1228, 1209, 1178, 1163, 1146, 1109, 989, 897, 876, 841, 812, 758, 569, 526 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23) C 63.76, H 6.32, N 6.76. Found C 63.64, H 6.25, N 6.70.

3.1.10. (*E*)-Ethyl 3-(3-(benzyloxy)-*N*-oxypyridin-2-yl)-acrylate (7c). To a solution of (*E*)-**6a**-**Et** (3.41 g, 12.0 mmol, 1.0 equiv) in glacial acetic acid (4.62 g, 4.4 ml, 76.8 mmol, 6.4 equiv), hydrogen peroxide (30%, 4.90 g, 4.4 ml, 43.2 mmol, 3.6 equiv) was added, and the mixture was heated for 12 h at 60 °C. The mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica (ethyl acetate) to give **7c** (2.77 g, 9.26 mmol, 77%) as a yellow solid. Mp 87 °C. R_f 0.35 ($CHCl_3$/MeOH 19:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.32 (t, J=7.1 Hz, 3H, CH_2CH_3), 4.26 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 5.23 (s, 2H, CH_2C$_6$H$_5$), 6.85 (ddd, J=8.7, 0.92, 0.30 Hz, 1H, Aryl-H), 7.07 (dd, J=8.7, 6.5 Hz, 1H, Aryl-H), 7.29–7.46 (m, 5H, Aryl-H), 7.64 (d, J=16.2 Hz, 1H. CH=CHCO$_2$Et), 7.94 (ddd, J=6.54, 0.95, 0.46 Hz, 1H, Aryl-H), 8.20 (d, J=16.2 Hz, 1H, CH=CHCO$_2$Et). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 60.7 (−, CH$_2$CH$_3$), 71.5 (−, CH$_2$C$_6$H$_5$), 109.0 (+, Aryl-C), 124.1 (+, Aryl-C), 126.4 (+, Aryl-C), 127.2 (+, 2C, Aryl-C), 128.6 (+, CH=CHCO$_2$Et), 128.9 (+, 2C, Aryl-C), 129.2 (+, Aryl-C), 133.8 (+, CH=CHCO$_2$Et), 134.9 (quat, Aryl-C), 136.6 (quat, Aryl-C), 156.4 (quat, Aryl-C), 167.7 (quat, CO$_2$Et). IR (KBr) ν: 3121, 3074, 2983, 1714, 1696, 1627, 1558, 1499, 1463, 1434, 1394, 1367, 1312, 1282, 1257, 1233, 1212, 1177, 1146, 1088, 1045, 988, 869, 782, 743, 721, 689, 632, 583, 545 cm^{-1}. MS (EI, 70 eV) 299.3 (1.02, M^+), 283.3 (0.69), 226.1 (16.7), 210.1 (8.54), 107.9 (1.41), 90.9 (100.0). Anal. Calcd for $C_{17}H_{17}NO_4$ (299.32) C 68.21, H 5.72, N 4.68. Found C 67.94, H 5.71, N 4.51.

3.1.11. (*E*)-Ethyl 3-(3-(methoxy)-*N*-oxypyridin-2-yl)-acrylate (7d). To the solution of (*E*)-**6b**-**Et** (2.07 g, 10.0 mmol, 1.0 equiv) in glacial acetic acid (4.08 g, 3.7 ml, 120.0 mmol, 12.0 equiv), hydrogen peroxide (30%, 3.85 g, 3.7 ml, 19.2 mmol, 1.9 equiv) was added, and the mixture was heated for 12 h at 60 °C. The resulting solution

was concentrated under reduced pressure and the residue was purified by chromatography on silica (ethyl acetate/MeOH 49:1) to give **7d** (1.80 g, 8.05 mmol, 81%) as a yellow solid. Mp 100 °C. R_f 0.24 ($CHCl_3$/MeOH 9:1). ^1H NMR (250 MHz, $CDCl_3$) δ: 1.34 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 3.97 (s, 3H, OCH_3), 4.28 (q, $J=7.1$ Hz, 2H, CH_2CH_3), 6.87 (ddd, $J=8.6$, 0.89, 0.38 Hz, 1H, Aryl-H), 7.16 (dd, $J=8.7$, 6.6 Hz, 1H, Aryl-H), 7.57 (d, $J=16.2$ Hz, 1H, CH=CHCO$_2$Et), 7.95 (ddd, $J=6.6$, 0.99, 0.43 Hz, 1H, Aryl-H), 8.14 (d, $J=16.2$ Hz, 1H, CH=CHCO$_2$Et). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 14.3 (+, CH_2CH_3), 56.6 (+, OCH_3), 60.7 (−, CH_2CH_3), 107.5 (+, Aryl-C), 124.3 (+, Aryl-C), 126.0 (+, Aryl-C), 129.3 (+, CH=CHCO$_2$Et), 133.4 (+, CH=CHCO$_2$Et), 136.1 (quat, Aryl-C), 157.4 (quat, Aryl-C), 167.6 (quat, CO$_2$Et). IR (KBr) ν: 3123, 2991, 2901, 1719, 1623, 1555, 1458, 1447, 1424, 1362, 1291, 1235, 1186, 1170, 1084, 984, 951, 872, 843, 785, 746, 684, 653, 622, 576, 545, 535, 511 cm^{-1}. MS (EI, 70 eV) 223.1 (3.16, M^+), 207.1 (13.9), 178.0 (22.2), 162.1 (38.4), 150.0 (54.6), 134.0 (20.4), 122.0 (39.7), 106.0 (10.3), 92.0 (100.0). Anal. Calcd for $C_{11}H_{13}NO_4$ (223.23) C 59.19, H 5.87, N 6.27. Found C 59.08, H 5.90, N 6.17.

3.1.12. (*E*)-Isopropyl 3-(3-(methoxy)-*N*-oxypyridin-2-yl)acrylate (7e). To a solution of (*E*)-**6b**-***i*Pr** (3.06 g, 13.8 mmol, 1.0 equiv) in glacial acetic acid (5.63 g, 5.0 ml, 166 mmol, 12.0 equiv), hydrogen peroxide (30%, 5.31 g, 5.0 ml, 46.8 mmol, 3.4 equiv) was added, and the mixture was heated for 12 h at 60 °C. The resulting solution was concentrated under reduced pressure, and the residue was purified by chromatography on silica (ethyl acetate/methanol 30:1) to give **7e** (2.93 g, 12.3 mmol, 90%) as a yellow solid. R_f 0.33 ($CHCl_3$/MeOH 9:1). ^1H NMR (250 MHz, $CDCl_3$) δ: 1.31 (d, $J=6.3$ Hz, 6H, CH(CH_3)$_2$), 3.96 (s, 3H, OCH_3), 5.15 (hept, $J=6.3$ Hz, 1H, CH(CH$_3$)$_2$), 6.84 (ddd, $J=8.6$, 0.48, 0.48 Hz, 1H, Aryl-H), 7.14 (dd, $J=8.7$, 6.6 Hz, 1H, Aryl-H), 7.55 (d, $J=16.2$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.96 (ddd, $J=6.6$, 0.99, 0.46 Hz, 1H, Aryl-H), 8.13 (ddd, $J=16.2$, 0.45, 0.45 Hz, 1H, CH=CHCO$_2$*i*-Pr). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.9 (+, 2C, CH(CH_3)$_2$), 56.5 (+, OCH_3), 68.1 (+, CH(CH$_3$)$_2$), 107.4 (+, Aryl-C), 124.1 (+, Aryl-C), 126.7 (+, Aryl-C), 129.0 (+, CH=CHCO$_2$*i*-Pr), 133.5 (+, CH=CHCO$_2$*i*-Pr), 136.3 (quat, Aryl-C), 157.4 (quat, Aryl-C), 167.2 (quat, CO$_2$*i*-Pr). IR (KBr) ν: 3117, 3094, 3061, 2979, 2954, 2932, 1712, 1629, 1595, 1562, 1477, 1422, 1375, 1361, 1313, 1293, 1265, 1221, 1203, 1100, 1074, 985, 959, 911, 871, 789, 740, 545 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 255.3 (4.1, $M+NH_4^+$), 238.3 (10.7, MH^+), 222.2 (100). Anal. Calcd for $C_{12}H_{15}NO_4$ (237.25): C 60.75, H 6.37, N 5.90. Found C 60.14, H 6.36, N 5.88.

3.1.13. (*E*)-Ethyl 3-(pyridin-2-yl)acrylate (9-Et).[21] To a stirred suspension of LiBr (10.4 g, 120 mmol, 1.2 equiv) in dry acetonitrile (250 ml) was added triethylamine (11.1 g, 15.3 ml, 110 mmol, 1.1 equiv), triethyl phosphonoacetate (22.4 g, 20.0 ml 100 mmol, 1.0 equiv) and finally pyridine-2-carbaldehyde (**8**) (10.7 g, 9.7 ml, 100 mmol, 1.0 equiv). The solution was stirred for 18 h at room temperature. H_2O (200 ml) was added and the aqueous layer was extracted with ethyl acetate (5×50 ml). The combined organic layers were dried over $MgSO_4$ and the solution was concentrated under reduced pressure. The crude product was dissolved in ethyl acetate (100 ml), and the solution was filtrated, concentrated and distilled under reduced pressure to get **9-Et** (15.2 g; 85.8 mmol, 86%, *E*/*Z*=95:5) as colorless oil ($bp_{0.1}$ 80 °C), R_f 0.33 (hexanes/ethyl acetate 1:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 4.28 (q, $J=7.2$ Hz, 2H, CH_2CH_3), 6.92 (d, $J=15.7$ Hz, 1H, CH=CHCO$_2$Et), 7.25–7.74 (m, 3H, Aryl-H), 7.69 (d, $J=15.7$ Hz, 1H, CH=CHCO$_2$Et), 8.58–8.66 (m, 1H, Aryl-H).

3.1.14. (*E*)- and (*Z*)-Isopropyl 3-(pyridin-2-yl)acrylate ((*E*)-9-*i*Pr and (*Z*)-9-*i*Pr). To a stirred suspension of LiBr (5.21 g, 60 mmol, 1.2 equiv) in dry acetonitrile (150 ml) under nitrogen atmosphere was added at room temperature triethylamine (5.57 g, 7.6 ml, 55 mmol, 1.1 equiv), triisopropyl phosphonoacetate (13.3 g, 50 mmol, 1.0 equiv) and finally pyridine-2-carbaldehyde (**8**) (5.36 g, 4.8 ml, 50 mmol). The solution was stirred 48 h at room temperature. H_2O (200 ml) was added and the aqueous layer was extracted with ethyl acetate (3×100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography on silica (ethyl acetate/hexanes 1:2) to yield (*E*)-**9-*i*Pr** (5.91 g, 30.9 mmol, 62%) and (*Z*)-**9-*i*Pr** (0.27 g, 1.4 mmol, 2.9%). (*E*)-**9-*i*Pr**: R_f 0.52 (ethyl acetate/hexane 1:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31 (d, $J=6.3$ Hz, 6H, CH(CH_3)$_2$), 5.15 (hept, $J=6.3$ Hz, 1H, CH(CH$_3$)$_2$), 6.89 (d, $J=15.6$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.23-7.73 (m, 3H, Aryl-H), 7.67 (d, $J=15.7$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 8.63–8.65 (m, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.9 (+, 2C, CH(CH_3)$_2$), 67.9 (+, CH(CH$_3$)$_2$), 123.0 (+, Aryl-C), 123.9 (+, Aryl-C), 124.1 (+, Aryl-C), 136.7 (+, CH=CHCO$_2$*i*-Pr), 143.0 (+, CH=CHCO$_2$*i*-Pr), 150.1 (+, Aryl-C), 153.1 (quat, Aryl-C), 166.2 (quat, CO$_2$*i*-Pr). MS (EI, 70 eV) *m/z* (%): 191.0 (19.6, MH^+), 148.9 (21.4), 145.9 (14.6), 131.9 (100.0). IR (film) ν: 3051, 2981, 2937, 2875, 1721, 1647, 1581, 1468, 1433, 1373, 1350, 1315, 1296, 1275, 1109, 1049, 985, 916, 876, 823, 787, 744 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32. Found C 69.00, H 6.82, N 7.38. (*Z*)-**9-*i*Pr**: R_f 0.40 (ethyl acetate/hexanes 1:1). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.24 (d, $J=6.2$ Hz, 6H, CH(CH_3)$_2$), 5.10 (hept, $J=6.3$ Hz, 1H, CH(CH$_3$)$_2$), 6.11 (d, $J=12.5$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 6.91 (d, $J=12.5$ Hz, 1H, CH=CHCO$_2$*i*-Pr), 7.16–7.21 (m, 1H, Aryl-H), 7.59–7.69 (m, 2H, Aryl-H), 8.58 (d, $J=4.8$ Hz, 1H, Aryl-H). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.7 (+, 2C, CH(CH_3)$_2$), 68.1 (+, CH(CH$_3$)$_2$), 122.9 (+, Aryl-C), 123.7 (+, Aryl-C), 124.3 (+, CH=CHCO$_2$*i*-Pr), 135.9 (+, Aryl-C), 138.9 (+, CH=CHCO$_2$*i*-Pr), 149.1 (+, Aryl-C), 153.7 (quat, Aryl-C), 166.3 (quat, CO$_2$*i*-Pr). MS (EI, 70 eV) *m/z* (%): 191.0 (10.3, MH^+), 247.9 (31.4), 131.9 (100.0), 104.9 (39.0), 77.9 (27.6). IR (film) ν: 3053, 2981, 2935, 2877, 1720, 1637, 1585, 1566, 1468, 1435, 1387, 1373, 1244, 1211, 1178, 1147, 1109, 1049, 995, 960, 904, 835, 798, 746 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_2$ (191.23): C 69.09, H 6.85, N 7.32. Found C 68.80, H 6.80, N 7.34.

3.2. General procedure GP1 for the dihydroxylation of 7

A mixture of AD-mix (1.40 g), methansulfonamide (95 mg, 1.0 mmol, 1.0 equiv) and **7** (1.0 mmol, 1.0 equiv) in *tert*-butanol–water (15 ml, 1:1 v/v) was stirred vigorously at room temperature. After 24 h water (5 ml) was added and

the aqueous layer was extracted ten times with $CHCl_3$/MeOH (9:1 v/v, 20 ml each). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by chromatography on silica to give **10**.

3.2.1. (2*R*,3*S*)-Ethyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate (10a). According to GP1 **10a** (86 mg, 0.39 mmol, 39%) was obtained as colorless solid. R_f 0.24 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20} = +14.1$ ($c=0.69$, $CHCl_3$). ^{1}H NMR (250 MHz, [D$_6$]-DMSO) δ: 1.20 (t, $J=7.1$ Hz, 3H, CH_2CH_3), 4.14 (q, $J=7.1$ Hz, 2H, CH_2CH_3), 4.69 (dd, $J=7.9$, 2.4 Hz, 1H, C*H*OHCO$_2$Et), 5.30 (d, $J=7.9$ Hz, 1H, CHO*H*CO$_2$Et), 5.39 (dd, $J=6.9$ Hz, 1H, C*H*OHCHOHCO$_2$Et), 5.94 (d, $J=6.9$ Hz, 1H, CHO*H*CHOHCO$_2$Et), 7.33 (ddd, $J=7.6$, 6.0, 2.3 Hz, 1H, Aryl-H), 7.39 (ddd, $J=7.7$, 7.6, 1.4 Hz, 1H, Aryl-H), 7.57 (dd, $J=7.5$, 2.3 Hz, 1H, Aryl-H), 8.22 (ddd, $J=5.9$, 1.5, 0.44 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, D_2O) δ: 13.5 (+, CH_2CH_3), 62.9 (−, CH_2CH_3), 69.4 (+, CHOHCHOHCO$_2$Et), 70.8 (+, CHOHCHOHCO$_2$Et), 125.9 (+, Aryl-C), 126.1 (+, Aryl-C), 131.6 (+, Aryl-C), 139.6 (+, Aryl-C), 150.4 (quat, Aryl-C), 173.3 (quat, CO$_2$Et). IR (KBr) ν: 3411, 3235, 2993, 1920, 2852, 1723, 1489, 1437, 1283, 1248, 1224, 1128, 1068, 831, 772, 682, 552 cm^{-1}. MS (DCI) *m/z* (%): 228.2 (42.5, MH$^+$), 212.2 (100.0), 210.2 (26.6), 194.1 (19.8), 178.1 (7.2), 125.1 (12.6), 108.1 (58.1). Anal. Calcd for $C_{10}H_{13}NO_5$ (227.21): C 52.86, H 5.77, N 6.16. Found C 52.53, H 5.70, N 6.11. Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 18.6 min (**10a**), 20.9 min ((*ent*)-**10a**).

3.2.2. (2*S*,3*R*)-Ethyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate ((*ent*)-10a). According to GP1 (*ent*)-**10a** (82 mg, 0.36 mmol, 36%) was obtained as colorless solid. Analytical data according to **10a**; $[\alpha]_D^{20} = -25.3$ ($c=1.03$, $CHCl_3$). Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 18.0 min (**10a**), 19.7 min ((*ent*)-**10a**).

3.2.3. (2*R*,3*S*)-Isopropyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate (10b). According to GP1 **10b** (158 mg, 0.66 mmol, 66%) was obtained as colorless solid. R_f 0.24 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20} = +26.7$ ($c=0.88$, $CHCl_3$). ^{1}H NMR (250 MHz, [D$_6$]-DMSO) δ: 1.21 (dd, $J=6.2$, 3.8 Hz, 6H, CH(C*H*$_3$)$_2$), 4.56 (dd, $J=7.9$, 2.5 Hz, 1H, C*H*OHCO$_2$*i*-Pr), 4.96 (hept, $J=6.3$ Hz, 1H, C*H*(CH$_3$)$_2$), 5.23 (d, $J=7.9$ Hz, 1H, CHO*H*CO$_2$*i*-Pr), 5.36 (dd, $J=6.9$, 2.4 Hz, 1H, C*H*OHCHOHCO$_2$*i*-Pr), 5.89 (d, $J=6.9$ Hz, 1H, CHO*H*CHOHCO$_2$*i*-Pr), 7.28–7.44 (m, 2H, Aryl-H), 7.55 (dd, $J=7.6$, 2.5 Hz, 1H, Aryl-H), 8.22 (ddd, $J=5.8$, 1.6, 0.66 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.57, 21.67 (+, 2C, CH(*C*H$_3$)$_2$), 67.8, 69.2, 69.8 (+, 3C, *C*HOHCHOHCO$_2$*i*-Pr, *C*HOHCO$_2$*i*-Pr and *C*H(CH$_3$)$_2$), 124.6 (+, Aryl-C), 125.1 (+, Aryl-C), 125.4 (+, Aryl-C), 138.7 (+, Aryl-C), 151.2 (quat, Aryl-C) 171.7 (quat, *C*O$_2$*i*-Pr). IR (film) ν: 3386, 3203, 3120, 2983, 2937, 1747, 1726, 1637, 1489, 1437, 1375, 1321, 1277, 1261, 1199, 1132, 1105, 1068, 970, 914, 827, 769, 682 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 483.3 (2.0), 467.3 (0.4), 242.1 (100, MH$^+$), 226.1 (65), 224.1 (24), 208 (6.9), 125.0 (4.1), 108.0 (30). HRMS ($C_{11}H_{16}NO_5$) calcd 242.1028, found 242.1028. Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 95:5, 0.8 ml/min, 20 °C, ret.-times: 51.4 min (**10b**), 62.9 min ((*ent*)-**10b**).

3.2.4. (2*S*,3*R*)-Isopropyl 2,3-dihydroxy-3-(*N*-oxypyridin-2-yl)propanoate ((*ent*)-10b). According to GP1 (*ent*)-**10b** (157 mg, 0.65 mmol, 65%) was obtained as colorless solid. Analytical data according to **10b**; $[\alpha]_D^{20} = -21.2$ ($c=0.99$, $CHCl_3$). Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (250 nm), Daicel Chiralcel OD-H, hexane/ethanol 95:5, 0.8 ml/min, 20 °C, ret.-times: 49.4 min (**10b**), 53.9 min ((*ent*)-**10b**).

3.2.5. (2*R*,3*S*)-Ethyl 3-(3-(benzyloxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate (10c). According to GP1 **10c** (185 mg, 0.55 mmol, 55%) was obtained as colorless solid. R_f 0.12 (ethyl acetate/MeOH 50:1). $[\alpha]_D^{20} = -39.0$ ($c=1.23$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.23 (t, $J=7.2$ Hz, 3H, CH_2CH_3), 4.14–4.29 (m, 2H, CH_2CH_3), 4.60 (d, $J=3.7$ Hz, 1H, C*H*OHCO$_2$Et), 5.03 (bs, 1H, O*H*), 5.12–5.24 (m, 2H, CH_2Ph), 5.71 (d, $J=3.7$ Hz, 1H, C*H*OHCHOHCO$_2$Et), 7.10 (dd, $J=8.7$, 0.7 Hz, 1H, Aryl-H, 7.24 (ddd, $J=8.7$, 6.4, 0.2 Hz, 1H, Aryl-H), 7.33–7.42 (m, 5H, Aryl-H), 7.66 (bs, 1H, O*H*), 7.92 (ddd, $J=6.4$, 0.74, 0.24 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.1 (+, CH_2CH_3), 61.4 (−, CH_2CH_3), 70.0 (+, CHOHCHOHCO$_2$Et), 71.4 (−, CH_2Ph), 74.9 (+, CHOHCO$_2$Et), 112.8 (+, Aryl-C), 124.7 (+, Aryl-C), 127.0 (+, 2C, Aryl-C), 128.6 (+, Aryl-C), 128.9 (+, 2C, Aryl-C), 133.3 (+, Aryl-C), 134.7 (quat, Aryl-C), 139.2 (quat, Aryl-C), 154.1 (quat, Aryl-C), 171.4 (quat, CO$_2$Et). IR (KBr) ν: 3335, 3094, 2981, 1746, 1569, 1438, 1388, 1289, 1199, 1128, 1062, 862, 791, 741, 697 cm^{-1}. MS (FAB, pos) *m/z* (%): 667.2 (3.9), 334.1 (100, MH$^+$), 318.1 (8.4), 230.0 (9.1). HRMS ($C_{17}H_{20}NO_6$) calcd 334.1291, found 334.1287. Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (260 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 52.7 min (**10c**), 58.1 min ((*ent*)-**10c**).

3.2.6. (2*S*,3*R*)-Ethyl 3-(3-(benzyloxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate ((*ent*)-10c). According to GP1 (*ent*)-**10c** (197 mg, 0.59 mmol, 59%) was obtained as colorless solid. Analytical data according to **10c**; $[\alpha]_D^{20} = +44.7$ ($c=0.97$, $CHCl_3$). Determination of the enantiomeric excess by chiral HPLC: Kontron HPLC 325, det.: UV (260 nm), Daicel Chiralcel OD-H, hexane/ethanol 90:10, 1 ml/min, 20 °C, ret.-times: 53.9 min (**10c**), 57.2 min ((*ent*)-**10c**).

3.2.7. (2*R*,3*S*)-Ethyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate (10d). According to GP1 **10d** (134 mg, 0.52 mmol, 52%) was obtained as colorless solid. Mp 103 °C. R_f 0.30 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20} = -122.0$ ($c=0.86$, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.29 (t, $J=7.1$ Hz, 3H, CH_2CH_3), 3.94 (s, 3H, OCH_3), 4.27 (q, $J=7.1$ Hz, 2H, CH_2CH_3), 4.56 (dd, $J=6.1$, 4.1 Hz, 1H, C*H*OHCO$_2$Et), 5.04 (d, $J=6.8$ Hz, 1H, O*H*), 5.59 (dd, $J=11.0$, 4.0 Hz, 1H, C*H*OHCHOHCO$_2$Et), 7.07 (dd, $J=8.8$, 0.81 Hz, 1H, Aryl-H), 7.31 (dd, $J=8.8$, 6.6 Hz, 1H,

Aryl-H), 7.59 (d, $J=11.1$ Hz, 1H, O*H*), 7.94 (dd, $J=6.5$, 0.84 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.2 (+, CH_2CH_3), 56.8 (+, OCH_3), 61.5 (−, CH_2CH_3), 69.8 (+, *C*HOHCHOHCO$_2$Et), 75.0 (+, *C*HOHCO$_2$Et), 111.4 (+, Aryl-C), 124.8 (+, Aryl-C), 133.1 (+, Aryl-C), 138.9 (quat, Aryl-C), 155.1 (quat, Aryl-C), 171.4 (quat, *C*O$_2$Et). IR (film) ν: 3392, 3097, 2990, 2938, 1756, 1739, 1604, 1570, 1467, 1430, 1364, 1339, 1280, 1196, 1131, 1079, 1057, 1029, 967, 877, 784, 767, 693, 680, 647, 597, 562, 519 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 258.2 (100.0, MH$^+$), 242.2 (75.4), 224.2 (12.8), 138.1 (59.6). Anal. Calcd for $C_{11}H_{15}NO_6$ (257.24): C 51.36, H 5.88, N 5.45. Found C 51.39, H 5.83, N 5.41. Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated an enantiomeric excess >97%.

3.2.8. (2*S*,3*R*)-Ethyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate ((*ent*)-10d). According to GP1 (*ent*)-**10d** (138 mg, 0.54 mmol, 54%) was obtained as colorless solid. Analytical data according to **10d**; $[\alpha]_D^{20}=+122.7$ ($c=1.21$, $CHCl_3$). Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated an enantiomeric excess >98%.

3.2.9. (2*R*,3*S*)-Isopropyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate (10e). A mixture of AD-mix α (11.0 g) and methansulfonamide (0.75 g, 7.88 mmol, 1.0 equiv) in *tert*-butanol–water (120 ml, 1:1 v/v) was stirred vigorously at room temperature. After 30 min the (*E*)-**7e** (1.87 g, 7.88 mmol, 1.0 equiv) was added and stirring was continued for 18 h. H_2O (30 ml) was added and the aqueous layer was extracted five times with $CHCl_3$/MeOH (9:1 v/v, 25 ml each). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent at reduced pressure afforded a yellow oil, which was fractionated by chromatography on silica gel ($CHCl_3$/MeOH 19:1) to give **10e** (1.99 g, 7.32 mmol, 93%) as a colorless solid. R_f 0.42 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=-101.7$ (*c* 1.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (dd, $J=8.6$, 6.3 Hz, 6H, CH(CH_3)$_2$), 3.94 (s, 3H, OCH_3), 4.54 (dd, $J=6.9$, 4.1 Hz, 1H, C*H*OHCO$_2$*i*-Pr), 4.97 (d, $J=$ 6.9 Hz, 1H, CHO*H*CO$_2$*i*-Pr), 5.14 (hept, $J=6.3$ Hz, 1H, C*H*(CH_3)$_2$), 5.57 (dd, $J=11.2$, 4.1 Hz, 1H, C*H*OHCHOHCO$_2$*i*-Pr), 7.00 (dd, $J=8.7$, 0.82 Hz, 1H, Aryl-H), 7.27 (dd, $J=8.7$, 6.5 Hz, 1H, Aryl-H), 7.51 (d, $J=11.2$ Hz, 1H, CHOHCHO*H*CO$_2$*i*-Pr), 7.92 (dd, $J=6.5$, 0.74 Hz, 1H, Aryl-H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 21.7, 21.8 (+, 2C, CH(*C*H$_3$)$_2$), 56.7 (+, O*C*H$_3$), 69.4 (+, *C*H), 69.8 (+, *C*H), 74.9 (+, *C*H), 111.1 (+, Aryl-C), 124.6 (+, Aryl-C), 133.1 (+, Aryl-C), 139.1 (quat, Aryl-C), 155.1 (quat, Aryl-C), 171.0 (quat, *C*O$_2$*i*-Pr). MS (DCI, NH_3) *m/z* (%): 272.2 (7.6, MH$^+$), 152.1 (10.2), 138.0 (100), 124.0 (16.7), 110.0 (28.0), 96.0 (6.2). IR (film) ν: 3369, 3281, 3103, 3011, 2985, 2919, 2852, 1744, 1603, 1571, 1473, 1435, 1375, 1355, 1291, 1218, 1193, 1134, 1110, 1093, 1080, 1055, 968, 915, 874, 826, 787, 760, 695, 648 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_6$ (271.27): C 53.15, H 6.32, N 5.16. Found C 53.10, H 6.44, N 5.30. Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol indicated an enantiomeric excess >97%.

3.2.10. (2*S*,3*R*)-Isopropyl 3-(3-(methoxy)*N*-oxypyridin-2-yl)-2,3-dihydroxypropanoate ((*ent*)-10e). According to GP1 (*ent*)-**10e** (138 mg, 0.54 mmol, 54%) was obtained as colorless solid. Analytical data according to **10e**; $[\alpha]_D^{20}=+105.9$ ($c=1.16$, $CHCl_3$). Chiral shift ^{1}H NMR spectroscopy using (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated an enantiomeric excess >93%.

3.2.11. Measurement of the enantiomeric excess of 10d–e and (*ent*)-10d-e. The measurement of the enantiomeric excess of **10d** and **10e** was performed by NMR utilizing the solvating agent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle alcohol) in $CDCl_3$. For this purpose, **10d–e** (4 mg) was dissolved in 1.0 ml of $CDCl_3$. To this solution was added (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (10 mg for **10e**, 21 mg for **10d**). The ^{1}H NMR spectrum of this mixture was run in order to determine the ee. A similar analysis was performed on racemic mixture of **10d** and **10e**.

3.3. Synthesis of swainsonine (1b)

3.3.1. (1*R*,2*S*,8a*S*)- and (1*R*,2*S*,8a*R*)-1,2-Dihydroxy-hexahydroindolizin-3(5*H*)-one (11a and 11b). A solution of (*ent*)-**10b** (8.06 g, 33.4 mmol, 1.0 equiv) in MeOH (50 ml) was stirred at room temperature in the presence of $PtO_2\cdot H_2O$ (82 mg, 0.33 mmol, 0.01 equiv) under an atmospheric pressure of hydrogen for 14 d. After removal of the catalyst by filtration through a celite pad, the solvent was removed under reduced pressure. The residue was purified by chromatography on silica ($CHCl_3$/MeOH 9:1) to give **11** as a mixture of epimers (5.08 g, 29.7 mmol, 89%, **11a**:**11b**=60:40). For analytical purposes, a small sample of **11** was separated by converting the diol to the corresponding bis-OTBDMS ether followed by chromatography on silica. Subsequent cleavage with TBAF resulted in pure samples of **11a** or **11b**, respectively. **11a**: R_f 0.15 (CHCl3/MeOH 9:1). $[\alpha]_D^{20}=-61.4$ ($c=1.04$, $CHCl_3$) ^{1}H NMR (250 MHz, CD_3OD) δ: 1.03–1.52 (m, 3H, Piperidin-H), 1.64–1.76 (m, 1H, Piperidin-H), 1.80–1.92 (m, 1H, Piperidin-H), 2.04–2.16 (m, 1H, Piperidin-H), 2.64 (dddd, $J=13.0$, 12.7, 3.7, 1.7 Hz, 1H, CH_2N), 3.07 (ddd, $J=11.5$, 6.5, 3.8 Hz, 1H, NC*H*), 3.65 (dd, $J=7.4$, 6.5 Hz, 1H, NCHC*H*OH), 3.92–4.02 (m, 1H, CH_2N), 4.02 (dd, $J=7.4$, 1.7 Hz, 1H, N(CO)C*H*OH). ^{13}C NMR (250 MHz, CD_3OD) δ: 24.1 (−, NCHCH$_2$*C*H$_2$), 25.3 (−, *C*H$_2$), 31.7 (−,*C*H$_2$), 40.7 (−, N*C*H$_2$), 60.5 (+, N*C*H), 77.6 (+, NCH*C*HOH), 80.9 (+, N(CO)*C*HOH), 173.0 (quat, N(*C*O)). IR (KBr) ν: 3444, 3347, 3256, 2963, 2932, 1871, 1686, 1460, 1425, 1278, 1253, 1151, 1080, 1026, 838, 654, 611, 555 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_3$ (171.19): C 56.13, H 7.56, N 8.18. Found C 55.79, H 7.62, N 8.08. **11b**: R_f 0.15 (CHCl3/MeOH 9:1). $[\alpha]_D^{20}=-58.4$ ($c=0.93$, $CHCl_3$) ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.13–153 (m, 3H, Piperidin-H), 1.53–1.72 (m, 1H, Piperidin-H), 1.73–2.05 (m, 2H, Piperidin-H), 2.51–2.76 (m, 1H, NCH_2), 3.40–3.64 (m, 1H, NC*H*), 3.94–4.13 (m, 1H, N(CO)C*H*OH), 4.20–4.39 (m, 2H, NCHC*H*OH, NCH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 23.7 (−, NCHCH$_2$*C*H$_2$), 24.9 (−, NCH$_2$*C*H$_2$), 25.9 (−, NCH*C*H$_2$), 41.0 (−, N*C*H$_2$), 58.7 (+, N*C*H), 73.1 (+, NCH*C*HOH), 76.3 (+, N(CO)*C*HOH), 171.2 (quat, N(*C*O)). IR (film) ν: 3362, 2926, 2856, 1676, 1446, 1357, 1281, 1227, 1152, 1103, 1004, 855, 804 cm^{-1}. MS (DCI, NH_3) *m/z* (%): 343.2 (5.2), 189.1 (100, MH$^+$), 172.1 (42), 155.1 (6.7), 138.0 (5.9). HRMS ($C_8H_{13}NO_3$) calcd 171.0895, found 171.0897.

3.3.2. (1*R*,2*S*,8a*S*)- and (1*R*,2*S*,8a*R*)-1-Hydroxy-3-oxo-octahydroindolizin-2-yl benzoate (12a and 12b). To a stirred solution of the epimeric mixture of **11** (**11a**:**11b**=60:40, 1.10 g, 6.43 mmol, 1.0 equiv) in pyridine (30.0 ml) and DMAP (0.01 g, 0.06 mmol, 0.01 equiv) was added dropwise with a syringe pump a solution of benzoyl chloride (0.81 g, 5.78 mmol, 0.9 equiv) in pyridine (5.0 ml) at −30 °C during 1 h. The mixture was stirred for an additional 80 min at −30 °C and was then allowed to warm up during 2 h to 0 °C and subsequently kept in the refrigerator (+4 °C) for 12 h. Ethyl acetate was added (50 ml) and the mixture was washed with 2 N HCl (20 ml). The aqueous layer was washed twice with ethyl acetate (50 ml) and the combined organic layers were washed with brine (50 ml) and then again with 2 N HCl (10 ml). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica (ethyl acetate/hexanes 5:1) to give **12** as a mixture of epimers (**12a**:**12b**=60:40, 1.49 g, 5.41 mmol, 84%). IR (KBr) *ν*: 3334, 3244, 2950, 2870, 1678, 1455, 1335, 1304, 1240, 1167, 1123, 1106, 1001, 915, 829, 731, 663, 507, 3464, 2940, 2859, 1693, 1445, 1372, 1317, 1287, 1267, 1219, 1147, 1107, 1080, 978, 930, 912, 867, 837, 799, 731, 573, 503, 436, 3505, 3065, 2943, 2858, 1698, 1601, 1447, 1341, 1318, 1273, 1157, 1113, 1105, 984, 860, 802, 708, 586, 449 cm^{-1}. (EI, 70 eV) *m/z* (%): 275.1 (4.9, $M^{+\cdot}$), 257.1 (5.1), 154.1 (30.7), 153.0 (92.0), 122.0 (13.1), 105.0 (100.0), 84.0 (63.6), 83.0 (21.7), 77.0 (47.5), 51.0 (13.0). HRMS ($C_{15}H_{17}NO_4$) calcd 275.1158, found 275.1158. For analytical purposes, a small sample of **12** was separated by column chromatography. **12a**: R_f 0.41 (ethyl acetate/hexanes 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.13–1.77 (m, 4H, CH_2), 1.90–2.08 (m, 2H, CH_2), 2.69–2.81 (m, 1H), 3.63–3.75 (m, 1H), 4.22–4.31 (m, 1H), 4.47 (dd, *J*=8.1, 5.7 Hz, 1H), 5.21 (d, *J*=5.7 Hz, 1H), 7.41–7.50 (m, 2H, Aryl-H), 7.60–7.64 (m, 1H, Aryl-H), 8.08–8.13 (m, 2H, Aryl-H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 23.8 (−, *C*H_2), 24.9 (−, *C*H_2), 26.7 (−, *C*H_2), 41.1 (−, *C*H_2), 58.5 (+, *C*H), 72.4 (+, *C*H), 80.6 (+, *C*H), 128.5 (+, 2C, Aryl-C), 128.6 (quat, Aryl-C), 130.23 (+, 2C, Aryl-C), 133.91 (+, Aryl-C), 165.5 (quat, *C*OPh), 168.2 (quat, N*C*O). **12b**: R_f 0.36 (ethyl acetate/hexanes 5:1). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.17–1.50 (m, 3H), 1.73–1.81 (m, 1H), 1.90–1.99 (m, 1H), 2.18–2.27 (m, 1H), 2.67–2.97 (m, 1H), 3.29–3.38 (m, 1H), 4.03 (t, *J*=6.2 Hz, 1H), 4.16–4.25 (m, 1H), 5.29 (dd, *J*=6.2, 1.5 Hz, 1H), 7.41–7.49 (m, 2H), 7.57–7.64 (m, 1H), 8.09–8.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 23.1 (−, *C*H_2), 23.9 (−, *C*H_2), 31.1 (−, *C*H_2), 40.1 (−, *C*H_2), 59.5 (+, *C*H), 78.8 (+, *C*H), 80.9 (+, *C*H), 128.5 (+, 2C, Aryl-C), 128.6 (quat, Aryl-C), 130.3 (+, 2C, Aryl-C), 133.9 (+, Aryl-C), 165.8 (quat, *C*O), 168.3 (quat, *C*O).

3.3.3. (1*S*,2*S*,8a*S*)- and (*1S*,*2S*,8a*R*)-*2*-Hydroxy-3-oxo-octahydroindolizin-1-yl benzoate (13a and 13b). A vigorously stirred solution of **12** (**12a**:**12b**=60:40, 1.10 g, 3.99 mmol, 1.0 equiv) and pyridine (0.63 g, 7.98 mmol, 2.0 equiv) in dry CH_2Cl_2 under nitrogen atmosphere was cooled to −30 °C. To this solution triflic anhydride (1.80 g, 6.38 mmol, 1.6 equiv) was added dropwise and the mixture was slowly allowed to reach room temperature. Stirring was continued for 1H, subsequently water (2.0 ml) was added and the reaction mixture was further stirred overnight. Water (15 ml) was added, and the mixture was extracted with CH_2Cl_2 (4×15 ml). The combined organic layers were extracted with aqueous $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica (ethyl acetate/hexane 5:1) to yield **13** as a mixture of epimers (0.58 g, 2.11 mmol, 53% yield). (EI, 70 eV) *m/z* (%): 275.1 (3.6, $M^{+\cdot}$), 153.0 (100.0), 105.0 (69.3), 84.0 (36.4), 77.0 (37.1). HRMS ($C_{15}H_{17}NO_4$) calcd 275.1158, found 275.1158. For analytical purposes, a small sample of **13** was separated by column chromatography: **13a**: R_f 0.12 (hexanes/ethyl acetate 1:5). $[\alpha]_D^{20}=-15.4$ (*c*=1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.18–1.53 (m, 3H), 1.63–1.73 (m, 1H), 1.88–1.99 (m, 1H), 2.04–2.13 (m, 1H), 2.74 (dt, *J*=35, 12.9 Hz, 1H), 3.55–2.63 (m, 1H), 4.12–4.20 (m, 1H), 4.53 (d, *J*=6.4 Hz, 1H), 5.23 (dd, *J*=6.4, 2.4 Hz, 1H), 7.28–7.45 (m, 2H), 7.52–7.59 (m, 1H), 8.05–8.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 23.6 (−, *C*H_2), 24.4 (−, *C*H_2), 29.5 (−, *C*H_2), 40.8 (−, *C*H_2), 61.0 (+, *C*H), 69.3 (+, *C*H), 72.5 (+, *C*H), 128.4 (+, 2C, Aryl-C), 129.4 (quat, Aryl-C), 130.0 (+, 2C, Aryl-C), 133.4 (+, Aryl-C), 166.2 (quat, *C*O), 170.5 (quat, *C*O). **13b**: R_f 0.21 (hexanes/ethyl acetate 1:5). $[\alpha]_D^{20}=-24.7$ (*c*=1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 1.38–1.57 (m, 3H), 1.70–1.82 (m, 2H), 1.90–1.97 (m, 1H), 2.67–2.79 (m, 1H), 2.8–2.99 (bs, 1H, OH), 3.63–3.70 (m, 1H), 4.13–4.22 (m, 1H), 4.47 (dd, *J*=5.6, 1.7 Hz, 1H), 5.78 (dd, *J*=5.6, 4.2 Hz, 1H), 7.41–7.48 (m, 1H), 7.54–7.61 (m, 1H), 8.02–8.07 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 22.9 (−, *C*H_2), 24.0 (−, *C*H_2), 24.9 (−, *C*H_2), 40.4 (−, *C*H_2), 56.6 (+, *C*H), 69.8 (+, *C*H), 70.7 (+, *C*H), 128.5 (+, 2C, Aryl-C), 129.2 (quat, Aryl-C), 129.9 (+, 2C, Aryl-C), 133.5 (+, Aryl-C), 165.9 (quat, *C*O), 171.4 (quat, *C*O).

3.3.4. (1*S*,2*S*,8a*S*)- and (1*S*,2*S*,8a*R*)-1,2-Dihydroxyhexahydroindolizin-3-one (14a and 14b). To a solution of **13** (0.52 g, 1.89 mmol) in anhydrous methanol (10 ml) was added under stirring 0.1 N MeONa (2 ml) at room temperature. Stirring was continued for 3 h (TLC control), subsequently a small piece of dry ice was added, and the mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica ($CHCl_3$/MeOH 9:1) to give **14** (0.25 g, 1.48 mmol, 78% yield). IR (KBr) *ν*: 3334, 3244, 2950, 2870, 1678, 1455, 1335, 1304, 1240, 1167, 1123, 1106, 1001, 915, 829, 731, 663, 507 cm^{-1}. MS (EI, 70 eV) *m/z* (%). 171.0 (47, $M^{+\cdot}$), 142.0 (34.0), 128.0 (16), 127.0 (10), 126.0 (40), 110.0 (14), 84 (100), 83.0 (26), 82.0 (12), 70.0 (11), 60.0 (24), 56.0 (16), 55.0 (29), 41.0 (19.3). HRMS ($C_8H_{13}NO_3$) calcd 171.0895, found 171.0896. For analytical purposes, a small sample of **14** was separated by column chromatography. **14a**[14]: R_f 0.43 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=-15.0$ (*c*=1.07, MeOH). ^{1}H NMR (600 MHz, [D_6]-DMSO) *δ*: 1.00–1.15 (m, 2H), 1.33–1.41 (m, 1H), 1.55–1.61 (m, 1H), 1.74–1.79 (m, 1H), 1.83–1.88 (m, 1H), 2.60 (dt, *J*=12.9, 3.52 Hz, 1H), 5.15 (dt, *J*=12.0, 3.3 Hz, 1H), 3.69–3.73 (m, 1H), 3.87 (dd, *J*=12.9, 4.8 Hz, 1H), 3.91 (t, *J*=5.4 Hz, 1H), 4.84 (d, *J*=5.4 Hz, 1H), 5.37 (d, *J*=6.4 Hz, 1H). ^{13}C NMR (75 MHz, [D_6]-DMSO) *δ*: 22.9 (−, *C*H_2), 24.1 (−, *C*H_2), 29.0 (−, *C*H_2), 39.3 (−, *C*H_2), 61.5 (+, *C*H), 69.6 (+, *C*H), 70.7 (+, *C*H), 170.4 (quat, *C*O). **14b**: R_f 0.38 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=-60.0$ (*c*=1.30, MeOH). ^{1}H NMR (600 MHz, [D_6]-DMSO) *δ*: 1.16–1.24 (m, 1H), 1.32–1.41 (m, 1H), 1.46–1.51 (m, 1H), 1.53–1.60 (m, 1H), 1.61–1.66 (m, 1H),

1.79–1.85 (m, 1H), 2.50–2.56 (m, 1H), 3.27 (dt, $J=11.4$, 3.7 Hz, 1H), 3.80 (dd, $J=12.9$, 4.8 Hz, 1H), 3.96–4.00 (m, 2H), 4.68 (d, $J=4.2$ Hz, 1H), 5.20 (d, $J=6.6$ Hz, 1H). ^{13}C NMR (75 MHz, [D$_6$]-DMSO) δ: 22.6 (−, *C*H$_2$), 23.8 (−, *C*H$_2$), 23.8 (−, *C*H$_2$), 38.9 (−, *C*H$_2$), 56.3 (+, *C*H), 67.2 (+, *C*H), 71.1 (+, *C*H), 171.4 (quat, *C*O).

3.3.5. (1*S*,2*S*,8a*S*)- and (1*S*,2*S*,8a*R*)-1,2-(Isopropylidenedioxy)-1,5,6,7,8,8a-hexahydro-3(2*H*)-indolizinone (15a and 15b). To a stirred solution of the diol **14** (0.20 g, 1.17 mmol, 1.0 equiv) in dry CH_2Cl_2 (10 ml) was added 2,2-dimethoxypropane (0.72 ml, 5.84 mmol, 5.0 equiv) followed by *p*-TsOH (0.01 g, 0.05 mmol, 0.04 equiv). The solution was stirred at room temperature for 2 h, concentrated under reduced pressure, and the residue was purified by chromatography on silica ($CHCl_3$/MeOH 9:1) to afford **15** (0.24 g, 0.14 mmol, 98%). IR (KBr) ν: 3334, 3244, 2950, 2870, 1678, 1455, 1335, 1304, 1240, 1167, 1123, 1106, 1001, 915, 829, 731, 663, 507, 3464, 2940, 2859, 1693, 1445, 1372, 1317, 1287, 1267, 1219, 1147, 1107, 1080, 978, 930, 912, 867, 837, 799, 731, 573, 503, 436 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 211.0 (17.1, M$^{+\cdot}$), 197.0 (10.5), 196.0 (100.0), 154.0 (13.2), 153.0 (16.9), 136.0 (69.9), 100.0 (29.5), 84.9 (22.5), 84.0 (16.9), 83.0 (51.3), 55.0 (11.6), 42.9 (14.2). HRMS ($C_{11}H_{17}NO_3$) calcd 211.1208, found 211.1212. For analytical purposes, a small sample of **15** was separated by column chromatography. **15a** (colorless solid)[14]. Mp 106–107 °C. R_f 0.32 (ethyl acetate/hexanes 5:1). $[\alpha]_D^{20}=+24$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (dddd, $J=3.5$, 12.7, 12.7, 12.7 Hz, 1H), 1.20–1.33 (m, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.45–1.59 (m, 1H), 1.62–1.72 (m, 1H), 1.87–2.01 (m, 2H), 2.70 (ddd, $J=3.5$, 12.9, 12.9 Hz, 1H), 3.46 (dd, $J=2.7$, 12.5 Hz, 1H), 4.13–4.21 (m, 1H), 4.34 (d, $J=6.6$ Hz, 1H), 4.62 (d, $J=6.6$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=23.8$ (−, *C*H$_2$), 24.6 (−, *C*H$_2$), 25.3 (+, *C*H$_3$), 26.8 (+, *C*H$_3$), 30.8 (−, *C*H$_2$), 40.5 (−, *C*H$_2$), 62.2 (+, *C*H), 77.4 (+, 2C, *C*H), 112.6 (quat C), 168.5 (quat, *C*O). **15b** (viscous oil) R_f 0.20 (ethyl acetate/hexanes 5:1). $[\alpha]_D^{20}=-15$ ($c=1.0$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21–1.48 (m, 2H), 1.39 (s, 3H), 1.44 (s, 3H), 1.62–1.81 (m, 3H), 1.91–2.00 (m, 1H), 2.63 (dt, $J=3.4$, 12.8 Hz, 1H), 3.42–3.51 (m, 1H), 4.10–4.18 (m, 1H), 4.64 (d, $J=2.6$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3 (−, *C*H$_2$), 24.1 (−, *C*H$_2$), 25.1 (−, *C*H$_2$), 26.0 (+, *C*H$_3$), 27.1 (+, *C*H$_3$), 40.1 (−, *C*H$_2$), 57.8 (+, *C*H), 74.4 (+, *C*H), 78.0 (+, *C*H), 112.6 (quat, *C*(CH$_3$)$_2$), 169.6 (quat, *C*O).

3.3.6. (1*S*,2*S*)-1,2-Isopropylidenedioxy-1,2,6,7-tetrahydroindolizin-3(5*H*)-one (17).[17] Aqueous NaOCl solution (3 ml, 12%) was added dropwise during 9 h to a stirred suspension of **15** (40.0 mg, 0.189 mmol) in ethyl acetate (3 ml) and $RuO_2\cdot H_2O$ (5 mg) under cooling at 0 °C. Isopropanol (1 ml) was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2×2 ml), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude product was dissolved in $CHCl_3$ (2 ml) and a small amount of HOAc was added. The solution was stirred for 1 h at room temperature, concentrated under reduced pressure and the residue was purified by chromatography on silica (hexanes/ethyl acetate 1:5) to afford **17** (19.8 mg, 0.094 mmol, 50%) and **15b** (11.6 mg, 0.055 mmol, 29%). Analogously **15a** was converted to **17** via **16a** in 79% yield. **16a**: R_f 0.51 ($CHCl_3$/MeOH 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21–1.28 (m, 1H), 1.38 (s, 3H), 1.41 (s, 3H), 1.70–1.95 (m, 5H), 2.84–2.96 (m, 1H), 3.80–3.89 (m, 1H), 3.91–4.04 (br s, 1H, OH), 4.47 (d, $J=5.8$ Hz, 1H), 4.86 (dd, $J=1.0$, 5.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.9 (−, *C*H$_2$), 24.0 (−, *C*H$_2$), 26.0 (+, *C*H$_3$), 27.2 (+, *C*H$_3$), 30.2 (−, *C*H$_2$), 37.0 (−, *C*H$_2$) 77.1 (+, *C*H), 81.3 (+, *C*H), 87.7 (quat C), 113.4 (quat C), 170.6 (quat, *C*O). **17**. Mp 67–69 °C. R_f 0.57 (ethyl acetate/hexanes 5:1). $[\alpha]_D^{20}=+25.5$ ($c=1.1$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 3H), 1.44 (s, 3H), 1.66–1.78 (m, 1H), 1.83–1.95 (m, 1H), 2.16–2.24 (m, 2H), 3.36–3.46 (m, 1H), 3.69–3.78 (m, 1H), 4.67 (d, $J=6.4$ Hz, 1H), 4.96 (d, $J=6.4$ Hz, 1H), 5.25 (t, $J=4.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.0 (−, *C*H$_2$), 21.5 (−, *C*H$_2$), 25.6 (+, *C*H$_3$), 26.9 (+, *C*H$_3$), 39.0 (−, *C*H$_2$), 73.7 (+, *C*H), 76.5 (+, *C*H), 104.6 (+, *C*H), 113.2 (+, *C*H), 136.0 (quat, *C*(CH$_3$)$_2$), 169.7 (quat, *C*O). IR (KBr) ν: 2984, 2940, 2893, 1722, 1686, 1458, 1414, 1378, 1314, 1252, 1213, 1153, 1093, 1067, 1041, 1010, 972, 930, 899, 868, 779, 710, 644, 617, 563, 519 cm^{-1}. MS (EI, 70 eV) *m*/*z* (%): 209.1 (59.1, M$^{+\cdot}$), 194.1 (26.1), 166.1 (14.1), 152.1 (100.0), 43.0 (10.3). HRMS ($C_{11}H_{15}NO_3$) calcd 209.1052, found 209.1053.

3.3.7. Swainsonine (1b). 17 was converted in two steps into swainsonine (**1b**) in 77% overall yield as described[17] in the literature. The spectroscopic data obtained for **1b** was identical to those described in the literature[3d]: ^{1}H NMR (300 MHz, D_2O): $\delta=1.02$–1.13 (m, 1H), 1.29–1.47 (m, 1H), 1.53–1.64 (m, 1H), 1.75–1.84 (m, 2H), 1.88–1.98 (m, 1H), 2.42 (dd, $J=11$, 4 Hz, 1H), 2.72–2.78 (m, 2H), 3.67 (ddd, $J=11$, 10, 5 Hz, 1H), 4.12 (dd, $J=6$, 4 Hz, 1H), 4.22 (ddd, $J=8$, 6, 3 Hz, 1H). ^{13}C NMR (75.5 MHz, D_2O): $\delta=22.8$ (−, *C*H$_2$), 32.1 (−, *C*H$_2$), 51.2 (−, *C*H$_2$), 60.2 (−, *C*H$_2$), 65.9 (+, *C*H), 68.6 (+, *C*H), 69.2 (+, *C*H), 72.4 (+, *C*H).

3.4. Synthesis of 2,8a-di-*epi*-swainsonine

3.4.1. (1*S*,2*R*,8*R*,8a*R*)-1,2-Dihydroxy-8-methoxy-hexahydroindolizin-3(5*H*)-one (18). A solution of **10e** (1.58 g, 5.82 mmol, 1.0 equiv) in glacial acetic acid (60 ml) was stirred in the presence of platinum on carbon (470 mg, 5% Pt/C, 0.24 mmol, 0.02 equiv) under an atmospheric pressure of hydrogen for 7 d. After removal of the catalyst by filtration through a celite pad, the solvent was removed under reduced pressure. To the crude product $CHCl_3$ (50 ml) and NEt_3 (2 ml) was added and the solution was stirred for 24 h at room temperature. Evaporation of the solvent at reduced pressure afforded a yellow oil, which was purified by chromatography on silica (chloroform/methanol 9:1). The crude product was recrystallized from ethyl acetate/methanol (4:1) to give **18** (551 mg, 2.74 mmol, 47%) as white crystals. Mp 181 °C. R_f 0.16 ($CHCl_3$/MeOH 9:1). $[\alpha]_D^{20}=+33.7$ (*c* 0.99, MeOH). ^{1}H NMR (300 MHz, [D$_6$]-DMSO) δ: 1.30–1.51 (m, 3H, Piperidine-H), 2.08–2.17 (m, 1H, Piperidine-H), 2.53–2.64 (m, 1H, C*H*$_2$N), 3.08 (dd, $J=6.8$, 2.5 Hz, 1H, C*H*N), 3.26 (s, 3H, OC*H*$_3$), 3.43–3.48 (m, 1H, C*H*OMe), 3.73–3.78 (m, 1H, C*H*$_2$N), 3.78–3.86 (m, 1H, NCHC*H*OH), 3.97–4.06 (m, 1H, NCOC*H*OH), 5.47 (d, $J=5.8$ Hz, 1H, NCHCHO*H*), 5.56 (d, $J=6.0$ Hz, 1H,

NCOCHO*H*). ^{13}C NMR (75.5 MHz, [D$_6$]-DMSO) δ: 16.8 (−, *C*H$_2$), 24.5 (−, *C*H$_2$), 38.1 (−, *C*H$_2$), 55.8 (+, O*C*H$_3$), 61.5 (+, N*C*H), 70.2 (+, *C*HOCH$_3$), 71.5 (+, NCH*C*HOH), 75.7 (+, NCO*C*HOH), 170.7 (quat, *C*O). MS (DCI, NH$_3$) *m*/*z* (%): 403.1 (5.17, 2MH$^+$), 219.0 (100.0, M+NH$_4^+$), 202.0 (100, MH$^+$), 185.9 (3.3). IR (film) ν: 3409, 3243, 2977, 2953, 1894, 2866, 2835, 1686, 1462, 1439, 1366, 1282, 1263, 1253, 1219, 1197, 1152, 1107, 1083, 1030, 976 cm^{-1}. Anal. Calcd for C$_9$H$_{15}$NO$_4$ (201.22): C 53.72, H 7.51, N 6.96. Found C 53.74, H 7.38, N 6.83.

3.4.2. (1*S*,2*S*,8*R*,8a*S*)-Octahydroindolizine-1,2,8-triol ((−)-2,8a-di-*epi*-swainsonine) (20). A mixture of **18** (0.25 g, 1.24 mmol) and HBr (48%, 0.6 ml) was heated at 140 °C for 30 min. The solution was evaporated to dryness under reduced pressure and evaporation was repeated after addition of ethanol (3.5 ml). The crude product was purified by chromatography on silica (CH$_2$Cl$_2$/MeOH/NH$_3$ 40:8:1) to give crude **19**, which was contaminated with ammonium bromide (0.31 g, 1.08 mmol, 88%) as a brownish solid, which was used in the next step without further purification. Analytical pure **19** can be obtained by recrystallization form ethyl acetate/methanol (2:1). **19**. Mp 181–184 °C, R_f 0.28 (CH$_2$Cl$_2$/MeOH/NH$_3$ 40:8:1), $[\alpha]_D^{20}=+56$ (*c* 1.10, MeOH). ^{1}H NMR (300 MHz, [D$_6$]-DMSO) δ: 1.29–1.88 (m, 4H), 2.52–2.64 (m, 1H), 2.99 (dd, *J*=6.5, 2.2 Hz, 1H), 3.74–3.87 (m, 3H), 3.98–4.06 (m, 1H), 4.80 (d, *J*=4.3 Hz, 1H), 5.32 (d, *J*=5.8 Hz, 1H), 5.52 (d, *J*=5.9 Hz, 1H). ^{13}C NMR (75.5 MHz, [D$_6$]-DMSO) δ: 16.7 (−, *C*H$_2$), 29.9 (−, *C*H$_2$), 38.2 (−, *C*H$_2$), 60.5 (+, *C*H), 62.1 (+, *C*H), 71.8 (+, *C*H), 76.0 (+, *C*H), 170.9 (quat, *C*O). IR (KBr) ν: 3406, 3246, 1684, 1463, 1366, 1281, 1255, 1215, 1197, 1153, 1105, 1081, 1030, 976, 873, 851, 814, 753, 658, 600, 555, 448 cm^{-1}. To a stirred solution of crude **19** (98 mg) in THF (5 ml) was added BH$_3$·Me$_2$S complex (150 µl) at 0 °C under nitrogen atmosphere. After warming to room temperature, the mixture was stirred for 12 h, and additional BH$_3$·Me$_2$S complex (100 µl) was added. After further stirring for 20 h, ethanol and water were added to the mixture. The aqueous layer was extracted with ethyl acetate (3×5 ml) and the combined organic layers were dried over MgSO$_4$. The mixture was concentrated, and the residue was purified by chromatography on silica (CH$_2$Cl$_2$/MeOH/NH$_3$ 40:8:1) to give **20·HBr** (51 mg, 0.20 mmol, 59%) as a colorless solid, which was recrystallized from ethyl acetate/methanol 1:1 to give **20·HBr** (28 mg, 0.11 mmol, 32%) to obtain crystals suitable for X-ray analysis. Treatment of **20·HBr** (28 mg, 0.11 mmol) on an ion exchange column (Dowex 1×8; 100–200 mesh, eluent water) yielded **20** (19 mg, 0.11 mmol, 32% yield starting from **18**). **20·HBr**: R_f 0.35 (CH$_2$Cl$_2$/Me OH/NH$_3$ 40:8:1). $[\alpha]_D^{20}=-12.7$ (*c*=1.28, MeOH). ^{1}H NMR (400 MHz, D$_2$O) δ: 1.60–1.79 (m, 2H), 1.87–2.01 (m, 2H), 2.93–3.02 (m, 1H), 3.17 (d, *J*=9.4 Hz, 1H), 3.37 (dd, *J*=12.6, 4.5 Hz, 1H), 3.40–3.52 (m, 2H), 4.08 (dd, *J*=9.4, 3.7 Hz, 1H), 4.27–4.31 (m, 2H). ^{13}C NMR (75.5 MHz, D$_2$O) δ: 17.1 (−, *C*H$_2$), 28.1 (−, *C*H$_2$), 52.5 (−, *C*H$_2$), 58.7 (−, *C*H$_2$), 61.1 (+, *C*H), 71.3 (+, *C*H), 73.0 (+, *C*H), 75.3 (+, *C*H). MS (DCI, NH$_3$) *m*/*z* (%): 174.1 (100.0, MH$^+$). **20**[18]. Mp 138–142 °C (lit.[19] mp 138–142 °C). $[\alpha]_D^{20}=-8.8$ (*c*=0.91, MeOH) (lit.[19] $[\alpha]_D^{26}=-24.0$ (*c*=1.14, MeOH)). ^{1}H NMR (400 MHz, D$_2$O) δ: 1.32–1.45 (m, 2H), 1.53–1.81 (m, 2H), 1.87–1.99 (m, 2H), 2.48 (dd, *J*=11.0, 7.3 Hz, 1H), 2.70–2.75 (m, 1H), 2.77–2.84 (m, 1H), 3.86 (dd, *J*=8.7, 3.6 Hz, 1H), 3.92–3.98 (m, 2H). ^{13}C NMR (75.5 MHz, D$_2$O) δ: 18.5 (−, *C*H$_2$), 29.6 (−, *C*H$_2$), 52.3 (−, *C*H$_2$), 60.3 (−, *C*H$_2$), 62.8 (+, *C*H), 71.5 (+, *C*H), 75.6 (+, *C*H), 77.7 (+, *C*H). IR (KBr) ν: 3415, 2922, 2822, 2297, 1334, 1240, 1209, 1154, 1105, 1006, 891, 812, 693 cm^{-1}. HRMS (EI, 70 eV) calcd 173.1052, found 173.1052.

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Evaluation of C-trialkylsilyl enol and thioenol ethers as intermediates in the synthesis of acylsilanes

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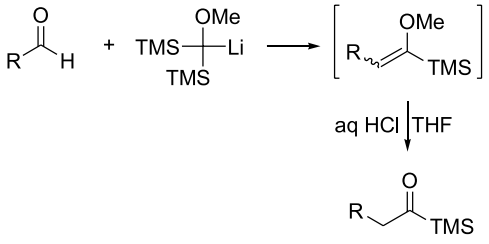
Abstract—C-silyl enol ethers or thioenol ethers have been prepared by a Peterson reaction, as intermediates for acylsilane synthesis. Bis(trialkylsilyl)(methoxy)- or -(methylsulfanyl)methanes bearing identical or different trialkylsilyl groups were used as starting materials in order to assess the selectivity of the Peterson elimination step. A good selectivity was observed only with ethers bearing the TMS and TBDMS groups. However, there is no practical interest to use such reagents owing to the difficulty to obtain them in correct yields. Bis(trimethylsilyl)(methylsulfanyl)methane proved to be a good reagent for the preparation of C-silyl thioenol ethers, which are hydrolyzed under classical acid conditions to give acylsilanes in fair overall yields. This convenient procedure was extended to the synthesis of bis(acylsilanes).

1. Introduction

Acylsilanes are interesting compounds exhibiting specific properties beside the usual ones of carbonyl derivatives.[1] The interest of their chemistry is strongly dependant on their more or less easy synthesis. Several strategies were reported, starting from compounds as various as aldehydes,[2,3] esters,[4] acyl chlorides,[5] alkyl halides or triflates,[6] epoxides,[7] diols,[8] and others. One of the more general methods, proposed simultaneously by Brook's and Corey's groups,[2] is based on the reversed polarity (umpolung) concept and uses dithioacetals as key intermediates. First developed essentially via the thioacetalization of aldehydes as starting materials, the methodology was further extended to the alternative approach using alkylation of 2-lithio-2-trimethylsilyldithiane as silylcarbonyl moiety equivalent.[6–8] These dithioacetal routes are very useful, and they were involved in the preparation of a wide range of acylsilanes, including functionalized acylsilanes and bis(acylsilanes).[6–8]

The dithioacetal methodology suffers some drawbacks inherent to the last step of carbonyl releasing, which needs oxidative hydrolytic conditions. Even if one can avoid the mercury salts initially proposed, the conditions are not trivial and not compatible with various functional groups. On the other hand, aldehydes are starting materials of choice, a lot of them being commercially available. Very few attention has been paid to other methods of preparation of acylsilanes from aldehydes. The one reported by Yoshida and co-workers[3] seems to have not been exploited much.[9] Based on a Peterson reaction, this method is interesting because the last step requires classical hydrolytic conditions (Scheme 1).

Being involved in some aspects of the chemistry of acylsilanes, especially functionalized ones, we were interested in a possible extension of this 'Peterson' approach. Our goals were to investigate the building blocks described in Scheme 2, as precursors of C-trialkylsilyl enol or thioenol ether type intermediates. Our interest for bis(acylsilanes) prompted us to also investigate a possible selectivity in the



Scheme 1.

Keywords: Organosilicon; Peterson olefination; Acylsilane; Enol ether; Thioenol ether.
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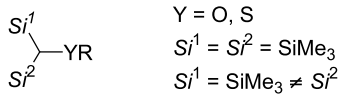


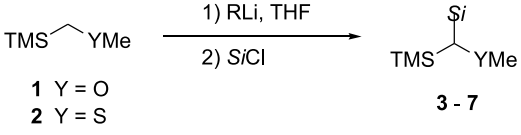
Scheme 2.

Peterson elimination step by differentiating the two trialkylsilyl groups.

2. Results and discussion

2.1. Synthesis of the bis(silylated) building blocks

The procedure and results are depicted in Scheme 3 and Table 1. The methoxy derivatives **3–5** have been prepared by applying to methoxymethyl(trimethyl)silane **1** the metallation–silylation sequence reported by Yoshida's group.[3] The reaction works well for bis(trimethylsilyl)-(methoxy)methane **3** as reported by Yoshida, but proved to be more difficult with (*tert*-butyl)dimethylsilyl (TBDMS) derivative **4**. Surprisingly, a better yield was obtained for the tris(isopropylsilyl) (TIPS) derivative **5**.



Scheme 3.

Table 1. Preparation of bis(silylated) building blocks **3–7**

Y	RLi	Si[a]	Product (%)
O	*s*-Bu	TMS	**3** (85)[3]
O	*s*-Bu	TBDMS	**4** (28)
O	*s*-Bu	TIPS	**5** (56)
S	*n*-Bu	TMS	**6** (65)[11]
S	*n*-Bu	TBDMS	**7** (62)

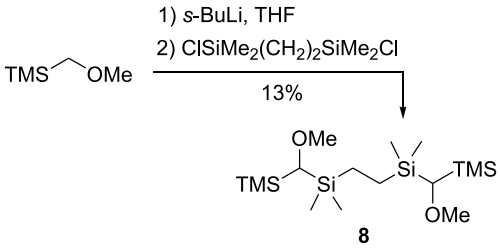
[a] TMS = trimethylsilyl, TBDMS = (*tert*-butyl)dimethylsilyl, TIPS = tris-(isopropylsilyl).

The bis(silylated) methylsulfanyl derivatives **6–7** were prepared from methylsulfanyl (trimethylsilyl)methane[10] according to a similar procedure, except that the presence of sulfur allows to use *n*-butyllithium (Scheme 3). As for oxygen series, only the bis(trimethylsilyl) derivative **6** had already been prepared, for different purposes.[11] In contrast to the oxygen analogue, the TBDMS derivative **7** has been obtained in fairly good yield (Table 1).

Just as variously substituted silyl groups are introduced to assess a possible selectivity in the Peterson reaction, the tetrasilyl reagent **8** has been synthesized, though in poor yield, in order to investigate a possible application in bis(acylsilane) synthesis (Scheme 4).

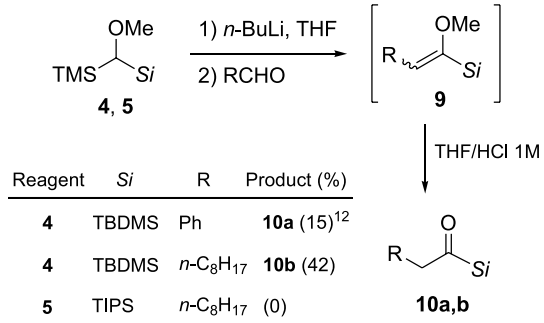
2.2. Peterson reaction using reagents 3–7

To the best of our knowledge, the chemoselectivity of the elimination step of the Peterson olefination process had never been investigated on bis(silylated) organometallic species. One could expect that the intramolecular formation



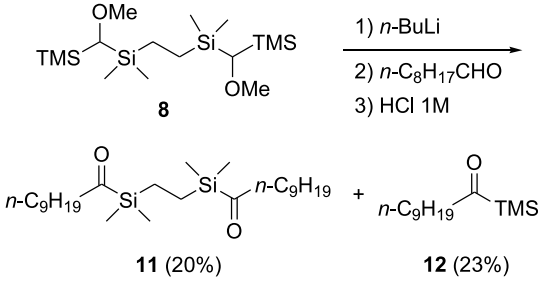
Scheme 4.

of the Si–O bond would be favoured with the less bulky TMS group. Indeed, when the reagent **4** is reacted with *n*-butyllithium and then with an aldehyde, a single acylsilane (**10a**[12] or **10b**) is isolated, albeit in low yield, after hydrolysis of the corresponding enol ether intermediate **9** (Scheme 5). No reaction was observed with the TIPS derivative **5** treated in the same conditions.



Scheme 5.

The steric hindrance around one silicon is a critical point since the reaction is no longer selective with the reagent **8**. In this case, the expected bis(acylsilane) **11** and decanoyltrimethylsilane **12**[13] are obtained in similar yields, owing to a too weak difference in the bulk around the silicon atoms (Scheme 6).



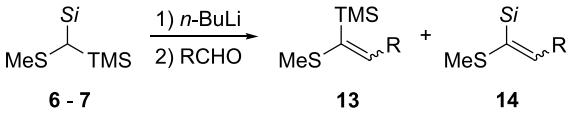
Scheme 6.

Except the bis(TMS) reagent **3**, which proved to be useful for acyl(trimethyl)silane synthesis,[3] the oxygenated reagents **4**, **5** and **8** are definitely not convenient owing to the low yields at the successive stages of the synthesis (Schemes 5 and 6). Hence we turned our attention to the methylsulfanyl analogues (Scheme 7, Table 2). Reagent **6**, which had never been considered in Peterson reaction, reacts effectively with benzaldehyde to give a high yield of the thioenol ether **13a**, as a 58/42 *E*/*Z* diastereomers mixture (NOE determination). The reaction was applied to a series

Table 2. Peterson reactions of reagents **6** and **7**

Si	R	Conversion (%)	Product (%)	**13/14**	Diast. ratio[a] (%)
TMS	Ph	100	**13a** (91)	—	58/42
TMS	Bn	64	**13b** (38)	—	67/33
TMS	$BnCH_2$	86	**13c** (52)	—	79/21
TMS	n-C_8H_{17}	100	**13d** (65)	—	52/48
TMS	Et_2CH	90	**13e** (67)	—	51/49
TMS	$EtCH{=}CH(CH_2)_4$	90	**13f** (68)	—	57/43
TBDMS	Ph	100	**13a**+**14g** (94)[b]	28/72[b]	[b]
TBDMS	n-C_8H_{17}	100	**13d**+**14h** (93)[b]	30/70[b]	[b]

[a] The nature of the diastereomers was determined only for **13a** (see text).
[b] Crude product; ratio **13/14** determined by ^1H NMR and GC; diaster. ratio undetermined.



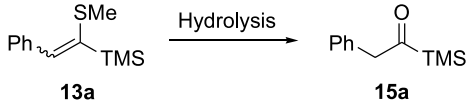
6 - 7 13 14

Scheme 7.

of aldehydes to give reasonable yields of the corresponding thioenol ethers **13b–13f**, sometimes accompanied by a minor amount of unreacted starting materials (Table 2). Owing to the loss of stereochemical information in the subsequent hydrolysis step, the nature of the stereomers was not further determined. In contrast to the methoxy derivative **4**, reaction in the same conditions of the *tert*-butyl substituted reagent **7** with aldehyde gives a mixture of the two thioenol ethers **13a**+**14g** or **13d**+**14h**. As expected, the major product results from elimination of the TMS group, but the selectivity is too weak to consider any application to bis(acylsilane) synthesis.

2.3. Conversion of thioenol ethers to acylsilanes

The starting purpose of this study was to find a route to acylsilane which does not need the strong oxidative conditions required for the removal of the dithioacetal functionality. We have thus studied the conditions of the final hydrolysis step. Hydrolysis of thioenol ether is not a trivial reaction, since either additives ($TiCl_4$, $CuSO_4$, HgO)[14] or very strong acids[15] are often necessary, even if some more classical conditions have been mentioned.[16] We have tried various conditions, among which only the one reported in Scheme 8 for **13a** as model compound gave satisfactory results. This C-silyl thioenol ether **13a** is cleanly but very slowly hydrolyzed using trifluoroacetic acid in a biphasic medium, or aqueous HCl in THF or acetone. Owing to the long reaction time, by-products resulting from cleavage of THF are formed and can make the purification process more complex. Hence refluxing aqueous HCl–acetone mixture was chosen as standard procedure and applied to compounds **13a–13f**, giving in fair yields the acylsilanes **15a–15f** (Table 3). It is noteworthy that these conditions are compatible with unsaturated compounds since **15f** is obtained in good yield, without isomerization.



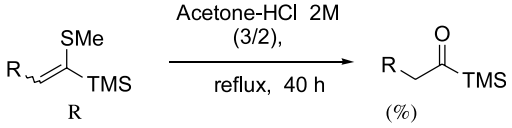
13a 15a

Conditions	% Yield
THF-HCl 3M (3/2), reflux, 40h	74[a]
Acetone-HCl 2M (3/2), reflux, 40h	75
Dichloroethane-H_2O (8/2) TFA (10 eq.), reflux, 40h	75

[a] By-product: $O[(CH_2)_4Cl)]_2$

Scheme 8.

Table 3. Hydrolysis of C-silyl thioenol ethers **13**



(%)

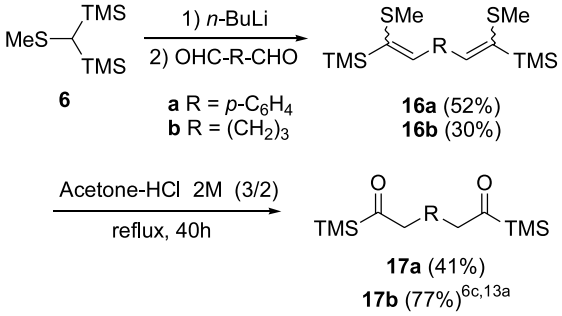
R	(%)
Ph	**15a** (75)[17]
Bn	**15b**[a] (74)[13c,17a]
$BnCH_2$	**15c** (60)[18]
n-C_8H_{17}	**15d** (54)[13]
Et_2CH	**15e** (67)
$EtCH{=}CH(CH_2)_4$	**15f** (76)

[a] Conv.=85% (total conv. for all other compounds).

The reaction sequence was finally applied to dialdehydes to prepare the bis(acylsilanes) **17** (Scheme 9). However, the overall transformation is less effective than previously reported synthesis.[6c]

3. Conclusion

A Peterson approach has been studied for the synthesis of acylsilanes via C-silyl enol–ether or thioenol ether. A good



6

a R = p-C_6H_4
b R = $(CH_2)_3$

16a (52%)
16b (30%)

17a (41%)
17b (77%)[6c,13a]

Scheme 9.

selectivity was observed with enol ethers bearing a TMS and a TBDMS group, which decreases significantly for less differentiated silyl groups, making this strategy unsuitable for the synthesis of bis(acylsilanes) with internal silicon. However, there is no practical interest to use such reagents owing to the difficulty to reach correct yields. In contrast, bis(trimethylsilyl)methylsulfanylmethane **6** proved to be a good reagent for the preparation of C-silyl thioenol ether **13**, which are converted to acylsilanes **15** by classical acid hydrolysis. The procedure is convenient, even if some yields should be optimized to make it more attractive.

4. Experimental

4.1. Materials and general methods

Melting points are uncorrected. FT-IR spectra were recorded on a MIDAC Corporation Spectrafile IR apparatus. ^{1}H, and ^{13}C spectra were recorded on a Bruker AC-250 or AC-500 spectrometer with $CDCl_3$ as the solvent. Tetramethylsilane ($\delta=0.00$ ppm) or $CHCl_3$ ($\delta=7.27$ ppm) were used as internal standards for ^{1}H, $CDCl_3$ ($\delta=77.23$ ppm) for ^{13}C NMR spectra. The abbreviations q and qu are used to design quartet and quintet, respectively, in the description of ^{1}H NMR spectra. GCMS spectra were obtained on Trace MS Thermoquest apparatus (70 eV) in electron impact mode. Elemental analyses were performed with a Perkin–Elmer CHN 2400 apparatus. High Resolution Mass Spectra (HRMS) were performed on Q-TOF Micromass in positive ESI mode (CV=30 V). Reactions were monitored by TLC (Merck F 254 silica gel). All anhydrous reactions were carried out under dry argon. THF was dried and distilled from sodium/benzophenone. Starting material **1**, **2** and aldehydes were distilled before use. TMSCl and TIPSCl were distilled on triphenylamine. Products were separated by chromatography on silica gel using a mixture of petroleum ether and ethyl acetate.

4.2. Preparation of compounds (4, 5 and 7) (Scheme 3, Table 1)

The methoxy derivatives **4** and **5** have been prepared by applying the metallation–silylation sequence[3] to methoxymethyl(trimethyl)silane **1**. The methylsulfanyl derivative **7** has been prepared according to the procedure reported by Seebach's group.[11]

4.2.1. Methoxy(*tert*-butyldimethylsilyl) trimethylsilyl methane (4). Yield: 28%; oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ −0.04 (s, 3H, Si*Me*$_2^t$Bu), 0.06 (s, 3H, Si*Me*$_2^t$Bu), 0.10 (s, 9H, $SiMe_3$), 0.94 (s, 9H, C(*CH*$_3$)$_3$), 2.75 (s, 1H, CH), 3.33 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ −6.6 (Si*Me*$_2^t$Bu), −4.9 (Si*Me*$_2^t$Bu), −0.7 ($SiMe_3$), 17.4 (*C*(CH$_3$)$_3$), 27.1 (C(*CH*$_3$)$_3$), 62.5 (OCH_3), 68.8 (CH); IR (film) 2955, 2929, 2857, 1471, 1249, 1087 cm^{-1}; GCMS (EI) *m/e* 232 (M^+), 73 (100).

4.2.2. Methoxy(triisopropylsilyl) trimethylsilyl methane (5). Yield: 56%; oil; ^{1}H NMR ($CDCl_3$, 250 MHz) d 0.15 (s, 9H, Si(CH$_3$)$_3$), 1.0–1.1 (m, 3H, 3×*CH*(CH$_3$)$_2$), 1.12 (d, $^{3}J=6.0$ Hz, 18H, 3×CH(*CH*$_3$)$_2$), 2.97 (s, 1H, CH), 3.34 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) d 0.0 (Si(CH$_3$)$_3$), 11.8 (*C*H(CH$_3$)$_2$), 19.2 (CH(*C*H$_3$)$_2$), 19.3 (CH(*C*H$_3$)$_2$), 62.9 (OCH_3), 68.3 (CH); IR (film) 2946, 2867, 2810, 1464, 1248, 1085, 845 cm^{-1}; GCMS (EI) *m/e* 274 (M^+), 115 (100).

4.2.3. Methylthio(*tert*-butyldimethylsilyl) trimethylsilyl methane (7). Yield: 62%; oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 3H, Si*Me*$_2^t$Bu), 0.07 (s, 3H, Si*Me*$_2$ ^{t}Bu), 0.14 (s, 9H, $SiMe_3$), 0.97 (s, 9H, C(CH$_3$)$_3$), 1.56 (s, 1H, CH), 2.12 (s, 3H, SCH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −5.2 (Si*Me*$_2^t$Bu), −2.8 (Si*Me*$_2^t$Bu), −0.1 ($SiMe_3$), 16.2 (CH or SCH_3), 18.2 (*C*(CH$_3$)$_3$), 21.0 (SCH_3 or CH), 27.4 (C(*CH*$_3$)$_3$); IR (film) 2955, 2928, 2856, 1470, 1250 cm^{-1}; GCMS (EI) *m/e* (%) 248 (M^+), 191 (100), 105, 75, 59.

4.3. Preparation of compound (8) (Scheme 4)

To a solution of (methoxymethyl)trimethylsilane **1** (1.37 g, 11.6 mmol) in dry THF (25 mL) cooled at −78 °C and under argon atmosphere, was added a 0.9 M ether solution of *s*-BuLi (13.5 mL, 12.2 mmol). The mixture was allowed to reach −25 °C then was stirred at this temperature for 40 min. After cooling at −78 °C, 1,2-bis(chlorodimethylsilyl)ethane (1.1 g, 5.3 mmol) was added. The cooling bath was removed and the resulting mixture was stirred for 2 h at room temperature. The crude was hydrolysed with brine (20 mL) then the aqueous phase was extracted with ether (3×25 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel using petroleum ether–EtOAc (98/2) to give the compound **8** (0.26 g, 13%).

4.3.1. Compound 8. Oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 6H, 2×SiCH$_3$), 0.05 (s, 6H, 2×SiCH$_3$), 0.07 (s, 18H, 2×SiMe$_3$), 0.51 (m, 4H, CH_2CH_2), 2.56 (s, 2H, 2×CH), 3.33 (s, 6H, 2×OCH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −4.0 (SiCH$_3$), −3.7 (SiCH$_3$), −1.3 ($SiMe_3$), 7.2 (CH_2), 63.1 (OCH_3), 70.3 (CH); IR (film) 2958, 2902, 1250, 1053, 839 cm^{-1}; GCMS (EI) *m/e* 379 (M^++1, 2), 73 (100).

4.4. Preparation of acylsilanes (10a,b) (Scheme 5)

The procedure described by J.-I. Yoshida and co-workers[3] was used to prepare acylsilanes **10a**,**b** starting from compounds **4** and **5**.

4.4.1. Decanoyl(*tert*-butyldimethyl)silane (10b). Yield: 42%; oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.18 (s, 6H, $SiMe_2$), 0.88 (t, $^{3}J=6.7$ Hz, 3H, CH_3), 0.93 (s, 9H, C(CH$_3$)$_3$), 1.2–1.5 (m, 12H, 6×CH_2), 1.50 (qu, $^{3}J=7.3$ Hz, 2H, *CH*$_2$CH$_2$CO), 2.59 (t, $^{3}J=7.3$ Hz, 2H, CH_2CO); Selected ^{13}C NMR data ($CDCl_3$, 62.9 MHz) δ −7.1 ($SiMe_2$), 14.0 (CH_3), 16.4 (*C*(CH$_3$)$_3$), 21.8 (CH_2), 22.6 (CH_2), 26.3 (C(*CH*$_3$)$_3$), 31.8 (CH_2), 50.2 (*C*H$_2$CO), 247.6 (CO); IR (film) 2930, 2860, 1630, 1460, 1250, 835 cm^{-1}; GCMS (EI) *m/e* 271 (M^++1, 1), 115 (100).

4.5. Preparation of bis(acylsilane) (11) (Scheme 6)

To a solution of compound **8** (0.19 g, 0.5 mmol) in THF (7 mL) was added *n*-butyllithium 2.5 M in hexane (0.4 mL, 1.0 mmol) at −78 °C. The mixture was warmed up to 0 °C and stirred at this temperature for 30 min. The solution was then recooled to −78 °C and nonylaldehyde (0.17 mL,

1.0 mmol) was added. The mixture was stirred at this temperature for 1 h and warmed up to room temperature for 2 h. Brine (10 mL) was added and the organic materials were extracted with ether (3×10 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure then the residue was dissolved in THF (7 mL). Hydrochloric acid (1 M, 1 mL) was added, and the mixture was stirred at room temperature overnight. The mixture was partitioned between saturated aqueous Na_2CO_3 and ether (10 mL). The organic layer was separated and the aqueous phase was extracted twice with ether (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether–EtOAc (98/2)) to give the bis(acylsilane) **11** (45 mg, 20%) and the acylsilane **12**[13] (26 mg, 23%).

4.5.1. 1,2-Bis[2′-(decanoyldimethylsilyl)]ethane (11). Oil; ^{1}H NMR ($CDCl_3$, 250 MHz,) δ 0.19 (s, 12H, 2×$SiMe_2$), 0.58 (s, 4H, 2×$SiCH_2$), 0.88 (t, ^3J=6.5 Hz, 6H, 2×CH_3), 1.2–1.3 (m, 24H, 12×CH_2), 1.4–1.5 (m, 4H, 2×CH_2CH_2-CO), 2.57 (t, ^3J=7.1 Hz, 4H, 2×CH_2CO); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ −5.3 ($SiMe_2$), 5.6 ($SiCH_2$), 14.1 (CH_3), 22.0 (CH_2), 22.6 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.8 (CH_2), 49.2 (CH_2CO), 248.2 (CO); IR (film) 2925, 1643, 1249, 837 cm^{-1}; GCMS (EI) *m/e* 454 (M^+), 387, 314, 189 (100).

4.6. General procedure for the Peterson olefination: preparation of compounds 13 and 14 (Scheme 7, Table 2)

To a solution of the (methylsulfanyl)bis(trialkylsilyl)-methane **6** or **7** (2.5 mmol) in 25 mL of THF was added *n*-butyllithium 2.5 M in hexane (1 mL, 2.5 mmol, 1.0 equiv) at −78 °C. The mixture was warmed up to 0 °C and stirred at this temperature for 1 h. The light yellow solution was cooled to −78 °C and the aldehyde (2.5 mmol, 1.0 equiv) was added. The mixture was stirred at this temperature for 1 h and warmed up to room temperature for 2 h. Brine (20 mL) was added and the organic materials were extracted with ether (3×10 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure, and the residue was purified by flash silica gel chromatography using petroleum ether (PE) to give the corresponding thioenol ether **13** and **14** (Scheme 7, Tables 2 and 4).

4.6.1. Selected data for compound 14g. First stereomer: ^{1}H NMR ($CDCl_3$) δ 0.340 (s, 3H, $SiMe^t_2Bu$), 0.344 (s, 3H, $SiMe^t_2Bu$), 1.10 (s, 9H, $SiMe^t_2Bu$), 2.13 (d, ^5J=0.8 Hz, 3H, SMe), 7.08 (br s, 1H, =CH), 7.3–7.7 (m, 5H, Ph); GCMS (EI) *m/e* (%) 264 (M^+), 207, 105 (100), 73. Second stereomer: ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 6H, $SiMe^t_2Bu$), 1.05 (s, 9H, $SiMe^t_2Bu$), 2.47 (s, 3H, SMe), 7.03 (s, 1H, =CH), 7.2–7.8 (m, 5H, Ph); GCMS (EI) *m/e* (%) 264 (M^+), 207, 105 (100), 73.

4.6.2. Selected data for compound 14h. First stereomer: selected ^{1}H NMR ($CDCl_3$) δ 6.26 (t, ^3J=7.6 Hz, 1H, =CH); GCMS (EI) *m/e* (%) 300 (M^+), 243, 195, 105 (100), 73. Second stereomer: selected ^{1}H NMR ($CDCl_3$) δ 5.74 (t, ^3J=7.6 Hz, 1H, =CH); GCMS (EI) *m/e* (%) 300 (M^+), 243, 195, 105 (100), 73.

4.7. Preparation of acylsilanes 15

4.7.1. Hydrolysis with THF–hydrochloric acid 3 M (3/2) (Scheme 8). The compound **15a** was obtained in 74% yield using the same procedure described for the preparation of bis(acylsilane) **11** except that 3 M hydrochloric acid was employed.

4.7.2. Hydrolysis with dichloroethane–H_2O (8/2), trifluoroacetic acid (10 equiv) (Scheme 8). To a solution of thioenol ether **13a** (0.11 g, 0.5 mmol) in a mixture of 1,2-dichloroethane–H_2O (8/2) was added trifluoroacetic acid (0.39 mL, 5 mmol). The mixture was heated under reflux and the reaction was followed by TLC until the disappearance of the starting compound (40 h). Then the reaction mixture was neutralized using saturated aqueous solution of $NaHCO_3$ (3 mL). The organic materials were extracted with ethyl acetate (3×5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash silica gel chromatography using PE–EtOAc (97/3) as eluent to give the acylsilane **15a** (72 mg, 75%).

4.7.3. Hydrolysis with acetone–hydrochloric acid 2 M 3:2 (Schemes 8 and 9, Table 3). To a solution of thioenol ether **13** (0.5 mmol, 1.0 equiv) in acetone (3 mL) was added a solution of 2 M hydrochloric acid (2 mL). The mixture was heated under reflux and the reaction was followed by TLC until the disappearance of the starting compound (40 h). Then the reaction mixture was neutralized using saturated aqueous solution of $NaHCO_3$ (3 mL). The organic materials were extracted with ethyl acetate (3×5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash silica gel chromatography using a mixture of petroleum ether/EtOAc as eluent to give the acylsilanes **15** (Schemes 8 and 9, Table 3).

4.7.4. Compound 15e. Yield: 67%; oil; ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9H, $SiMe_3$), 0.82 (t, ^3J=7.3 Hz, 6H, 2×CH_3), 1.1–1.3 (m, 4H, 2×CH_2), 1.89 (m, 1H, CH), 2.51 (d, ^3J=6.6 Hz, 2H, CH_2CO); ^{13}C NMR ($CDCl_3$) δ −3.1 ($SiMe_3$), 11.0 (2×CH_3), 26.1 (2×CH_2), 34.9 (CH), 52.8 (CH_2CO), 249.3 (C=O); IR (film) 2962, 2930, 2876, 1642, 1250 cm^{-1}; GCMS (EI) *m/e* (%) 186 (M^+), 171, 101, 75, 73 (100). Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.25; H, 11.55.

4.7.5. Compound 15f. Yield: 76%; oil; ^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9H, $SiMe_3$), 0.93 (t, ^3J=7.5 Hz, 3H, CH_3CH_2), 1.2–1.4 (m, 4H, $CH_2CH_2CH_2CH$), 1.50 (tt, ^3J=^3J=7.3 Hz, 2H, CH_2CH_2CO), 1.9–2.0 (m, 4H, 2×CH_2CH=), 2.57 (t, ^3J=7.3 Hz, 2H, CH_2CO), 5.3–5.4 (m, 2H, 2×CH=); ^{13}C NMR ($CDCl_3$) δ −3.2 ($SiMe_3$), 14.3 (CH_3), 20.5 (CH_2CH=), 22.0 (CH_2CH_2CO), 26.9 (CH_2CH=), 28.9 ($CH_2CH_2CH_2$-CO), 29.5 (CH_2CH_2CH=), 48.4 (CH_2CO), 129.0 (CH=), 131.7 (CH=), 248.6 (C=O); IR (film) 2961, 2933, 1644, 1462, 1249 cm^{-1}; GCMS (EI) *m/e* (%) 226 (M^+), 197, 183, 101, 75, 73 (100); HRMS (ESI) calcd for $C_{13}H_{26}ONaSi$ *m/e*=249.1651; found 249.1650.

Table 4. Spectral data of compounds **13a–13f**

Compound	IR (cm^{-1})[a]	GC–MS[a] *m/z*	^1H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ, *J* (Hz)
13a[b]	2955, 1601, 1489, 1248	222 (M^+), 207, 134, 105, 73 (100)	0.05 (s, 9H, $SiMe_3$), 2.35 (d, ^5J=0.6 Hz, 3H, SMe), 6.81 (br s, 1H, =CH), 7.2–7.6 (m, 5H, Ph)	0.1 ($SiMe_3$), 15.0 (SMe), 126.6 (CH), 127.8 (2×CH), 128.5 (2×CH), 132.1 (CH), 137.6 (C_q), 140.1 (C_q)
13a[c]			0.28 (s, 9H, $SiMe_3$), 2.19 (s, 3H, SMe), 6.93 (s, 1H, =CH), 7.2–7.6 (m, 5H, Ph)	−0.5 ($SiMe_3$), 17.8 (SMe), 127.2 (CH), 127.9 (2×CH), 129.3 (2×CH), 138.7 (CH), 139.7 (C_q), 140.4 (C_q)
13b[b]	2955, 1602, 1581, 1494, 1248	236 (M^+), 221, 115, 105, 73 (100)	0.30 (s, 9H, $SiMe_3$), 2.36 (s, 3H, SMe), 3.86 (d, ^3J=6.7 Hz, 2H, CH_2), 6.41 (t, ^3J=6.7 Hz, 1H, =CH), 7.3–7.5 (m, 5H, Ph)	−0.7 ($SiMe_3$), 18.0 (SMe), 36.7 (CH_2), 126.0 (CH), 128.46 (2×CH), 128.53 (2×CH), 138.0 (C_q), 140.3 (C_q), 144.6 (CH)
13b[c]			0.41 (s, 9H, $SiMe_3$), 2.29 (s, 3H, SMe), 3.70 (d, ^3J=7.6 Hz, 2H, CH_2), 5.83 (t, ^3J=7.6 Hz, 1H, =CH), 7.3–7.5 (m, 5H, Ph)	0.0 ($SiMe_3$), 14.6 (SMe), 38.2 (CH_2), 126.1 (CH), 128.3 (2×CH), 130.9 (CH), 135.7 (C_q), 140.8 (C_q)[d]
13c[b]	3027, 2955, 1587, 1496, 1453, 1248	250 (M^+), 159 (100), 111, 105, 73	0.16 (s, 9H, $SiMe_3$), 2.15 (s, 3H, SMe), 2.6–2.8 (m, 4H, 2×CH_2), 6.18 (t, ^3J=6.0 Hz, 1H, =CH), 7.2–7.3 (m, 5H, Ph)	−0.8 ($SiMe_3$), 17.9 (SMe), 32.2 (CH_2), 35.1 (CH_2), 125.76 (CH), 128.2 (2×CH), 128.4 (2×CH), 137.7 (C_q), 141.6 (C_q) 145.6 (CH)
13c[c]			0.22 (s, 9H, $SiMe_3$), 2.19 (d, ^5J=2.0 Hz, 3H, SMe), 2.6–2.8 (m, 4H, 2×CH_2), 5.66 (t, ^3J=7.3 Hz, 1H, =CH), 7.2–7.3 (m, 5H, Ph)	−0.2 ($SiMe_3$), 14.5 (SMe), 34.4 (CH_2), 36.6 (CH_2), 125.84 (CH), 128.3 (2×CH), 132.2 (CH), 134.4 (C_q), 141.5 (C_q)[d]
13d[b]	2924, 1587, 1465, 1248	258 (M^+), 243, 159, 105, 73 (100)	0.23 (s, 9H, $SiMe_3$), 0.89 (t, ^3J=6.6 Hz, 3H, =CH_3), 1.1–1.5 (m, 14H), 2.19 (s, 3H, SMe), 6.15 (t, ^3J=6.7 Hz, 1H, =CH)	−0.1 ($SiMe_3$), 14.1 (CH_3), 18.1 (CH_3), 22.7 (CH_2), 28.8–29.6 (4×CH_2), 30.5 (CH_2), 31.9 (CH_2), 136.6 (C_q), 147.3 (CH)
13d[c]			0.17 (s, 9H, $SiMe_3$), 0.89 (t, ^3J=6.2 Hz, 3H, CH_3), 1.1–1.5 (m, 14H), 2.20 (s, 3H, SMe), 5.64 (t, ^3J=7.4 Hz, 1H, =CH)	−0.8 ($SiMe_3$), 14.7 (CH_3), 20.3 (CH_3), 30.4 (CH_2), 32.5 (CH_2), 133.2 (C_q), 134.1 (CH)[d]
13e[b]	2960, 1548, 1460, 1248	216 (M^+), 187, 105, 73 (100)	0.19 (s, 9H, $SiMe_3$), 0.87 (t, ^3J=7.3 Hz, 6H, 2×CH_3), 1.1–1.3 (m, 4H, 2×CH_2), 2.21 (s, 3H, SMe), 2.7–2.9 (m, 1H), 5.88 (d, ^3J=9.3 Hz, 1H, =CH)	0.40 ($SiMe_3$), 11.8 (2×CH_3), 15.2 (SMe), 27.5 (2×CH_2), 44.6 (CH), 136.7 (C_q), 152.6 (CH)
13e[c]			0.25 (s, 9H, $SiMe_3$), 0.85 (t, ^3J=7.3 Hz, 6H, 2×CH_3), 1.4–1.6 (m, 4H, 2×CH_2), 2.19 (s, 3H, SMe), 2.7–2.9 (m, 1H); 5.43 (d, ^3J=10.6 Hz, 1H, =CH)	−0.44 ($SiMe_3$), 11.6 (2×CH_3), 18.4 (SMe), 28.1 (2×CH_2), 42.9 (CH), 140.3 (CH)[d]
13f[b]	2961, 1587, 1460, 1248	256 (M^+), 241, 105, 73 (100)	0.16 (s, 9H, $SiMe_3$), 0.95 (t, ^3J=7.5 Hz, 3H, CH_3), 1.4–1.6 (m, 4H, 2×CH_2), 2.0–2.1 (m, 4H, 2×CH_2), 2.22 (s, 3H, SMe), 2.37 (q, ^3J=6.9 Hz, 2H, CH_2), 5.3–5.4 (m, 2H, 2×=CH), 6.14 (t, ^3J=6.9 Hz, 1H, =CH)	−0.8 ($SiMe_3$), 14.4 (CH_3), 18.1 (CH_3), 20.5 (CH_2), 26.9 (CH_2), 28.6 (CH_2), 29.5 (CH_2), 30.3 (CH_2), 129.0 (CH), 131.72 (CH), 136.8 (C_q), 147.1 (CH)
13f[c]			0.23 (s, 9H, $SiMe_3$), 0.95 (t, ^3J=7.5 Hz, 3H, CH_3), 1.4–1.6 (m, 4H, 2×CH_2), 2.0–2.1 (m, 4H, 2×CH_2), 2.1–2.3 (m, 2H, CH_2), 2.22 (s, 3H, SMe), 5.3–5.4 (m, 2H, 2×=CH), 5.60 (t, ^3J=7.7 Hz, 1H, =CH)	−0.1 ($SiMe_3$), 14.7 (CH_3), 18.1 (CH_3), 20.5 (CH_2), 27.0 (CH_2), 29.4 (CH_2), 29.9 (CH_2), 32.4 (CH_2), 128.9 (CH), 131.75 (CH), 133.9 (CH), 143.1 (C_q)

[a] IR and GC–MS spectra on the mixture of stereomers.
[b] Major isomer.
[c] Minor isomer.
[d] Selected data.

4.8. Preparation of compounds (16a,b) and bis(acylsilanes) (17a,b) (Scheme 9)

The compounds **16a**,**b** were obtained in 52 and 30% yields respectively using the general procedure for the Peterson olefination (Scheme 7) except that 2 equiv of **6**, 2 equiv of *n*-BuLi and 1 equiv of bis(aldehyde) were used. The compounds **17a**,**b** were obtained in 41 and 77% yields respectively using the hydrolysis with acetone–hydrochloric acid 2 M (3:2) (Schemes 8 and 9).

4.8.1. Compound 16a. Yield: 52%; Mixture of 3 stereomers (54/21/25, determined by GC); oil; ^1H NMR ($CDCl_3$) δ 0.10 (s, $SiMe_3$), 0.29 (s, $SiMe_3$), 2.23 (s, SMe), 2.36 (s, SMe), 6.79 (s, =CH), 6.91 (s, =CH), 7.13 (s, Ar sym.), 7.19 (d, ^3J=8.0 Hz, Ar unsym.), 7.61 (d, ^3J=8.0 Hz, Ar unsym.), 7.66 (s, Ar sym.); ^{13}C NMR ($CDCl_3$) δ −0.52 ($SiMe_3$), −0.47 ($SiMe_3$), 0.28 ($SiMe_3$), 0.34 ($SiMe_3$), 15.2 (2× SMe), 17.8 (SMe), 17.9 (SMe), 128.1 (CH Ar), 128.2 (CH Ar), 129.0 (CH Ar), 129.1 (CH Ar), 131.97 (=CH), 132.04 (=CH), 136.0 (C_q), 136.5 (C_q), 138.3 (=CH), 138.4 (=CH), 139.0 (C_q), 139.5 (C_q), 140.3 (C_q), 140.8 (C_q); IR (film) 2953, 2908, 1553, 1494, 1247 cm^{-1}; GCMS (EI) *m/e* (%) 366 (M^+), 215, 207, 105, 73 (100).

4.8.2. Compound 16b. Yield: 30%; Mixture of 3 stereomers (49/20/31 determined by GC); oil; ^1H NMR ($CDCl_3$) δ 0.17 (s, $SiMe_3$), 0.23 (s, $SiMe_3$), 1.4–1.6 (m, $CH_2CH_2CH_2$), 2.19 (s, SMe), 2.24 (q, ^3J=7.4 Hz, =CHCH_2), 2.41 (q, ^3J=7.4 Hz, =CHCH_2), 5.61 (t, ^3J=7.2 Hz, =CH), 5.64 (t, ^3J=7.2 Hz, =CH), 6.14 (t, ^3J=6.4 Hz, =CH), 6.17 (t, ^3J=6.4 Hz, =CH); Selected ^{13}C NMR data ($CDCl_3$) δ −0.7 ($SiMe_3$), −0.0 ($SiMe_3$), 14.6 (SMe), 14.7 (SMe), 18.0 (SMe), 18.1 (SMe), 28.4 (CH_2), 29.6 (CH_2), 30.0 (CH_2), 30.2 (CH_2), 32.1 (CH_2), 32.2 (CH_2), 133.1 (=CH), 133.3 (=CH), 137.3 (C_q), 146.2 (=CH), 146.5 (=CH); IR (film) 2955, 1640, 1587, 1438, 1248 cm^{-1}; GCMS (EI) *m/e* (%) 332 (M^+), 317, 197, 181, 105, 73 (100).

4.8.3. Compound 17a. Yield: 41%; oil; ^1H NMR ($CDCl_3$) δ 0.10 (s, 18H, 2×$SiMe_3$), 3.82 (s, 4H, 2×CH_2), 7.07 (s, 4H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ −2.8 ($SiMe_3$), 55.1 (CH_2),

130.1 (CH Ar), 131.6 (C_q Ar), 244.1 (C=O); IR (film) 3026, 2957, 1638, 1510, 1421, 1249 cm^{-1}, GCMS (EI) *m/e* (%) 306 (M^+), 278, 205, 175, 147, 75, 73 (100); HRMS (ESI) calcd for $C_{16}H_{26}NaO_2Si_2$ *m/e*=329.1369; found 329.1356.

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A concise benzotriazolyl-mediated synthesis of 9-methoxycepharanone A

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Abstract—A concise synthesis of 9-methoxycepharanone A is described. The key step is the benzotriazolyl-assisted assemblage of an arylmethyleneisoindolinone ring system comprising the enol ether unit. Radical cyclization followed by deprotections and ultimate formation of the methylenedioxy group complete the total synthesis of the title compound.

1. Introduction

Aristolactams **1** are a minor group of alkaloids biogenetically derived from isoquinolines and structurally related to aporphines.[1] The richest source of this family of alkaloids which are characterized by a tetracyclic skeleton with a phenanthrene core is undoubtedly plants of the family *Aristolochiaceae*.[2] The leaves and roots of *Aristolochia* species have been used since antiquity in obstetrics and still find some applications in folk medicine in Taiwan and Southern China.[3] They are also considered to be the principal detoxification metabolites of aristolochic acids which have been implicated in an endemic renalyse known as CHN (Chinese Herbs Nephropathy).[4] Several alternative routes have been developed for the elaboration of these highly fused phenanthrene lactams. The main general synthetic approaches involve (i) the contraction of the lactone ring of dibenzochromanone derivatives[5] (route a), (ii) the photoinduced electrocyclic ring closure of iodostilbenic precursors[6] (route b), (iii) the inter[7] and intra[8] benzyne cycloaddition of (di)enamides (routes c and d) and (iv) the tributyltin-mediated radical cyclization of bromoarylmethyleneisoindolinones[9] (route e) (retrosynthetic Scheme 1).[10]

However, most of these methods are inadequate for the synthesis of models with diverse and dense functionalities on their compact framework particularly with alkoxy and/or hydroxy phenolic functions in specific positions on the basic phenanthrene nucleus. In particular, a certain number of methoxylated models **1** ($R^1 = OCH_3$) which can be regarded in one sense as having an enol ether moiety embedded in a phenanthrene unit still remain inaccessible by these conceptually different synthetic tactics. This is notably the case of 9-methoxycepharanone A (**1a**) (Fig. 1) which has been extracted from the roots of *Aristolochia auricularia* and which has been found to contain the highest reported amount of total aristolochic acids of any species.[11] We wish therefore to delineate in this paper a tactically new synthetic approach to these methoxylated aristolactams illustrated by the first total synthesis of 9-methoxycepharanone A (**1a**) isolated from *Annonaceae* species.

2. Results and discussion

We initially envisaged taking advantage of the transient formation of adducts equipped with a metalated hydroxybenzyl appendage from the two complementary procedures developed in our group for the building up of the arylmethylene isoindolinones **3**[9] (retrosynthetic Scheme 1).

These conceptually different procedures hinge upon a Horner olefination process involving a phosphorylated isoindolinone **4** (path a)[9a] and/or a hydroxylalkylation/E_1cb *anti* elimination sequence applied to an isoindolinone precursor **5** (path b).[9b] For this purpose the unsubstituted models **4a**[12] or **5a**[13] were initially synthesized by earlier techniques developed in our laboratory (Scheme 2). They were subsequently exposed to potassium bis(trimethylsilyl)-amide (KHMDS, 1 equiv, THF, −78 °C) and the corresponding metallated isoindolinones were then allowed to

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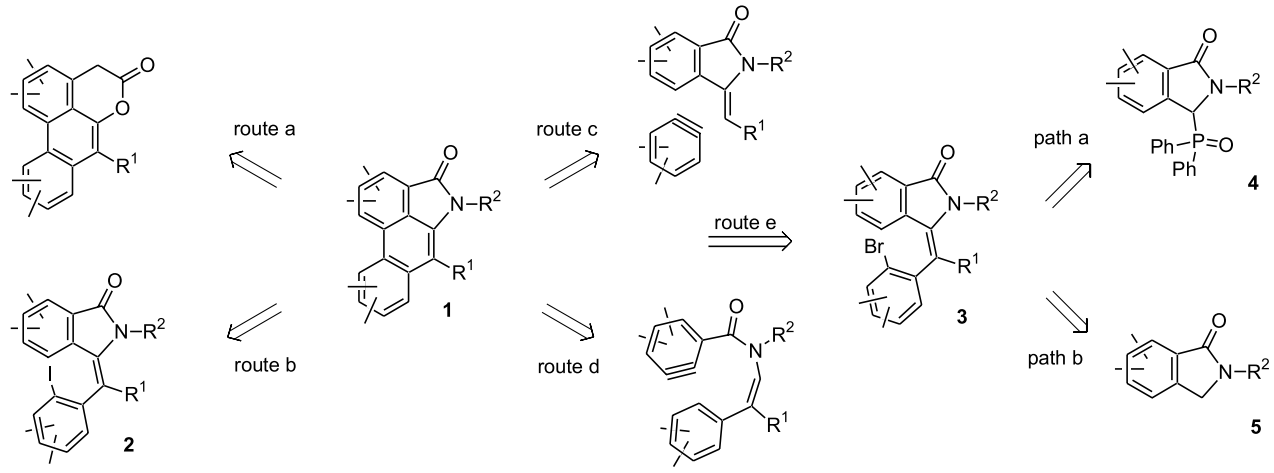


Scheme 1.

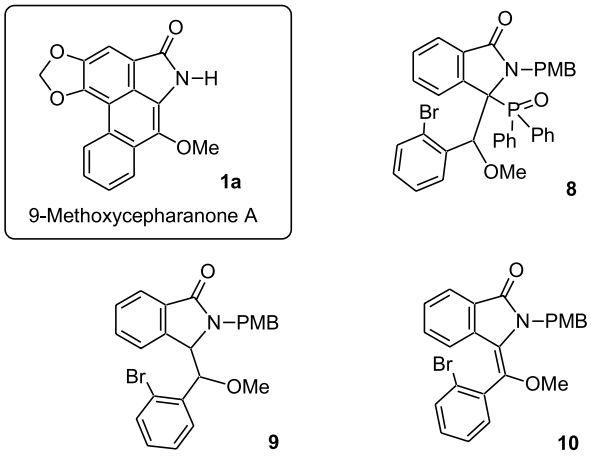
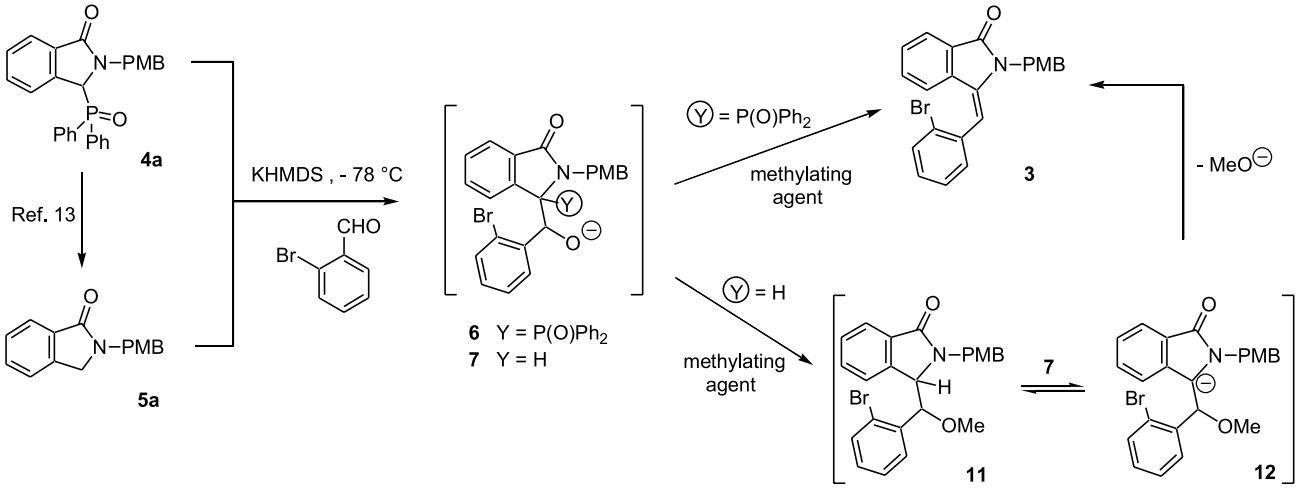


Figure 1.

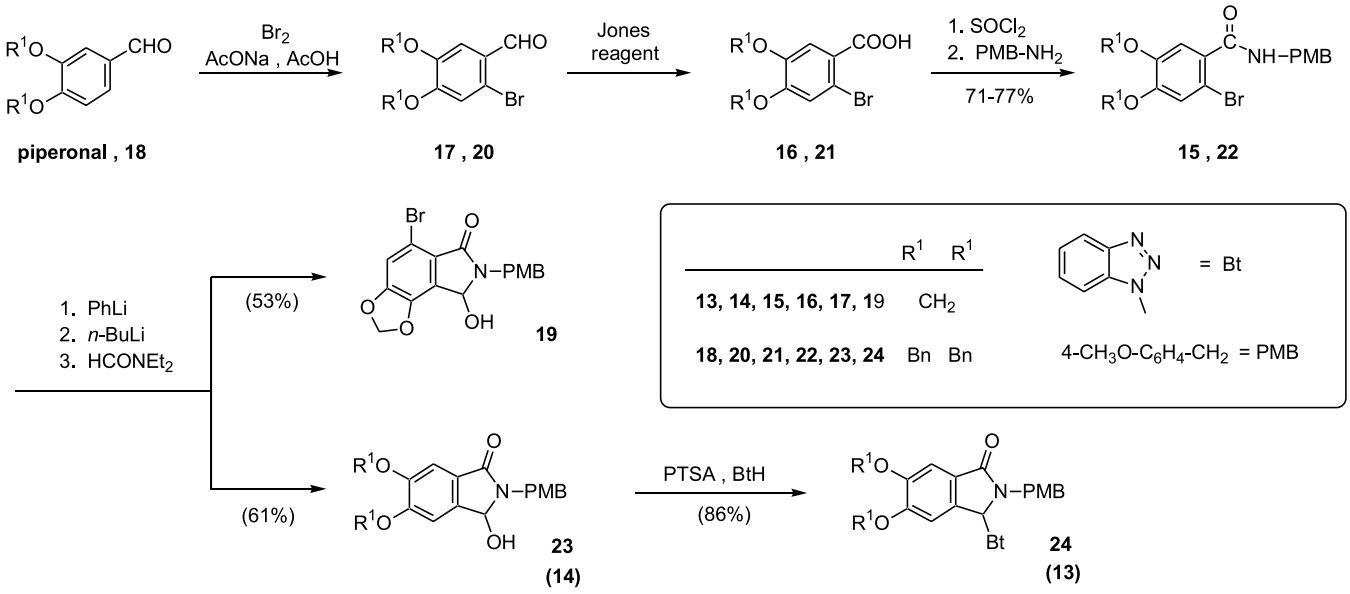
react with *ortho*-bromobenzaldehyde to provide the transient adducts **6** and **7** (Scheme 2). At this stage all attempts to methylate in situ the oxanions **6** or **7** met with no success even by varying the reaction conditions, namely by employing different bases (LHMDS, NaHMDS) or varied methylating agents (MeI, MeOTf). In both cases the elimination product **3** was invariably obtained and no trace of the expected products **8** or **9** respectively, good candidates for the elaboration of the stilbenic enol ether **10**, could be detected (Fig. 1).

One can reasonably assume that for the reaction carried out with the phosphorylated parent compound **4**, Horner olefination occurs prior to in situ *O*-alkylation. The exclusive formation of **3** upon *O*-methylation of adduct **7** still remains open to discussion. One can tentatively assume that *trans* metallation between oxanion **7** and adduct **11** occurs followed by E1cb elimination leading to enelactam **3** and that additionally the methoxylate released from **12** is of sufficient kinetic basicity to deprotonate the adduct **11** as it is formed (Scheme 2), a precedented phenomenon.[14]

We then conjectured that this problem could be circumvented by the assembly of an adduct structurally related to **6** or **7** but equipped this time with a temporary blocking group Y easily connectable to the indolinone framework, liable to allow the metallation-hydroxyalkylation-*O*-alkylation sequence and to facilitate the ultimate creation of the mandatory enol ether unit. The choice of benzotriazole was

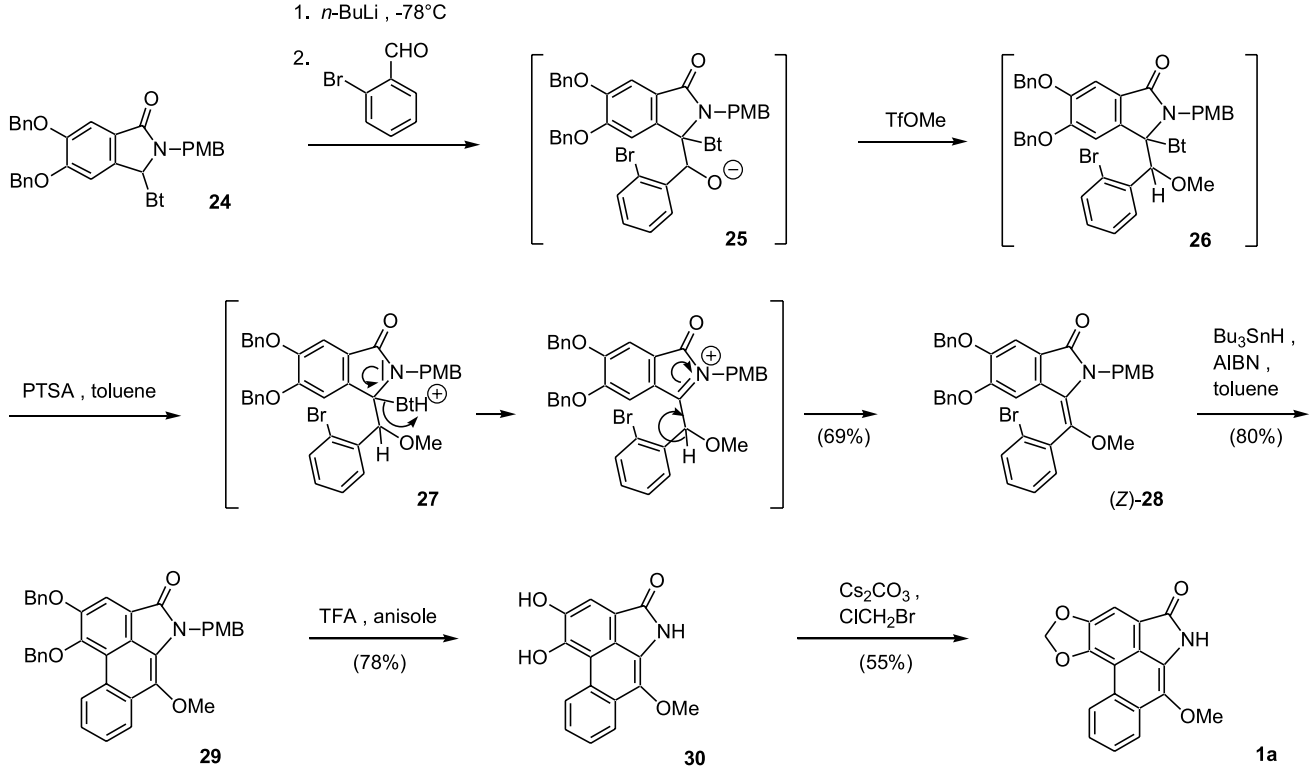


Scheme 2.



Scheme 3.

dictated by reliance on the ability of this remarkable synthetic auxiliary[15] to be involved in the generation of α-aminocarbanionic entities[16] and to generate *N*-acylenamines under basic and acidic conditions.[17] Consequently, we embarked on the synthesis of the methylenedioxyisoindolinone **13** with a pendant benzotriazolyl unit. We assumed that the construction of this compound would be achievable by using benzotriazole to trap the *N*-acyliminium species which would be derived from the appropriate hydroxylactam **14**. For the synthesis of this *N,O*-hemiacetal we initially synthesized the bromobenzamide derivative **15** from piperonal according to the synthetic route portrayed in Scheme 3. Compound **15** was then sequentially exposed to phenyllithium and *n*-butyllithium to induce the required metallation/interconversion sequence followed by quenching with DMF as the formylating agent. Unexpectedly this operation led solely to the formation of the hydroxylactam **19**. It is likely that due to the cooperative effect of the carboxamide function and of the methylenedioxy group which both rank highly in the hierarchy of *ortho*-directing metalating groups[18] metalation at their common 'in between' site is promoted thus sparing the bromine atom.



Scheme 4.

Experimenting different bases under varied conditions did not prevent the formation of this undesirable compound. We then anticipated that bromine–lithium exchange should be favored over metalation by replacement of the weakly sterically demanding methylenedioxy group by bulky dialkoxylated substitution patterns. For this purpose the sterically hindered dibenzyl derivative **22** was synthesized according to the four step sequence depicted in Scheme 3 starting from the benzyl protected isovaniline derivative **18**. Gratifyingly quenching with DMF of the dilithiated species generated by sequential treatment of **22** with PhLi and *n*-BuLi led to the desired hydroxylactam **23**. The steric congestion of the parent model **22** renders the *ortho* proton inaccessible and in the competitive process involving interconversion versus deprotonation the bromine/lithium exchange is favored.

Treatment of the *N,O*-hemiacetal **23** with *para*-toluenesulfonic acid (PTSA) and quenching of the transient iminium salt with benzotriazole allowed the installation of the benzotriazole unit on the isoindolinone framework. The resulting compound **24** was smoothly deprotonated with *n*-BuLi in THF at −78 °C followed by quenching with 2-bromobenzaldehyde. The transient oxanion **25** was intercepted in situ with methyl trifluoromethanesulfonate and the whole operation delivered the rather congested adduct **26** which was treated without isolation with PTSA. Gratyfyingly this operation induced elimination of the temporary synthetic auxiliary according to the mechanistic pathway depicted in Scheme 4 to provide the protected isoindolinone **28** with the required pendant enol ether unit in a fairly good yield (69%). The use of the bulky *para*-methoxybenzylgroup (PMB) on the lactam nitrogen was rewarded here: compound **28** was obtained as a mixture of *Z* and *E* isomers but with the required *Z* isomer predominating by a very large margin (*Z*/*E* 95:5). The oxidative radical cyclization of the bromostilbenic intermediate (*Z*)-**28** proceeded uneventfully to furnish the primarily annulated compound **29** with a satisfactory yield (80%). Treatment of this fused phenanthrene lactam with trifluoroacetic acid (TFA) in the presence of the cation scavenger anisole resulted in the concomitant removal of the benzyl protection of the phenolic hydroxy groups and of the lactam nitrogen to provide the methoxylated biphenolic compound **30**. The regeneration of the required methylenedioxy group was readily secured by treatment of **30** with bromochloromethane in the presence of cesium carbonate and this simple operation delivered the target natural product 9-methoxycepharanone A (**1a**) in a very satisfactory overall yield (12% over the last six steps). The spectral data of **1a** were identical to those reported for the natural product.[3a]

3. Experimental

3.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μ; 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert-Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300 (300 and 75 MHz, for ^1H, and ^{13}C), $CDCl_3$ as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

3.1.1. 3-[1-(2-Bromophenyl)methyl-(*E*)-ene]-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (3). Compound **3** was obtained from **4a**[12] or **5a**[13] by following already described procedures.[9a,14] Pale yellow crystals; yield 75–82%; mp 178–179 °C; ^1H NMR (δ) 3.77 (s, 3H, OCH_3), 5.08 (s, 2H, NCH_2), 6.37 (s, 1H, CH═), 6.85 (d, J= 8.6 Hz, 2H, aromatic H), 7.12 (d, J=7.8 Hz, 1H, CH═), 7.16–7.35 (m, 5H, aromatic H), 7.44 (t, J=7.6 Hz, 2H, aromatic H), 7.64 (d, J=7.1 Hz, 1H, aromatic H), 7.89 (d, J=7.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 42.8, 55.3, 110.9, 114.1, 123.0, 123.5, 124.8, 127.3, 128.6, 128.9, 129.5, 129.6, 130.4, 131.6, 131.8, 132.9, 134.9, 135.6, 136.4, 158.9, 166.7. Anal. calcd for $C_{23}H_{18}BrNO_2$ (420.3): C, 65.73; H, 4.32; N, 3.33%. Found: C, 65.65; H, 4.15; N, 3.08%.

3.2. 2-Bromobenzoic acid derivatives

The benzaldehyde derivatives **17**,[19] **18**[20] and **20**[21] were synthesized according to literature methods.

The 2-bromobenzoic acid derivatives **16**[22] and **21** were obtained by oxidation with Jones reagent[23] of the corresponding benzaldehyde derivatives **17** and **20**.

3.2.1. 2-Bromo-4,5-dibenzyloxybenzoic acid (21). Yield 81%; mp 157–158 °C; ^1H NMR (δ) 5.17 (s, 2H, CH_2), 5.19 (s, 2H, CH_2), 7.21 (s, 1H, aromatic H), 7.32–7.45 (m, 10H, aromatic H), 7.69 (s, 1H, aromatic H); ^{13}C NMR (δ) 71.1, 71.3, 115.8, 118.2, 119.7, 121.6, 127.3, 127.4, 128.1, 128.3, 128.6, 128.7, 135.7, 136.3, 147.4, 152.8. Anal. calcd for $C_{21}H_{17}BrO_4$ (413.3): C, 61.03; H, 4.15%. Found: C, 61.35; H, 3.94%.

3.3. 2-Bromobenzamides 15 and 22

The carboxylic acids **16** and **21** were initially converted into their corresponding acid chlorides ($SOCl_2$, DMF cat., CH_2Cl_2) and then allowed to react under standard conditions with *para*-methoxybenzylamine to furnish the 2-bromobenzamides **15** and **22**.

3.3.1. 6-Bromo-1,3-benzodioxole-5-[*N*-(4-methoxybenzyl)carboxamide] (15). Yield 71%; mp 137–138 °C (from hexane–toluene); ^1H NMR (δ) 3.78 (s, 3H, OCH_3), 4.51 (d, J=5.6 Hz, 2H, NCH_2), 5.98 (s, 2H, OCH_2O), 6.34 (t, J=5.6 Hz, 1H, NH), 6.85 (d, J=8.8 Hz, 2H, aromatic H), 6.94 (s, 1H, aromatic H), 7.00 (s, 1H, aromatic H), 7.27 (d, J=8.8 Hz, 2H, aromatic H); ^{13}C NMR (δ) 47.3, 55.3, 109.6, 110.7, 113.1, 114.0, 114.1, 129.4, 129.7, 130.9, 147.4, 146.9, 166.8. Anal. calcd for $C_{16}H_{14}BrNO_4$ (364.2): C, 52.77; H, 3.87; N, 3.85%. Found: C, 52.60; H, 3.94; N, 4.05%.

3.3.2. 4,5-Dibenzyloxy-2-bromo-*N*-(4-methoxybenzyl)-carboxamide (22). Yield 77%; mp 145–146 °C (from

hexane–toluene); ^{1}H NMR (δ) 3.79 (s, 3H, OCH_3), 4.53 (d, J=5.4 Hz, 2H, NCH_2), 5.11 (s, 4H, 2×OCH_2), 6.45 (t, J=5.4 Hz, 1H, NH), 6.87 (d, J=8.6 Hz, 2H, aromatic H), 7.05 (s, 1H, aromatic H), 7.26–7.42 (m, 13H, aromatic H); ^{13}C NMR (δ) 43.8, 55.3, 71.3, 110.4, 114.1, 116.1, 118.9, 127.3, 127.4, 128.1, 128.2, 128.6, 128.7, 129.3, 129.6, 129.8, 136.1, 136.4, 148.2, 150.6, 159.1, 166.6. Anal. calcd for $C_{29}H_{26}BrNO_4$ (532.4): C, 65.42; H, 4.92; N, 2.63%. Found: C, 65.65; H, 4.94; N, 2.34%.

3.4. General procedure for the synthesis of the isoindolinones 19 and 23

A solution of PhLi (1.22 mL, 1.8 M in cyclohexane/diethyl ether, 2.2 mmol) was added dropwise at −78 °C under Ar to a stirred solution of the benzamide derivatives **15** or **22** (2.0 mmol) in THF (70 mL). After stirring for 20 min at −78 °C *n*-BuLi (1.38 mL, 1.6 M in hexanes, 2.2 mmol) was added dropwise followed by DMF (365 mg, 5.0 mmol). The reaction mixture was stirred at −78 °C for 1 h then allowed to warm to room temperature over a period of 2 h and finally quenched by addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with Et_2O (3×50 mL) and the combined organic layers were dried ($MgSO_4$). Evaporation of solvent in vacuo left a solid residue which was purified by flash column chromatography with ethyl acetate/hexanes (50:50) as eluent. Isoindolinones **19** and **23** were finally purified by recrystallization from hexane–toluene.

3.4.1. 5-Bromo-8-hydroxy-7-(4-methoxybenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-*e*]isoindol-1-one (19). Yield 416 mg (53%); mp 187–188 °C; ^{1}H NMR (δ) 3.71 (s, 3H, OCH_3), 4.22 (d, J=15.0 Hz, 1H, NCH_2), 4.77 (d, J=15.0 Hz, 1H, NCH_2), 5.62 (d, J=9.0 Hz, 1H, C*H*OH), 6.17 (s, 1H, OCH_2O), 6.24 (s, 1H, OCH_2O), 6.82 (d, J=9.0 Hz, 1H, OH), 6.88 (d, J=8.5 Hz, 2H, aromatic H), 7.23 (d, J=8.5 Hz, 2H, aromatic H), 7.28 (s, 1H, aromatic H); ^{13}C NMR (δ) 41.7, 55.1, 76.4, 103.5, 108.9, 113.6, 113.9, 122.7, 125.7, 129.2, 129.3, 142.5, 151.9, 158.5, 163.5. Anal. calcd for $C_{17}H_{14}BrNO_5$ (392.2): C, 52.06; H, 3.60; N, 3.57%. Found: C, 52.31; H, 3.38; N, 3.49%.

3.4.2. 5,6-Dibenzyloxy-3-hydroxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (23). Yield 587 mg (61%); mp 148–149 °C; ^{1}H NMR (δ) 3.74 (s, 3H, OCH_3), 4.16 (d, J=14.4 Hz, 1H, NCH_2), 4.90 (d, J=14.4 Hz, 1H, NCH_2), 5.03 (s, 2H, OCH_2), 5.08 (s, 2H, OCH_2), 5.40 (d, J=11.4 Hz, 1H, OH), 6.80 (d, J=8.6 Hz, 2H, aromatic H), 7.01 (d, J=11.4 Hz, 1H, CH), 7.03 (s, 1H, aromatic H), 7.21 (d, J=8.6 Hz, 2H, aromatic H), 7.25–7.39 (m, 11H, aromatic H); ^{13}C NMR 42.1, 55.2, 70.8, 71.0, 80.5, 107.2, 108.5, 114.1, 124.1, 127.2, 127.6, 128.0, 128.1, 128.5, 128.6, 129.2, 129.9, 136.2, 136.3, 138.0, 150.2, 152.4, 159.0, 167.5. Anal. calcd for $C_{30}H_{27}NO_5$ (481.55): C, 74.83; H, 5.65; N, 2.91%. Found: C, 75.68; H, 5.80; N, 2.72%.

3.4.3. 3-(Benzotriazol-1-yl)-5,6-dibenzyloxy-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (24). A solution of isoindolinone **23** (578 mg, 1.2 mmol), benzotriazole (155 mg, 1.3 mmol) and PTSA (5 mg, cat) in 30 mL of toluene was refluxed for 3 h. After evaporation of the toluene under vacuum the crude reaction mixture was dissolved in CH_2Cl_2 (30 mL), washed twice with aq Na_2CO_3 (5%) then water and dried (Na_2SO_4). The solvent was evaporated and the product was triturated with Et_2O to afford a white solid which was recrystallized from hexane–toluene. Yield 601 mg (86%); mp 163–164 °C; ^{1}H NMR (δ) 3.71 (s, 3H, OCH_3), 3.79 (d, J=14.7 Hz, 1H, NCH_2), 4.90 (d, J=14.7 Hz, 1H, NCH_2), 5.00 (s, 2H, OCH_2), 5.28 (s, 2H, OCH_2), 6.41 (d, J=8.3 Hz, aromatic H), 6.69 (d, J=8.1 Hz, 2H, aromatic H), 6.75 (s, 1H, CH), 7.09–7.13 (m, 3H, aromatic H), 7.17–7.49 (m, 12H, aromatic H), 7.57 (s, 1H, aromatic H), 8.02 (d, J=8.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 43.4, 55.2, 71.0, 71.2, 71.7, 108.3, 108.4, 110.3, 114.0, 120.1, 124.5 (two peaks overlapping), 127.0, 127.3, 127.9, 128.0, 128.1, 128.2, 128.5, 128.7, 129.9, 130.6, 132.7, 135.6, 136.2, 147.0, 151.2, 153.1, 159.1, 167.0. Anal. calcd for $C_{36}H_{30}N_4O_4$ (582.7): C, 74.21; H, 5.19; N, 9.62%. Found: C, 73.98; H, 5.35; N, 9.57%.

3.4.4. 5,6-Dibenzyloxy-3-[1-(2-bromophenyl)-1-methoxymethyl-(*Z*)-ene]-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-isoindol-1-one (28). A solution of *n*-BuLi (0.7 mL, 1.6 M in hexanes, 1.1 mmol) was added dropwise with stirring under Ar at −78 °C to a solution of **24** (583 mg, 1.0 mmol) in THF (20 mL). The red solution was stirred at −78 °C for 15 min then a solution of *ortho*-bromobenzaldehyde (202 mg, 1.1 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was allowed to warm to −40 °C over 5 min then recooled to −78 °C. A solution of methyl trifluoromethanesulfonate (181 mg, 1.1 mmol) in THF (1 mL) was added at once and the reaction mixture was allowed to warm at room temperature. Water (20 mL) was added and the resulting mixture was extracted with Et_2O (3×15 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated in vacuo to left a solid residue which was dissolved in toluene (20 mL). After addition of a catalytic amount of PTSA, the solution was stirred at room temperature for 1 h. The toluene was evaporated in vacuo and the residue dissolved in CH_2Cl_2 (30 mL). The solution was washed with aq. sat. $NaHCO_3$, brine and finally water and dried ($MgSO_4$). After removal of CH_2Cl_2 the crude product was purified by flash column chromatography with ethyl acetate/hexanes (30:70) as eluent. Yield 457 mg (69%); mp 170–171 °C; ^{1}H NMR (δ) 3.10 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.66 (s, 2H, OCH_2), 5.18 (s, 2H, NCH_2), 5.36 (s, 2H, OCH_2), 5.46 (s, 1H, aromatic H), 6.84 (d, J=8.5 Hz, 2H, aromatic H), 7.17–7.21 (m, 4H, aromatic H),), 7.29–7.44 (m, 12H, aromatic H), 7.63 (d, J=7.6 Hz, 1H, aromatic H); ^{13}C NMR (δ) 45.4, 55.3, 55.9, 70.2, 70.9, 106.1, 107.5, 113.6, 119.6, 122.0, 125.9, 126.8, 127.2, 127.8, 127.9, 128.2, 128.4, 128.5, 130.0, 131.3, 131.4, 133.3, 133.5, 133.9, 136.4, 136.7, 138.6, 149.1, 151.7, 158.3, 167.0. Anal. calcd for $C_{28}H_{32}BrNO_5$ (662.6): C, 68.89; H, 4.87; N, 2.11%. Found: C, 69.03; H, 4.79; 2.40%.

3.4.5. 1,2-Dibenzyloxy-6-methoxy-5-(4-methoxybenzyl)-4,5-dihydrodibenzo[*cd,f*]indol-4-one (29). To a solution of **28** (430 mg, 0.65 mmol) in dry degassed benzene (300 mL) refluxing under Ar, was added a solution of *n*-Bu_3SnH (295 mg, 1.0 mmol) and AIBN (65.5 mg, 0.4 mmol) in dry degassed benzene (50 mL) by syringe over a period of 10 min. Once addition had finished, refluxing was kept up for a further 3 h. The benzene was evaporated under reduced pressure, and the residue was dissolved in CH_3CN (50 mL). The solution was washed with hexane (3×30 mL) and

concentrated in vacuo to a yellow oil which was purified by flash column chromatography with ethyl acetate/hexanes (40:60) as eluent. Recrystallization from EtOH afforded **29** as yellow crystals. Yield 303 mg (80%); mp 117–118 °C; ^{1}H NMR (δ) 3.74 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.25 (s, 2H, NCH_2), 5.30 (s, 2H, OCH_2), 5.36 (s, 2H, OCH_2), 6.83 (d, J=8.1 Hz, 2H, aromatic H), 7.37–7.61 (m, 14H, aromatic H), 7.92 (s, 1H, aromatic H), 8.12 (d, J=8.1 Hz, 1H, aromatic H), 9.33 (d, J=8.1 Hz, 1H, aromatic H); ^{13}C NMR (δ) 44.7, 55.2, 62.8, 72.2, 75.1, 111.5, 113.9, 119.4, 120.8, 124.3, 124.9, 126.1, 127.4, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 130.4, 131.0, 136.3, 136.4, 136.8, 150.4, 152.9, 158.8, 167.8. Anal. calcd for $C_{38}H_{31}NO_5$ (581.7): C, 78.47; H, 5.37; N, 2.41%. Found: C, 78.41; H, 5.13; N, 2.22%.

3.4.6. 1,2-Dihydroxy-6-methoxy-4,5-dihydrodibenzo[*cd, f*]indol-4-one (30). A solution of **29** (290 mg, 0.5 mmol) and anisole (550 mg, 5 mmol) in trifluoroacetic acid (20 mL) was refluxed under Ar for 60 h. The solvent and excess anisole were removed under vacuum. The residue was dissolved in CH_2Cl_2 (20 mL) and NEt_3 (1 mL) was added with stirring. Water (2 mL) was then added, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated under vacuum to yield a solid residue which was recrystallized from EtOH. Yellow crystals, yield 110 mg (78%); mp 326–327 °C; ^{1}H NMR (DMSO-*d6*; δ) 4.06 (s, 3H, OCH_3), 7.53–7.59 (m, 3H, aromatic H), 8.15 (d, J=5.6 Hz, 1H aromatic H), 9.29 (s, 1H, aromatic H), 10.37 (s, 2H, 2×OH), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO-*d6*; δ) 60.7, 111.1, 112.2, 115.0, 120.8, 122.1, 125.0, 125.4, 126.4, 127.6, 128.1, 129.6, 133.8, 144.9, 148.3, 168.5. Anal. calcd for $C_{16}H_{11}NO_4$ (281.3): C, 68.33; H, 3.94; N, 4.98%. Found: C, 68.49; H, 3.83; N, 5.27%.

3.5. 9-Methoxycepharanone A (1a)

A suspension of **30** (80 mg, 0.28 mmol) and Cs_2CO_3 (204 mg, 0.63 mmol) in DMF (5 mL) was stirred at room temperature for 30 min. Bromochloromethane (81 mg, 0.63 mmol) was added and the mixture was stirred at 50 °C for an additional 12 h. CH_2Cl_2 (50 mL) was then added and the resulting solution was successively washed with water, brine and dried (Na_2SO_4). After removal of the solvent under vacuum, the crude solid residue was recrystallized from EtOH. Yellow crystals; yield 45 mg (55%). The analytical data of synthetic **1a** matched those reported for the natural product.[3a]

Acknowledgements

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Novel triazinium-imidothioate zwitterions: intermediates in the reaction of [1,3,4]thiadiazolo[2,3-d][1,2,4]triazolo[1,5-a][1,3,5]-triazinium cations with amines☆

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Abstract—Starting with bis([1,3,4]thiadiazolo)[1,3,5]triazinium halides **1**, a novel class of heterocyclic compounds, the [1,3,4]thiadiazolo[2,3-d][1,2,4]triazolo[1,5-a][1,3,5]triazinium halides **5** were prepared. The reaction between **5** and primary or secondary amines **6** yielded highly substituted guanidines **8** and fused tricyclic bis([1,2,4]triazolo)[1,5-a:1′,5′-d][1,3,5]triazinium halides **9**. The formation of the reactive triazinium-imidothioate zwitterions **7**, which is controlled by the influence of negative hyperconjugation, was proven by NMR data and the X-ray structure of **7c**. The subsequent ring-closure/ring-opening steps can be understood in terms of an S_N(ANRORC) process accompanied by intramolecular proton-transfer reactions. The zwitterions **7** were reacted with EtI forming cationic derivatives **10** or hydrolyzed at pH 6–7 to give novel heterocyclic ethanethioamides **11**.

1. Introduction

In 1998, we reported on the convenient synthesis of a novel tricyclic bis-(1,3,4-thiadiazolo)-1,3,5-triazinium ring system **SNS** (Fig. 1) by reaction of 2-amino-1,3,4-thiadiazoles with either 1-(haloalkyl)pyridinium halides or *N*,*N*′-methylenebis(pyridinium) halides.[1,2] In the subsequent period, we focused our research on the extension of these novel reaction paths for the following reasons: (a) these cationic compounds **SNS** should possess biological activities[3,4] (b) their applicability as conveniently accessible precursors for the preparation of a wide variety of novel heterocyclic compounds deserves significant interest. The surprising reactivity of these novel so-called '5/6/5-heterocycles' is based on a significant electrophilicity of the C3a- and C4a-centers of the central triazinium ring [$q_{C3a}=q_{C4a}=+0.30$ e (NPA-B3LYP/6-311++G(d,p) results)].

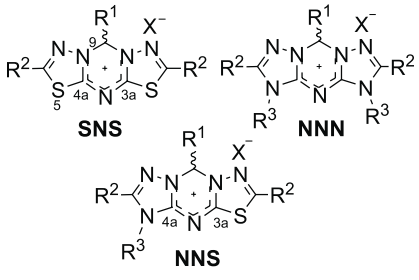

Figure 1. Novel tricyclic 5/6/5 heterocyclic systems.

Consequently, these heterocyclic compounds are capable to react with nitrogen nucleophiles such as primary or secondary amines to give novel highly substituted guanidines **GUA** and bis(azolyl)alkanes or 'aminales', **AMI-I**, **AMI-II**, **AMI-III** (Fig. 2) as a result of interesting intramolecular ring transformations followed by hydrolysis reactions, respectively.[5–9]

The reaction of the **SNS** heterocycles with primary aliphatic amines and especially benzylamines has a very complicated hypersurface. Controlled by reaction conditions, unusual novel **NNN** or **NNS** tricyclic 5/6/5 systems can be synthesized.[8] The highly reactive zwitterionic triazinium-imidothioate intermediates **3** (Scheme 1) are the first

☆ Bis-(1,3,4-thiadiazolo)-1,3,5-triazinium halides. Part 8; Part 7 see Ref. 9.

Keywords: Nitrogen heterocycles; Nucleophilic addition; Guanidines; Imidothioate zwitterions; Sulfur heterocycles.
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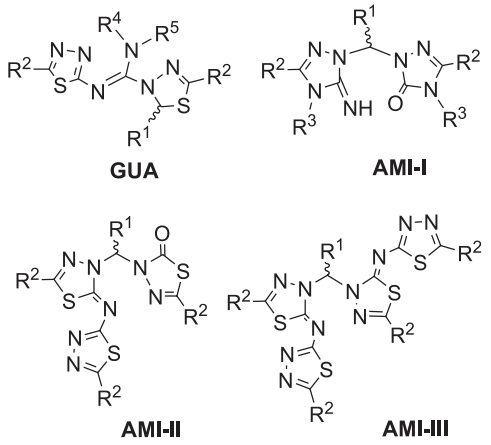
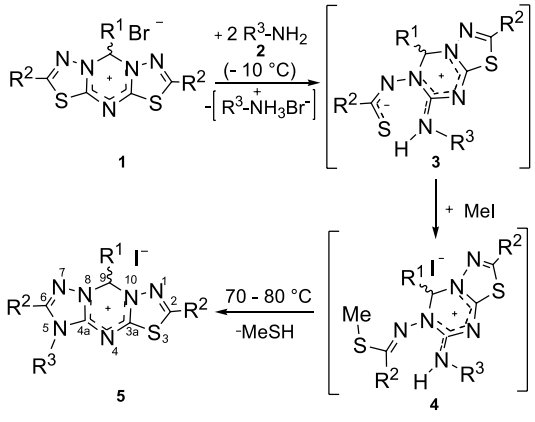


Figure 2. Novel heterocyclic compounds resulting from **SNS** and **NNN** systems.

structures which can be isolated in the course of these fast multi-step reactions between **SNS** compounds and primary amines. The formation of the betainic structures **3** is controlled by the influence of negative hyperconjugation ($n_{N(ex)}/\sigma^*_{C(4a)-S(5)}$ interaction) while predominantly the electronic properties of these intermediates determine the consecutive reactions paths. In general, the over all reaction can be classified as novel examples for the S_N(ANRORC) mechanism.[10] DFT calculations give reasonable explanations for the complexity of all these transformations including those details with result from the reaction conditions and the nature of the R^3 amine substituent.[8,11] This interesting reaction behaviour of the **SNS** cations towards primary and secondary amines especially in combination with the convenient access to highly substituted guanidines prompted us to extend the investigation to the related **NNN** cations. Although there are a variety of synthetic methods available to prepare guanidines, only a few methods have been developed for synthesis of



Compounds 1,2,3,4,5	R^1	R^2	R^3	Yield (%)
a	4-MePh	Me	Bzl	70
b	4-MePh	Me	4-ClBzl	98
c	2-HOPh	Et	1-Bu	92
d	2-HOPh	Et	Bzl	79
e	naphthyl	Me	4-ClBzl	91

Scheme 1. Synthetic route to **NNS** compounds **5**.

substituted guanidines bearing up to three heterocyclic moieties.[5]

Moreover, as the guanidine unit is well known to be an important structural key component in biologically active natural compounds[12–14] as well as for potential auxiliaries in asymmetric syntheses,[15] the development of covenient and efficient new methods which allow access to modified guanidines are of great interest.[16–18] In this paper, we describe our studies on the reactivity of cationic **NNS** heterocycles with some selected primary and secondary amines. The results are compared with those recently obtained from analogous investigations performed with the **SNS** and **NNN** cations.[7–9]

2. Results and discussion

2.1. Syntheses of thiadiazolo-triazolo-triazinium (or 'NNS') cations

The bis-(thiadiazolo)-1,3,5-triazinium compounds **1a–e**[1,5] ('SNS cations') were used to synthesize **NNS** analogs **5** (Scheme 1). Compounds **5** will be used as precursors for our novel ring transformation reactions (vide infra). In a previous report,[8] we have given a detailed description and explanation for the pathway **1**→**3**→**4**→**5**. As already mentioned, the properties of the isolable zwitterions **3** determine the subsequent reaction steps. These steps can be interpreted to be the results of the charge separation in these intermediates and of consecutive inter- or intramolecular proton shifts from the acidic iminium moiety in **3**. Although feasible, neither the isolation of **3** nor of the intermediate salts **4** which are immediately formed from the compounds **3** after addition of MeI is necessary for the development of a convenient synthesis protocol for the tricyclic compounds **5a–e** as presented here. The novel **NNS** compounds **5b–e** were prepared in a one-pot procedure with yields up to 92%. The ring-closure step **4**→**5** requires heating of the reaction mixture (70–80 °C).

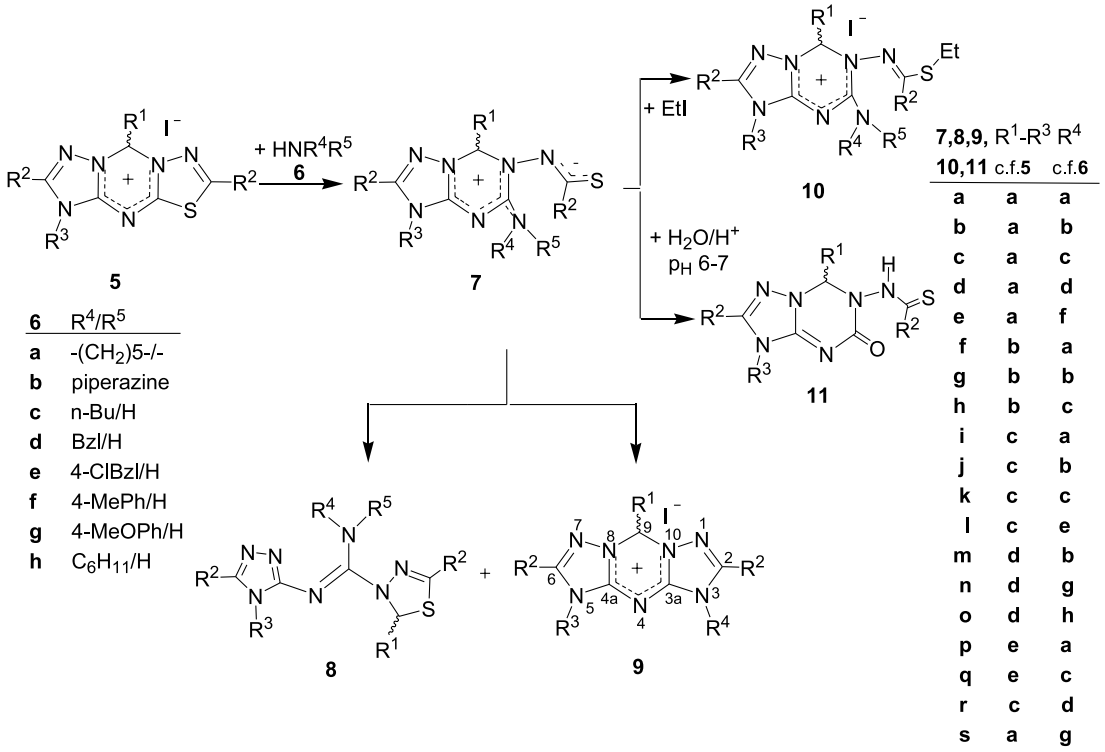
The structural assignments of the novel compounds **5** are based on NMR spectroscopic data, mass spectra (CI), IR spectra, elemental analyses and X-ray of **5** (R^1=4-MePh; R^2=Me; R^3=2-MeOBzl); cf. Ref. [8]). In contrast to the both symmetric **SNS** and **NNN** cations, which exhibit only three different ^{13}C NMR signals at the tricyclic 5/6/5 structure element, the asymmetric compounds **5** show five ^{13}C signals in the expected range (C2=157 ppm; C3a=169; C4a=148; C6=151; C9=76). The asymmetric structure of **5** is also supported by ^{1}H NMR spectra. In addition to the signal of the sp^3 CH(9) at approximate 8 ppm (which is similar to that of the **SNS** compounds), now different chemical shifts are observed for both the alkyl substituents (Me or Et) at the azole rings. This goes parallel with a significant high field shifting of the CH hydrogens of R^2 at the fused 1,2,4-triazole ring.

2.2. Reactions of NNS compounds 5 with amines 6

Because of the structural similarity of **SNS**, **NNN** and **NNS** heterocycles, we expected comparable electronic properties for **5a–e**, which should allow the prediction for further

synthetic use of these compounds. As indicated by calculated charges q at the C(4a) and C(3a) carbons (model compound **5M** with $R^1=R^2=R^3=Me$; $q_{4a}=+0.64$, $q_{3a}=+0.31$), due to their structural similarities with the **SNS** cations[8,11] the **NNS** compounds **5** should reveal comparable properties and, especially, a significant electrophilicity.[19] The q_{3a}–q_{4a} charge difference can be explained with structural properties: The C(4a) position is directly surrounded with three ring nitrogen atoms and thus possesses a higher positive charge in comparison with the C(3a) position which is bonded to two nitrogen atoms and one sulfur atom. It is noteworthy, that despite of this charge difference, we do not find any indication for a reactivity competition between these centers for the nucleophilic attack of amines. In all cases investigated so far always the C(3a) center was attacked by compounds **6**. This leads to the novel triazinium-imidothioate-zwitterions **7** (Scheme 2), the analogs of the previously synthesized intermediates **3** (Scheme 1). The zwitterions **7** are the key intermediates for the consecutive reaction cascade to give novel highly substituted guanidines **8** and/or novel fused **NNN** heterocycles **9**, whose substituents R^3 and R^4 now can be modified due to a large assortment of different amines **6**. Thus, the over all synthetic procedure which starts with **1** to give **8** (or **9**) allows the introduction of a wide variety of substituents R^3, R^4 and R^5. Especially in the **NNN** cations **9**, R^3 and R^4 can be different. The **8**:**9** ratio in the product mixture depends on the reaction conditions and especially on the nature of R^4 and R^5 of nucleophiles **6**. Moreover, the relatively stable zwitterionic intermediates **7** allow the reaction with electrophiles, such as EtI forming the novel salts **10c**,**h**, and **10q** in yields up to 90% as well as the simple hydrolytic reaction at p_H 6–7 which lead to novel oxo-ethanethioamides **11c**, and **11h** in yields up to 90% as well. The latter belong to a compound type which contains the C–C(S)–N–N–C(O)–N structure element for which only a few examples have been described in the literature, especially due to their potential biological activity.[20–22] The zwitterions **7c**,**h**,**k**, and **7q** (yields up to 98%) proved to be stable at room temperature for longer periods as crystalline material and in ethyl acetate solution. However, with the exception of **7q**, in $CHCl_3$ or MeOH solution they are of moderate stability only up to 278 K so that for the species **7** the essential NMR measurements were performed at 263 K. Dipolar structures which show a remote relationship of **7** have been described previously.[23]

As expected, the reaction of the **NNS** heterocycles **5** and the secondary amines **6a** or **6b** (piperidine, piperazine) yields up to 95% guanidines **8a**,**b**,**f**,**g**,**i**,**j**,**m**, and **8p** as main products. These results are almost identical with those obtained from the analogous reaction pathways of **SNS** cations with the same amines to give the product **GUA** (see the introduction[8]) which differ to **8** by exchange of one sulfur by a nitrogen atom with R^3. A further different reaction behavior of **5** compared with that of the **SNS** cations was detected after exchange of **6a** or **6b** for the primary amines **6c**,**d**,**e**,**f**,**g**, and **6h** (aliphatic, benzylic, aromatic). These reactions cause in many cases not only a guanidine formation (**8c**,**d**,**e**,**h**,**k**,**o**,**q**,**r**, and **8s**) but also the formation of novel fused **NNN** cations **9c**,**e**,**h**,**k**,**l**,**n**,**q**,**r**, and **9s** as a result of a cyclization of **7** to a 1,2,4-triazole ring under extrusion of H_2S as an alternative pathway. As expected, the **8**:**9** ratio depends both on the nature of primary amine **6** and the used **NNS** compound **5** (Table 1). However, the exact reasons (structural, electronic or choice of the reaction conditions etc.) for such differences are not clear at present even after inspection of the reaction



Scheme 2. Synthesis of guanidines **8** and **NNN** compounds **9**.

products of **5a**,**b**,**c**, and **5e** and just one amine **6c** (cf. Table 2).

Interestingly, the naphthyl compound **5e** reacted with **6c** to give at conditions comparable to the another amine additions a mixture of **8e** and **9e** and a certain amount of the unreacted zwitterion **7q** (34%). The remarkable stability of **7q** is also observed in the hydrolysis test (H_2O; p_H 6–7; room temperature, no hydrolysis product **11q** was formed). Further interesting results were obtained when the **NNS** heterocycles **5** were reacted with primary aromatic amines such as **6f**, and **6g**. Aniline does not react at all with **5a** or **5b**. Just 53% conversion was achieved in case of **5a** and *p*-toluidine **6f** with a product distribution of 76% guanidine **8e** and only 8% of the **NNS** cation **9e** after changing the general procedure to 40 h at 60 °C. The product analysis of the reaction of **5a** and 4-methoxyaniline **6g** (*p*-anisidine) opens a different reaction channel. Beside 25% of **8s** and 26% of **9s**, we have isolated the Schiff base CH_3–C_6H_4–CH=N–C_6H_4–OCH_3[24] which obviously was formed by the attack of the nucleophile **6g** at the C9 instead at C3a center, followed by an opening of the central triazinium ring. The reaction of **5d** and **6g** yielded 11% of **9n** and only traces of the guanidine **8n** as recognized in the corresponding NMR spectra of the raw product mixture in which in addition the already known azine 2-HO–C_6H_4–CH=N–C_6H_4–OCH_3 was detected.[25] The complete product analysis including a mechanistic interpretation especially for the application of the 2-hydroxyphenyl substituted **5c** and **5d** (see Scheme 1) and aromatic amines, which yielded the interesting ring cleavage compounds as main products, are currently under detailed investigation.

Table 1. Synthesis of guanidines **8** and **NNS** cations **9** using **NNS** cations **5** and *n*-butylamine **6c** (R^1–R^3 and R^4 cf. Schemes 1 and 2)

5	8 (%)	9 (%)
a	**c** (25)	**c** (75)
b	**h** (12)	**h** (88)
c	**k** (43)	**k** (57)
e	**g** (23)[a]	**q** (43)

[a] Together with 34% zwitterion **7q**.

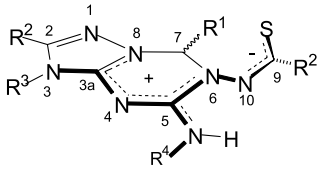


Figure 3. Imidothiate zwitterions **7**.

Table 2. Selected ^{1}H NMR data (ppm) of zwitterions **7c**, **7h**, **7k**, and **7q**

Compound	2-CH_3	9-CH_3	7-CH	3-N CH_2	5C–NH	5C–NCH_2
7c	2.20	2.38	8.14	5.03	6.43	4.01
7h	2.20	2.27	8.17	4.99	6.40	3.37
7k	2.68[a]	2.38[a]	7.57	3.90	[b]	3.29
7q	2.20	2.30	8.77	4.95	6.68	4.01

[a] CH_2 from Et group.
[b] No signal in CD_3OD.

Reactions of **7c**,**h**, and **7q** and EtI were performed analogously to the procedure already described for **SNS** zwitterions.[8] By this procedure, the thioethyl salts **10c**,**h**, and **10q** have been synthesized in yields up to 70% (crystalline products with well-defined melting points). At room temperature, they are more stable than the comparable alkyl sulfides synthesized from the **SNS** cations.

2.3. Structural assignments

Structural assignments of the reaction products **7**–**11** were based on NMR investigations (in special cases by HMQC, HMBC, COSY, and TOCSY experiments), mass spectra (CI, FAB), IR spectra (KBr), elemental analysis, and in some cases by X-ray analysis. All ^{1}H and ^{13}C NMR spectroscopic data of the isolated products **7c**,**h**,**k**, and **7q** are in agreement with the triazolo-triazinium betaine structure (for the numbering see Fig. 3; for NMR data see Tables 2 and 3) and are similar to the corresponding data of the previously described thiadiazolo-triazinium betaines (cf. Ref. 8; i.e., the reaction of **SNS** compounds with primary amines).

The first X-ray structure of a fused heterocyclic **NNS** zwitterion **7c** is depicted in Figure 4. The N6–C5–N4–C3a–N8 subunit of the 1,3,5-triazinium ring is nearly planar and represents a conjugated system (with bond lengths between 133 and 136 pm) including the exocyclic C5–NH bond and the fused 1,2,4-triazole ring. These C–N bond lengths indicate that the positive charge which stems from the exocyclic iminium group is efficiently delocalized. As expected the C7–N6 and C7–N8 bonds are significantly longer as they are not integrated in the conjugated system. The sp^3-C7 atom (δ_{CH}: 8.14 ppm and δ_{C7}: 70.3 ppm in NMR spectra) is placed out of the triazolium ring plane. The C7 atom is that center which characterizes the half chair conformation of the central six-membered heterocyclic ring. The negative charge of the zwitterion **7c** is delocalized over the ethanimidothioate side chain S–C9–N10 (δ_{C9}: 194.9 ppm). Therefore, the S–C9 bond (171.8 pm) is significantly shorter than a normal S–C single bond and the C–S distance is longer than a typical double C=S bond. Moreover, both the C9–N10 bond value (131.7 pm) and the shifting of the ^{13}C signal of C9–CH_3 group to 32.9 ppm are in good agreement with of the properties of a thia-aza allyl anion moiety. No unexpectedly, the crystals **7c** show

Table 3. Selected ^{13}C NMR data (ppm) of zwitterions **7c**, **7h**, **7k**, and **7q**

Compound	2-CH_3	9-CH_3	C-2	C-3a	C-5	C-7	C-9	CH_2–3N	CH_2NH
7c	13.9	32.9	148.1	149.4	155.8	70.3	194.9	46.2	40.8
7h	13.9	33.0	147.8	149.4	153.6	70.2	194.9	45.5	41.1
7k	17.9[a]	37.8	152.0	150.0	153.4	70.4	200.8	41.6	40.2
7q	13.9	32.7	147.8	149.7	153.2	64.2	197.5	45.6	41.1

[a] CH_2 from Et group.

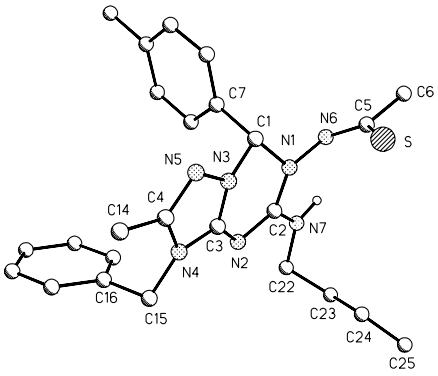


Figure 4. Crystal structure of **7c**, selected bond lengths [pm] and bond angles [deg]: N1–C1 146.4(3), N1–C2 135.9(3), N1–N6 143.0(3), N6–C5 131.2(3), S1–C5 170.1(3), N7–C2 132.5(3), N7–C22 146.7(3), N3–C1 146.2(3), N2–C2 135.8(3); C2–N1–N6 118.5(2), N6–N1–C1 114.7(2), C2–N1C1 121.5(2), C5–N6–N1 113.2(2), C2–N7–C22 122.5(2), N3–C1–N1 103.2(2).

intermolecular hydrogen bonds between in the outer sphere partially positively charged NH group at C5 and the partially negatively charged N10 atom (numbering cf. Fig. 3).

The formation of the guanidines **8** as a result of the reaction of **NNS** compounds **5** with amines **6** demands fast consecutive ring opening and ring closure reactions to give **7** and further, the C7–N8 bond fission of the central 1,3,5-triazolium moiety (see Fig. 3). There is not doubt about the resulting structures as all of them have been confirmed by detailed spectroscopic structure assignments and in case of **8i** and **8r**, by X-ray analyses (Figs. 5 and 6). The crystals of **8i** show intermolecular hydrogen bonds between the phenylic OH group and the N2 atom of 4*H*-1,2,4-triazole ring. In all cases **8**, the arrangement of the original fused aromatic 1,2,4-triazole ring and the newly created dihydro-1,3,4-thiadiazole ring show *E*-configuration with respect to the imine double bond. Characteristic bond lengths and bond angles are in agreement with the expected properties of a guanidine unit which has been substituted by moieties originating from the nucleophiles **6** and the **NNS** structures **5**.

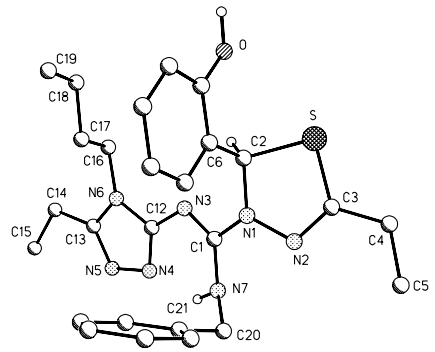
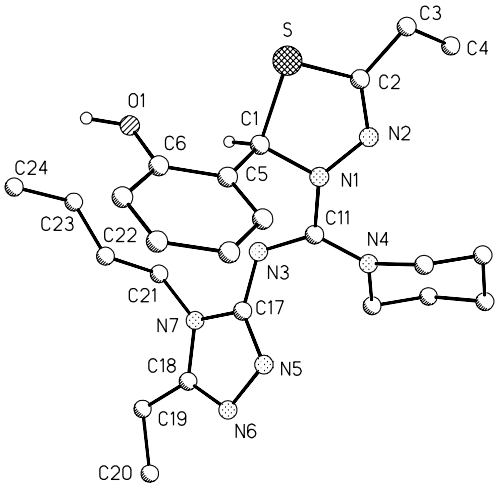


Figure 6. Crystal structure of **8r**, selected bond lengths [pm] and bond angles [deg]: N1–C1 137.53(19), N3–C1 130.6(2), N7–C1 136.16(19), N1–C2 147.59(19), S–C2 183.81(17), N3–C12 136.77(19); N3–C1–N7 126.40(14), N7–C1–N1 117.99(19), N3–C1–N1 115.60(13), N1–C2–C6 113.31(14), N1–C2–S 102.57(11).

The novel **NNN** cations **9c**,**e**,**h**,**l**,**n**,**q**,**r**, and **9s** (Scheme 2) possess at the N3 and N5 positions of the fused 1,2,4-triazole units different alkyl and aryl groups while in case of the **NNN** compounds which were synthesized from **SNS** educts and benzylamines[8] they are in all cases identical. The C atoms C2, C3a, C4a, and C6 of the asymmetric cations **9** ($R^3 \neq R^4$) show four ^{13}C signals in a very narrow interval (149–151 ppm), while the symmetrical structures **9d**, and **9k** ($R^3 = R^4$) show just two signals at 150 and 153 ppm. This is supported by the crystal structure of **9d**.[8] The structural assignments of novel heterocyclic alkanethioamides **11** are based on IR and NMR spectroscopic data, mass spectra (CI) and elemental analyses and were further supported by X-ray analysis (**11c**, Fig. 7). The crystals **11c** possess intermolecular hydrogen bonds between the NH group at C20 of the thioamide unit and the carbonyl oxygen of the oxo-dihydro-1,3,5-triazin moiety.

2.4. Some mechanistic considerations

The principles for the mechanistic background of the transformations presented here have been investigated previously. These pathways can be understood in terms of an S_N(ANRORC) process and are supported by B3LYP/



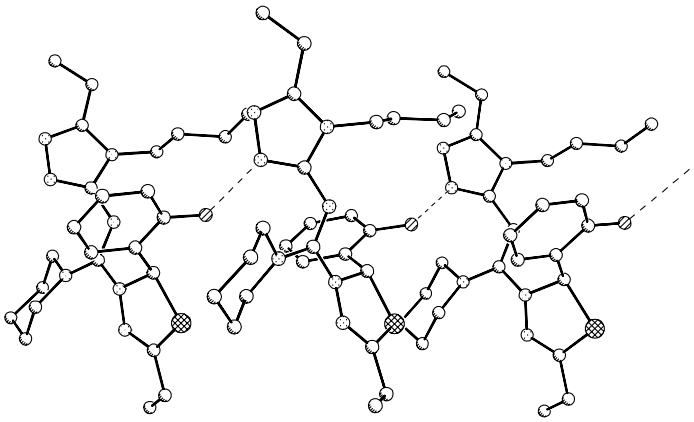


Figure 5. Crystal structure of **8i**, selected bond lengths [pm] and bond angles [deg]: N1–C11 138.7(2), N3–C11 138.7(2), N3–C11 130.6(2), N4–C11 135.5(2), N1–C1 147.9(2), S–C1 183.5(2), N3–C17 136.4(2), N2–C2 127.4(2); N3–C11–N1 115.00(16), N3–C11–N4 128.70(17), N4–C11–N1 116.26(25), N1–C1–C5 112.95(15), N1–C1–S 102.41(12).

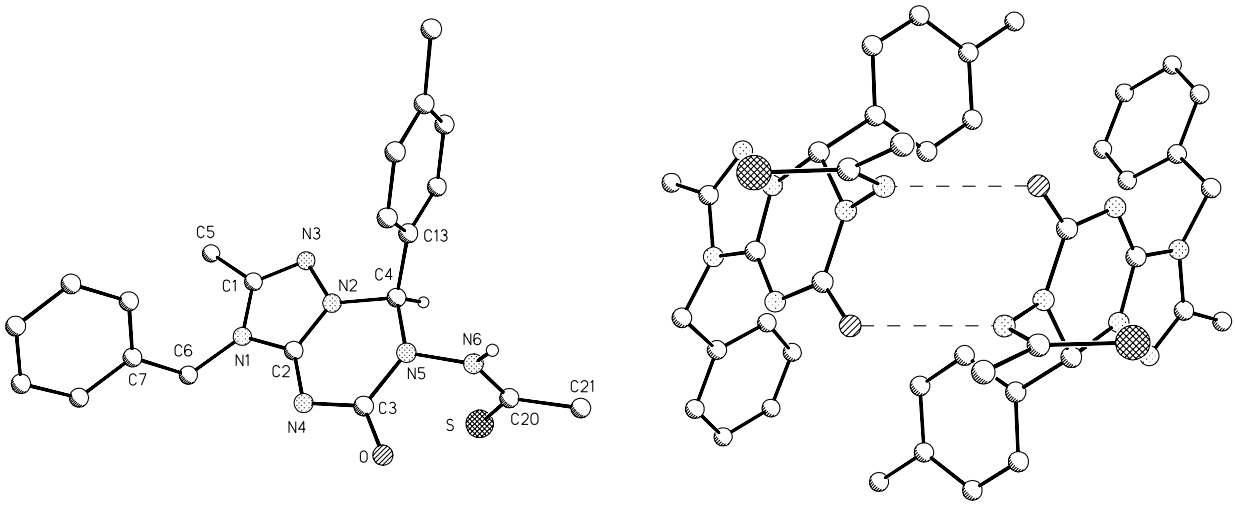
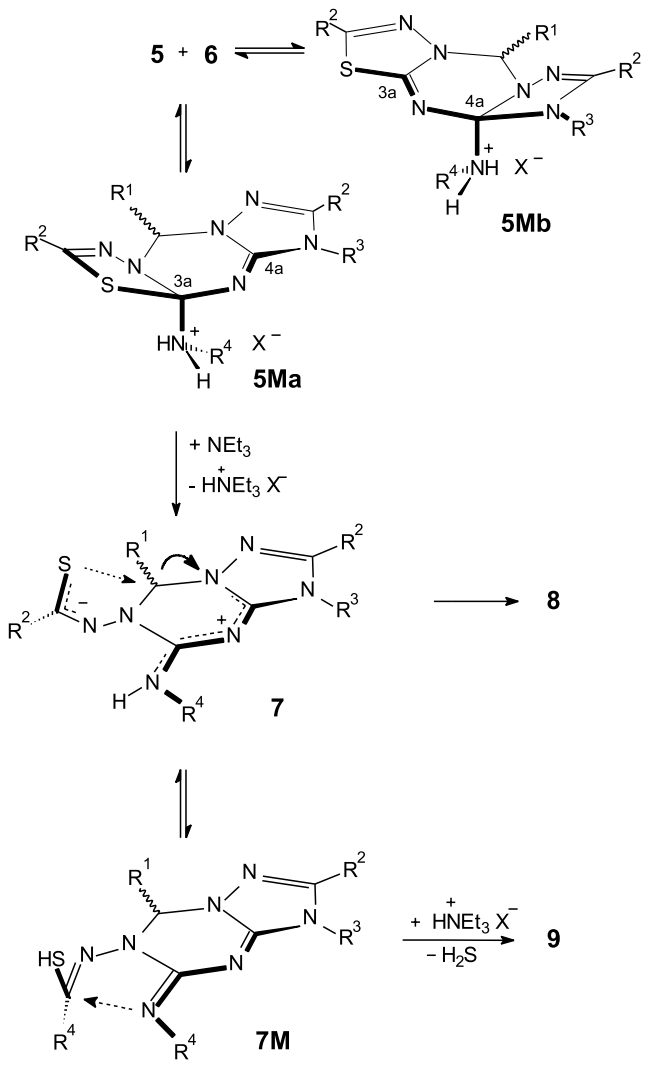


Figure 7. Crystal structure of **11c**, selected bond lengths [pm] and bond angles [deg]: O–C3 123.5(2), S–C20(2), C20–C21 148.8(3), N6–C20 134.3(3), N5–N6 139.3(2), N5–C3 140.6(3), N4–C3 136.2(3), N5–C4 146.9(3); N6–C20–S 123.34(17), N6–C20–C21 113.7(2), C21–C20–S 122.96(18), O–C3–N4 122.21(19), O–C3–N5 118.00(19), N4–C3–N5 119.72(18).



Scheme 3. Reaction pathways from **NNS** compound **5** to guanidines **8** and **NNN** compounds **9**.

6-311++G(d,p) calculations.[8,10] Here some further details (Scheme 3): The ring-closure/ring-opening steps are initiated by the nucleophilic attack of the amine **6** at the electrophilic C3a atom of **5** to give **5 Ma**. The conceivable competitive reaction path via the attack at the more positively charged C4a center (formation of **5Mb**) appears to be less favorable, presumably due to the smaller ring-opening tendency of the 1,2,4-triazole unit (i.e., fission of the C4a–N bond) compared with that of the 1,3,4-thiadiazole ring (fission of the C3a–S bond). Further, after the inexpensive cleavage of the latter, both the subsequent ring closure/ring-opening processes yielding the guanidines **8** and/or after the ring closure reactions to give the **NNN** cations **9** under extrusion of H_2S obviously do not have their counterparts for reactions paths which would start with the conceivable attack at the C4a position. Thus, at least under the condition applied, an intermediate such **5Mb** (Scheme 3) obviously is not suited to initiate an alternative reaction path. The two competing pathways **5Ma**→**7**→**8** and **7**→**7M**→**9** are most plausible from an energetic point of view.

3. Conclusions

We have developed novel syntheses for highly substituted guanidines **8** and so-called 5/6/5 tricyclic **NNN** compounds **9**. They can be obtained from easily accessible [1,3,4]-thiadiazolo[2,3-d][1,2,4]triazolo[1,5-a][1,3,5]triazinium hal ides **5** and amines **6** via zwitterionic intermediates **7**. Compounds **5** are of interest due to their potentially biological activities, their ability to act as ligands for a variety of metals, and as suitable precursors for further synthetic applications. The initial attack of the amines **6** occur at the C3a position of the fused **NNS** cation **5**. The consecutive reaction cascades can be classified as further novel examples for S_N(ANRORC) mechanisms. Triaznium-imidothioate zwitterions **7** have been isolated and X-rayed for the first time.

4. Experimental

4.1. General methods

All solvents were dried and distilled prior to use. Column chromatography: Fluka silicagel 60, 0.0036–0.2 mm (70–230 mesh ASTM), elution with EtOAc; pentane/EtOAc; Et_2O/EtOAc. Melting points: Büchi B-549 or Lindstrom copper block apparatus, IR: Nicolet Avatar 320 (KBr) or Nicolet Impact 400 (ATR), NMR: BRUKER DRX 400 and BRUKER AVANCE 250; NMR spectra were recorded at 250/400 MHz and 62.5/100 MHz for proton and carbon, respectively. For ^{1}H and ^{13}C, DMSO-d_6 (H, $\delta=2.49$ ppm; C, $\delta=39.5$ ppm) and $CDCl_3$ (H, $\delta=7.24$ ppm; C, $\delta=77.0$ ppm) were used as solvents, and TMS was used as internal standard, MS: SSQ 710. Finnigan MAT. Elemental analyses (C, H, N, S): Leco CHNS-932; halogens were determined by the Schöninger method through potentiometric titration. Compound **5a** has been described previously.[8] The amines **6a–6h** (VWR International; Merck) are commercially available and were purified by distillation (**6b** was used without further purification). Nomenclature of new compounds: IUPAC Naming On I-Lab Via ACD/ChemSketch (www.acdlabs.com).

4.2. General procedure for the preparation of NNN compounds 5

A solution of an amine **2** (51 mmol) in THF (20 mL) was added to a stirred suspension of **1** (25 mmol) in THF (400 mL) while cooling to −10 °C. After 0.5 h, a solution of methyliodide (3.55 g, 25 mmol) was added. The mixture was stirred another for half hour at −10 °C and afterwards warmed to 70–80 °C for 7 h. The precipitated compounds **5** were filtered off, washed with water and extracted with chloroform. After drying of the chloroform solution over $MgSO_4$, and concentration in vacuo, the solid crude product was purified by extraction with *t*-butyl methyl ether or petroleum ether (bp 40–70 °C).

4.2.1. 5-(4-Chlorobenzyl)-2,6-dimethyl-9-(4-methylphenyl)-5,9-dihydro[1,3,4]thiadiazolo[2,3-d][1,2,4]triazolo-[1,5-a][1,3,5]triazin-8-ium iodide (5b). Yield 98%; mp 137 °C. ^{1}H NMR ($CDCl_3$): $\delta=2.29$ (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 7.20–7.39 (m, 8H, CH_{phenyl}), 7.73 (s, 1H, sp^3CH). ^{13}C NMR ($CDCl_3$): $\delta=12.2$, 17.5, 21.5, 47.2, 79.4, 128.2, 2×129.6, 130.1, 130.2, 131.1, 135.1, 142.1, 148.4, 151.1, 157.0, 169.3. MS (DCI/H_2O), *m*/*z* (%): 423 (100) $[C_{21}H_{20}ClN_6S]^+$. **5b** perchlorate preparation from **5b** (137.7 mg), 4.5 ml MeOH and $Zn(ClO_4)_2$ (46 mg): mp 210 °C. Anal. calcd for $C_{21}C_{20}Cl_2N_6O_4S$ (523.39): C, 48.19; H, 3.85; Cl, 13.55; N, 16.06; O, 12.23; S, 6.13. Found: C, 47.92; H, 3.88; Cl, 13.16; N, 16.29; S, 5.98.

4.2.2. 5-Butyl-2,6-diethyl-9-(2-hydroxyphenyl)-5,9-dihydro[1,3,4]thiadiazolo[2,3-d][1,2,4]triazolo[1,5-a][1,3,5]-triazin-8-ium iodide (5c). Yield 92%; mp 221–223 °C. ^{1}H NMR (DMSO-d_6): $\delta=0.94$ (t, 3H, CH_3), 1.16 (m, 6H, 2×CH_3), 1.37 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 2.87 (m, 2H, CH_2), 2.92 (m, 2H, CH_2), 4.05 (m, 2H, CH_2), 6.85–7.66 (m, 4H, CH_{ph}), 7.80 (s, 1H, sp^3CH), 10.42 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): $\delta=12.5$, 2×13.5, 17.9, 19.0, 24.0, 30.2, 42.7, 76.3, 116.3, 119.1, 119.7, 132.8, 147.5, 154.2, 156.5, 162.4, 168.1. MS (FAB/dmba), *m*/*z* (%): 385 (100) $[C_{19}H_{25}N_6OS]^+$. **5c** perchlorate preparation from **5c** analogous to **5b**: mp 189 °C. Anal. calcd for $C_{19}H_{25}ClN_6O_5S$ (484.95): C, 47.06; H, 5.20; Cl, 7.31; N, 17.33; O, 16.50; S, 6.61. Found: C, 46.80; H, 5.78; Cl, 7.63; N, 17.50; S 6.61.

4.2.3. 5-Benzyl-2,6-diethyl-9-(2-hydroxyphenyl)-5,9-dihydro[1,3,4]thiadiazolo[2,3-d][1,2,4]triazolo[1,5-a][1,3,5]-triazin-8-ium iodide (5d). Yield 79%, mp 237 °C. ^{1}H NMR (DMSO-d_6): $\delta=0.95$ (t, 3H, CH_3), 1.14 (t, 3H, CH_2), 6.83–7.66 (m, 9H, CH_{ph}), 8.00 (s, 1H, sp^3CH), 10.39 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): $\delta=9.9$, 12.9, 18.5, 24.5, 46.0, 76.9, 116.8, 119.6, 120.1, 127.6, 128.9, 129.5, 132.0, 133.4, 134.3, 148.3, 154.8, 157.0, 163.1, 169.0. MS (DCI/H_2O), *m*/*z* (%): 419 (24) $[C_{22}H_{23}N_6OS]^+$. Anal. calcd for $C_{22}H_{23}IN_6OS$ (546.42): C, 48.36; H, 4.24; I, 23.22; N, 15.38; O, 2.93; S, 5.93. Found: C, 48.18; H, 4.06; I, 23.24; N, 15.38; S 5.67.

4.2.4. 5-(4-Chlorobenzyl)-2,6-dimethyl-9-(1-naphthyl)-5,9-dihydro[1,3,4]thiadiazolo[2,3-d][1,2,4]triazolo[1,5-a]-[1,3,5]triazin-8-ium iodide (5e). Yield 91%; mp 233–234 °C. ^{1}H NMR (DMSO-d_6): $\delta=2.31$ (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 5.31–5.46 (dd, 2H, CH_2), 7.48–8.21 (m, 11H, $CH_{ph,napht}$), 7.94 (s, br, 1H, sp^3CH). ^{13}C NMR (DMSO-d_6): $\delta=10.8$, 16.8, 45.5, 79.6, 121.5, 125.5, 126.6, 128.2, 129.0(3C), 129.7(3C), 132.7(2C), 133.4(2C), 147.8, 151.3, 158.5, 169.2. MS (FAB/dmba), *m*/*z* (%): 459 (100) $[C_{24}H_{20}ClN_6S]^+$. Anal. calcd for $C_{24}H_{20}ClIN_6S$ (586.88): C, 49.12; H, 3.43; Cl, 6.04; I, 21.62; N, 14.32; S, 5.46. Found: C, 48.85; H, 3.21; N, 14.19; S, 5.36.

4.3. General preparation of zwitterions 7

A solution of *n*-butylamine **6c** (0.15 mL, 1.5 mmol) in triethylamine (5 mL) was gradually added to a stirred solution of **5** (1.25 mmol) in chloroform (10 mL) at −10 °C. Firstly, the mixture was stirred 2 h at −10 °C and afterwards 1 h at 0–5 °C. The solvent was evaporated in the cold and the residue was washed with ice water. The solid precipitate was filtered off and dried in vacuo at room temperature.

4.3.1. *N*-[3-Benzyl-5-(butylamino)-2-methyl-7-(4-methylphenyl)-3,7-dihydro-6*H*-[1,2,4]triazolo[1,5-a]-[1,3,5]triazin-8-ium-6-yl]ethanimidothioate (7c). Yield 90%; mp 102 °C. IR (KBr) $\nu=1601$ cm^{-1} (C=N, exocyclic). ^{1}H NMR ($CDCl_3$; 263 K): $\delta=0.94$ (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.01 (m, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.43 (s, br, 1H, NH), 6.97–7.52 (m, 9H, CH_{ph}), 8.14 (s, 1H, sp^3CH). ^{13}C NMR ($CDCl_3$): $\delta=11.6$, 13.9, 20.1, 21.4, 32.5, 32.9, 40.8, 46.2, 70.3, 126.8, 127.9, 129.4, 129.7, 133.3, 133.5, 140.0, 148.1, 149.4, 153.7, 155.8, 194.9. MS (DCI/H_2O), *m*/*z* (%) 462 (100) $[C_{25}H_{32}N_7S]^+$. Anal. calcd for $C_{25}H_{31}N_7S$ (461.62): C, 65.05; H, 6.77; N, 21.24; S, 6.94. Found: C, 65.25; H, 7.03; N, 21.41; S 6.76.

4.3.2. *N*-[3-(4-Chlorobenzyl)-5-butylamino-2-methyl-7-(4-mehylphenyl)-3,7-dihydro-6*H*-[1,2,4]triazolo[1,5-a]-[1,3,5]triazin-8-ium-6-yl]ethanimidothioate (7h). Yield

79%; mp 138 °C. IR (KBr) $\nu = 1604\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 0.89$ (t, 3H, CH_3), 1.30 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.37 (m, 2H, CH_2), 4.99 (s, 2H, CH_2), 6.40 (s, br, 1H, NH), 7.11–7.34 (m, 8H, CH_{ph}), 8.17 (s, 1H, sp^3CH). ^{13}C NMR ($CDCl_3$): $\delta = 11.6$, 13.9, 20.0, 21.4, 33.0, 31.7, 41.1, 45.5, 70.2, 124.7, 126.6, 129.3, 129.6, 131.8, 132.8, 135.0, 140.3, 147.8, 149.3, 153.6, 194.9. MS (DCI/H_2O), *m/z* (%) 496 $[C_{25}H_{31}ClN_7S]^+$. Anal. calcd for $C_{25}H_{30}ClN_7S$ (496.07): C; 60.53; H, 6.10; Cl, 7.15; N, 19.76; S 6.46. Found: C, 59.97; H, 6.57; Cl, 7.21; N, 19.43; S 6.28.

4.3.3. *N*-[3-Butyl-5-butylamino-2-ethyl-7-(2-hydroxyphenyl)-3,7-dihydro-6*H*-[1,2,4]triazolo[1,5-a][1,3,5]triazin-8-ium-6-yl]propanimidothioate (7k). Yield 98%; mp 160 °C. IR (KBr) $\nu = 1616\ cm^{-1}$ (C=N, exocyclic). ^1H NMR (CD_3OD, 263 K): $\delta = 0.95$ (t, 3H, CH_3), 1.02 (t, 3H, CH_3), 1.10 (t, 3H, CH_3), 1.23 (t, 3H, CH_3), 1.36–1.46 (m, 4H, $2\times CH_2$), 1.58 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 2.38–2.50 (2m, 2H, CH_2), 2.70 (m, 2H, CH_2), 3.29–3.51 (2m, 2H, CH_2), 3.95 (m, 2H, CH_2), 6.72–7.41 (m, 4H, CH_{ph}), 7.57 (s, 1H, sp^3CH). ^{13}C NMR (CD_3OD, 263 K): $\delta = 8.8$, 12.7, 12.9, 13.9, 17.9, 19.3, 19.5, 30.4, 32.0, 37.8, 40.2, 41.6, 70.3, 115.4, 118.3, 121.4, 130.8, 131.1, 150.0, 152.0, 153.4, 156.4, 200.8. MS (DCI/H_2O), *m/z* (%): 458 (41) $[C_{23}H_{36}N_7OS]^+$. Anal. calcd for $C_{23}H_{35}N_7OS$ (457.63): C, 60.37; H, 7.71; N, 21.42; O, 3.50; S, 7.01. Found C, 59.37; H, 7.91; N, 21.23; S 6.69.

4.3.4. *N*-[3-(4-Chlorobenzyl)-5-(butylamino)-2-methyl-7-(1-naphthyl)-3,7-dihydro-6*H*[1,2,4]triazolo[1,5-a][1,3,5]-triazin-8-ium-6-yl]ethanimidothioate (7q). Yield 86% (preparation in MeCN instead of $CHCl_3$); mp 122 °C. IR (KBr) $\nu = 1604\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$, 263 K): $\delta = 0.89$ (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 4.01 (m, 2H, CH_2), 4.95–5.10 (dd, 2H, CH_2), 6.68 (s, br, 1H, NH), 6.35–7.86 (m, 11H, $CH_{ph,naphthyl}$), 8.77 (s, 1H, sp^3CH). ^{13}C NMR ($CDCl_3$, 263 K): $\delta = 11.4$, 13.9, 19.9, 31.8, 32.7, 41.1, 45.6, 64.2, 123.1, 125.2, 125.6, 126.3, 126.5, 127.2, 128.3, 128.6, 128.7, 129.4, 129.6, 131.0, 132.0, 135.0, 147.8, 149.7, 153.2, 197.5. MS (DCI/H_2O), *m/z* (%): 532 (25) $[C_{28}H_{31}ClN_7S]^+$. Anal. calcd for $C_{28}H_{30}CLN_7S$ (532.10): C, 63.20; H, 5.68; Cl, 6.66; N, 18.43; S 6.03. Found: C, 62.98; H, 5.94; Cl, 6.41; N, 18.56; S 6.30.

4.4. General procedure for reactions between NNS compounds 5 with amines 6

To a well-stirred solution/suspension of the corresponding **NNS** compound **5** (5 mmol) in $CHCl_3$ (30 mL) the amine **6** (10.1 mmol) [synthesis variant (SV) A] resp, a solution of amine **6** (5 mmol) in triethylamine (30 mL) [synthesis variant (SV) B] was gradually added at ambient temperature. After stirring over a period of 24 h, the resulting solution/suspension was concentrated in vacuo. The residue was washed with cold water and extracted three times with $CHCl_3$. The combined extracts were dried with $MgSO_4$ and concentrated in vacuo, and the residues, which in the most cases are mixtures of the products **8** and **9** were subjected to column chromatography (vide supra) or fractional crystallization from EtOH, MeCN, EtOAc, *t*-butyl methyl ether.

4.4.1. *N*-{[2-(4-Methylphenyl)-5-methyl-1,3,4-thiazol-3(2*H*)-yl](piperidin-1-yl)methylene}-4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-amine (8a), (SV A). Yield 95%; mp 74 °C. IR (ATR) $\nu = 1569\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 1.46$ (m, 2H, $CH_{2(pip)}$), 1.54 (m, 4H, $CH_{2(pip)}$), 2.18 (s, 6H, $2\times CH_3$), 2.25 (s, 3H, CH_3), 3.08 (m, 4H, $CH_{2(pip)}$), 4.51 (dd, 2H, $CH_{2(benzyl)}$), 6.91–7.32 (m, 9H, CH_{ph}), 6.97 (s, 1H, $CH_{thiadiazole}$). ^{13}C NMR ($CDCl_3$): $\delta =$ 11.6, 16.8, 21.1, 24.3, 15.5, 45.3, 49.6, 72.7, 125.9, 126.9, 127.4, 128.4, 129.9, 136.5, 137.9, 138.0, 146.1, 147.7, 153.4, 155.2. MS (DCI/H_2O), *m/z* (%): 474 (100) $[C_{26}H_{32}N_7S]^+$. Anal. calcd for $C_{26}H_{31}N_7S$ (473.63): C, 65.93; H, 6.60; N, 20.70; S, 6.77. Found: C; 66.05; H, 7.07; N, 20.86; S, 6.64.

4.4.2. 1,4-Bis-{[(4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)imino][2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methyl}piperazine (8b), (SV B). Yield 64%; mp 212 °C. IR (KBr) $\nu = 1595\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 2.18$ (s, 6H, CH_3), 2.20 (s, 6H, CH_3), 2.28 (s, 6H, CH_3), 3.12–3.31 (m, 8H, $CH_{2(pipa)}$), 4.46–4.61 (dd, 4H, $CH_{2(benzyl)}$), 6.91–7.26 (m, 18H, CH_{ph}), 7.02 (s, 1H, $CH_{thiadiazole}$). ^{13}C NMR ($CDCl_3$): $\delta = 11.6$, 16.8, 21.2, 45.4, 48.1, 72.4, 126.1, 126.9, 127.5, 128.5, 129.3, 136.3, 137.3, 138.3, 146.7, 148.0, 152.4, 154.8. MS (DCI/H_2O), *m/z* (%): 863 (3) $[C_{46}H_{51}N_{14}S_2]^+$. Anal. calcd for $C_{46}H_{50}N_{14}S_2$ (863.11): C, 64.01; H, 5.84; N, 22.72; S, 7.43. Found: C; 63.92; H, 6.12; N, 22.72; S, 7.84.

4.4.3. *N*-Butyl-2-(4-methylphenyl)-*N*′-(4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)-5-methyl-1,3,4-thiadiazole-3(2*H*)-carboximidamide (8c), (SV A). Yield 25% (determined by ^1H NMR analysis of the mixture **8c/9c**). Mp 74 °C. IR (KBr) $\nu = 1633\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 0.87$ (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.51 (m, 2H, CH_2), 4.52–4.75 (dd, 2H, $CH_{2(benzyl)}$), 6.91–7.21 (m, 9H, CH_{ph}), 7.16 (s, 1H, $CH_{thiadiazole}$), 8.96 (s, broad, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta = 11.4$, 13.9, 16.8, 20.1, 21.1, 32.6, 44.9, 45.1, 72.9, 125.7, 126.8, 127.4, 128.0, 129.3, 136.3, 137.9, 138.5 145.1, 147.6, 153.6, 157.1. MS (DCI/H_2O), *m/z* (%): 462 (100) $[C_{25}H_{32}N_7S]^+$. Anal. calcd for $C_{25}H_{31}N_7S$ (461.6): C, 65.05; H, 6.77; N, 21.24; S, 6.94. Found: C, 64.68; H, 6.95; N, 20.87; S, 6.95.

4.4.4. *N*-Benzyl-2-(4-methylphenyl)-*N*′-(4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)-5-methyl-1,3,4-thiadiazole-3(2*H*)-carboximidamide (8d), (SV B). Yield 13% (determined from the mixture **8d/9d** by extract of the raw product with *t*-Bu-Me-ether and following column chromatography); mp 67 °C. IR (KBr) $\nu = 1630\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 2.15$ (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.58–4.80 (ddd, 2H, $CH_{2(benzyl)}$), 4.92–5.03 (dd, 2H, $CH_{2(benzyl)}$), 6.81–7.34 (m, 14H, CH_{ph}), 7.35 (s, 1H, $CH_{thiadiazole}$), 9.57 (s, broad, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta = 11.4$, 16.6, 21.1, 45.0, 48.6, 72.9, 126.6, 126.8, 127.5, 128.0, 128.3, 128.9, 128.9, 129.2, 135.4, 136.1, 137.7, 139.6, 145.5, 147.9, 153.3, 156.9. MS (FAB/dmba), *m/z* (%): 496 (100) $[C_{28}H_{30}N_7S]^+$. Anal. calcd for $C_{28}H_{29}N_7S$ (495.6): C, 67.85; H, 5.90; N, 19.78; S, 6.47. Found C, 68.06; H, 5.88; N, 19.48; S, 6.64.

4.4.5. *N*-(4-Methylphenyl)-2-(4-methylphenyl)-*N′*-(4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)-5-methyl-1,3,4-thiadiazole-3(2*H*)-carboximidamid (8e), (SV B with modified general procedure: 40 h at 60 °C, only 53% conversion). Yield 76%; mp 168 °C. IR (KBr) $\nu=$ 1633 cm^{-1} (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta=$ 2.08 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 4.58–4.95 (dd, 2H, CH_2), 7.09 (s, 1H, sp^3CH), 6.92–7.34 (m, 13H, CH_{ph}). ^{13}C NMR ($CDCl_3$): $\delta=$11.3, 16.6, 20.9, 21.2, 45.1, 73.0, 122.8, 125.9, 126.9 127.5, 128.6, 128.9, 129.3, 133.3, 136.0, 137.4, 138.1, 138.2, 145.9, 148.0, 150.6, 156.6. MS (DCI/H_2O), *m/z* (%): 496 (45) $[C_{28}H_{30}N_7S]^+$. Anal. calcd for $C_{28}H_{29}N_7S$ (495.64): C, 67.85; H, 5.90; N, 19.78; S, 6.47. Found: C, 68.02; H, 6.18; N, 19.55; S, 6.25.

4.4.6. *N*-{[2-(4-Methylphenyl)-5-methyl-1,3,4-thiazol-3(2*H*)-yl](piperidin-1-yl)methylene}-4-chlorobenzyl-5-methyl-4*H*-1,2,4-triazol-3-amine (8f), (SV A). Yield 59%, mp 138 °C. IR (KBr) $\nu=$1595 cm^{-1} (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta=$1.28 (br, 6H, $CH_{2(pip)}$), 2.23 (s, 6H, 2× CH_3), 2.31 (s, 3H, CH_3), 3.16 (m, 4H, $CH_{2(pip)}$), 4.55 (s, 2H, $CH_{2(benzyl)}$), 6.86–7.24 (m, 8H, CH_{ph}), 7.05 (s, 1H, $CH_{thiadiazole}$). ^{13}C NMR ($CDCl_3$): $\delta=$11.6, 16.9, 21.2, 24.3, 25.6, 44.7, 49.6, 72.7, 125.8, 128.4, 128.6, 129.2, 133.3, 135.0, 138.0, 138.1, 146.2, 147.5, 153.5, 155.3. MS (DCI/H_2O), *m/z* (%): 508 (100) $[C_{26}H_{31}ClN_7S]^+$. Anal. calcd for $C_{26}H_{30}ClN_7S\times1H_2O$ (526.09): C; 59.36; H, 6.13; Cl, 6.74; N, 18.64; O, 3.04; S, 6.09. Found: C, 59.56; H, 6.63; Cl, 7.01; N, 18.89; S, 5.91.

4.4.7. 1,4-Bis-{[(4-Chlorobenzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)imino][2*H*-2-(4-methylphenyl)-5-methyl-1,3,4-thiadiazol-3-yl]methyl}piperazine (8g), (SV A with 5.05 mmol 6b). Yield 84%; mp 202-204 °C. IR (KBr) $\nu=$ 1595 cm^{-1} (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta=$2.21 (s, 6H, CH_3), 2.22 (s, 6H, CH_3), 2.31 (s, 6H, CH_3), 3.34–3.42 (m, 8H, CH_2), 4.45–4.59 (dd, 4H, CH_2), 6.83–7.06 (m, 16H, CH_{ph}), 7.39 (s, 2H, sp^3CH). ^{13}C NMR ($CDCl_3$): $\delta=$ 11.6, 16.8, 21.2, 44.7, 48.2, 72.4, 125.8, 128.3, 129.3, 129.7, 133.6, 134.9, 137.2, 138.4, 146.8, 147.8, 152.5, 154.8. MS (FAB/dmab), *m/z* (%): 931 (31) $[C_{46}H_{49}Cl_2N_{14}S_2]^+$. Anal. calcd for $C_{46}H_{48}Cl_2N_{14}S_2$ (932.00): C, 59.28; H, 5.19; Cl, 7.61; N, 21.04; S, 6.88. Found C, 59.02; H, 5.28; Cl, 7.52; N, 20.93; S, 6.52.

4.4.8. *N*-Butyl-2-(4-methylphenyl)-*N′*-(4-chlorobenzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)-5-methyl-1,3,4-thiadiazole-3(2*H*)-carboximidamid (8h), (SV A). Yield 12% (determined by ^1H NMR analysis of the mixture **8h/9h**), plastic compound. IR (KBr) $\nu=$1630 cm^{-1} (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta=$0.97 (t, 3H, CH_3), 1.44 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 2.14 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.62 (m, 2H, CH_2), 4.50–4.83 (dd, 2H, $CH_{2(benzyl)}$), 6.75–7.18 (m, 8H, CH_{ph}), 7.38 (s, 1H, sp^3CH), 9.06 (s, br, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta=$11.3, 13.9, 16.8, 20.1, 121.1, 32.6, 44.3, 45.1, 72.9, 125.5, 126.8, 128.1, 129.3, 133.2, 134.4, 138.0, 138.5, 145.2, 147.4, 157.1. MS (DCI/H_2O), *m/z* (%): 496 (60) $[C_{25}H_{31}ClN_7S]^+$. Anal. calcd for $C_{25}H_{30}ClN_7S$ (496.07): C, 60.53; H, 6.10; Cl, 7.15; N, 19.76; S, 6.46. Found C, 60.68; H, 5.98; Cl, 6.81; N, 19.48; S, 6.59.

4.4.9. *N*-{[5-Ethyl-2-(2-hydroxyphenyl)-1,3,4-thiazol-3(2*H*)-yl](piperidin-1-yl)methylene}-4-butyl-5-ethyl-4*H*-1,2,4-triazol-3-amine (8i), (SV A). Yield 93%; mp 161 °C; crystals for Xray from aqueous MeOH. IR (KBr) $\nu=$ 1584 cm^{-1} (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta=$0.88 (t, 3H, CH_3), 1.15 (t, 3H, CH_3), 1.29 (m, 2H, CH_2), 1.32 (t, 3H, CH_3), 1.52 (m, 8H, CH_2), 2.42 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 3.54 (m, 4H, CH_2), 3.80 (m, 2H, CH_2), 7.07 (s, 1H, sp^3CH), 6.77–7.23 (m, 4H, CH_{ph}), 9.94 (s, br, 1H, OH). ^{13}C NMR ($CDCl_3$): $\delta=$11.6, 2×13.5, 18.9, 19.9, 24.4, 24.6, 25.5, 31.3, 42.1, 49.7, 68.9, 117.5, 118.8, 119.8, 126.6, 129.5, 2×150.2, 152.0, 154.5, 156.2. MS (DCI/H_2O), *m/z* (%): 470 (23) $[C_{24}H_{36}N_7OS]^+$. Anal. calcd for $C_{24}H_{35}N_7OS$ (469.64): C, 61.38; H, 7.51; N, 20.88; O, 3.41; S, 6.83. Found, C, 61.02; H, 7.72; N, 20.92; S, 6.59.

4.4.10. 1,4-Bis-{[(4-butyl-5-ethyl-4*H*-1,2,4-triazol-3-yl)-imino][2*H*-2-(2-hydroxyphenyl)-5-ethyl-1,3,4-thiadiazol-3-yl]methyl}piperazine (8j), (SV A with 5.05 mmol 6b). Yield 75% (mixture of diastereomers, not exactly separable because of insufficient solubility in organic solvents); mp 158 °C. IR (KBr) $\nu=$1598, 1576 cm^{-1} (C=N, exocyclic). NMR not possible in solution. MS (FAB, dmab), *m/z* (%): 855 (16) $[C_{42}H_{59}N_{14}O_2S_2]^+$. Anal. calcd for $C_{42}H_{58}N_{14}O_2S_2\times H_2O$ (873.15): C, 57.77; H, 6.93; N, 22.46; O, 5.50; S, 7.34. Found: C, 58.11; H, 7.74; N, 22.74; S, 7.04.

4.4.11. *N*-Butyl-2-(2-hydroxyphenyl)-*N′*-(4-butyl-5-ethyl-4*H*-1,2,4-triazol-3-yl)-5-ethyl-1,3,4-thiadiazole-3(2*H*)-carboximidamide (8k), (SV A). Yield 43% (determined from the mixture **8k/9k** by extract of the raw product with EtOAc); mp 175 °C. IR (KBr) $\nu=$1634 cm^{-1} (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta=$0.80 (t, 3H, CH_3), 0.94 (t, 3H, CH_3), 1.26–1.42 (m, 12H, 2×CH_3; 3×CH_2), 1.67 (m, 2H, CH_2), 2.55–2.65 (m, 4H, CH_2), 3.54–3.70 (m, 4H, CH_2), 6.79–7.25 (m, 4H, CH_{ph}), 7.51 (s, 1H, sp^3CH), 8.89 (s, br, 1H, NH), 10.67 (s, br, 1H, OH). ^{13}C NMR ($CDCl_3$): $\delta=$11.3, 11.8, 2×13.8, 2×18.8, 19.8, 24.8, 31.5, 31.5, 32.5, 41.9, 45.3, 67.1, 116.6, 119.4, 126.3, 127.3, 129.2, 151.8, 153.5, 153.8, 154.0, 156.6. MS (DCI/H_2O), *m/z* (%): 458 (100) $[C_{23}H_{36}N_7OS]^+$. Anal. calcd for $C_{23}H_{35}N_7OS$ (457.63): C, 60.37; H, 7.71; N, 21.42; O, 3.50; S, 7.01. Found: C, 60.04; H, 8.24; N, 21.69; S, 6.71.

4.4.12. 1,4-Bis-{[(4-benzyl-5-ethyl-4*H*-1,2,4-triazol-3-yl)imino][2*H*-2-(2-hydroxyphenyl)-5-ethyl-1,3,4-thiadiazol-3-yl]methyl}piperazine (8m), (SV B with 2.51 mmol 6b). Yield 90%; mp 137–141 °C, 164 °C (mixture of diastereomers). IR (KBr) $\nu=$1596, 1564 cm^{-1} (C=N, exocyclic). ^1H NMR (DMSO): $\delta=$1.00–1.11 (m, 12H, CH_3), 2.44–2.80 (m, 8H, CH_2), 3.08–3.19 (m, 8H, CH_2), 4.55 (dd, 4H, CH_2), 7.16 (s, 2H, sp^3CH), 7.00–7.46 (m, 18H, CH_{ph}). ^{13}C NMR ($CDCl_3$): $\delta=$11.4, 11.9, 18.6, 24.5, 44.6, 48.2, 66.9, 115.8, 119.4, 126.0, 127.1, 128.0, 128.8, 129.1, 129.6, 137.4, 1151.8, 153.3, 153.7, 154.0, 155.0. MS (FAB/dmab), *m/z* (%): 923 (9) $[C_{48}H_{55}N_{14}O_2S_2]^+$. Anal. calcd for $C_{48}H_{54}N_{14}O_2S_2\times H_2O$ (941.18): C, 61.26; H, 6.00; N, 20.83; O, 5.10; S, 6.81. Found: C, 61.40; H, 6.06; N, 20.93; S, 6.37.

4.4.13. *N*-(Cyclohexyl)-2-(2-hydroxyphenyl)-*N′*-(4-benzyl-5-ethyl-4*H*-1,2,4-triazol-3-yl)-5-ethyl-1,3,4-thiadiazole-3(2*H*)-carboximidamide (8o), (SV B). Yield 52%; mp

203 °C. IR (KBr) $\nu = 1618\ cm^{-1}$ (C=N, exocyclic). ^1H NMR (DMSO): $\delta = 1.05$ (t, 3H, CH_3), 1.18 (t, 3H, CH_3), 1.16–2.06 (m, 10H, $CH_{2\ cyclohexyl}$), 2.44 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 4.18 (1H br, $CH_{cyclohexyl}$), 4.61–4.75 (dd, 2H, CH_2), 6.72–7.20 (m, 9H, CH_{ph}), 7.40 (s, 1H, sp^3CH), 9.20 (s br, 1H, NH), 9.93 (s br, 1H, OH). ^{13}C NMR (DMSO): $\delta =$ 11.7, 11.4, 18.1, 24.1, 25.1, 33.6, 34.0, 43.8, 52.6, 66.3, 115.1, 119.1, 124.7, 127.2, 127.4, 128.3, 128.7, 136.9, 147.8, 150.9, 151.4, 152.3, 153.0, 156.2. MS (DCI/H_2O), *m/z* (%): 519 (100) $[C_{28}H_{35}N_7OS]^+$. Anal. calcd for $C_{28}H_{35}N_7OS$ (517.69): C, 64.96; H, 6.81; N, 18.94; O, 3.09; S, 6.19. Found: C, 64.59; H, 7.32; N, 18.95; S, 5.96.

4.4.14. *N*-{[5-Methyl-2-(1-naphthyl)-1,3,4-thiazol-3(2*H*)-yl](piperidin-1-yl)methylene}-4-(4-chlorobenzyl)-5-methyl-4*H*-1,2,4-triazol-3-amine (8p), (SV A). Yield 90%; mp 161 °C. IR (KBr) $\nu = 1574\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 1.28$ (s, 6H, $CH_{2(pip)}$), 2.07 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.27 (m, 4H, $CH_{2(pip)}$), 6.51–6.75 (m, 4H, CH_{ph}), 7.40–7.89 (m, 7H, CH_{naph}), 7.67 (s, 1H, sp^3CH). ^{13}C NMR ($CDCl_3$): $\delta = 11.5$, 17.1, 24.3, 25.7, 44.4, 49.9, 70.1, 122.3, 123.0, 125.4, 125.9, 126.6, 128.0, 128.3, 128.6, 128.9, 129.0, 133.1, 133.8, 124.2, 135.4, 147.5, 147.9, 153.2, 155.2. MS (DCI/H_2O), *m/z* (%): 544 (16) $[C_{29}H_{31}ClN_7S]^+$. Anal. calcd for $C_{29}H_{30}ClN_7S$ (544.11): C, 64.02; H, 5.56; Cl, 6.52; N, 18.02; S, 5.89. Found: C, 63.93; H, 5.99; Cl, 6.90; N, 17.86; S, 5.62.

4.4.15. *N*-Butyl-2-(1-naphthyl)-*N′*-[4-(4-chlorobenzyl)-5-methyl-4*H*-1,2,4-triazol-3-yl]-5-methyl-1,3,4-thiadiazole-3(2*H*)-carboximidamide (8q), (SV A). Yield 23%; (simultaneous with 34% zwitterion **7q** and 43% **NNN 9q**, separated by column chromatography); mp 117 °C. IR (KBr) $\nu = 1604\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 0.92$ (t, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 1.94 (s, 3H, CH_3), 2.16 (s, 2H, CH_3), 3.65 (m, 2H, CH_2), 3.89–4.28 (dd, 2H, CH_2), 6.18–6.90 (m, 4H, CH_{ph}), 7.19 (s, 1H, sp^3CH), 7.28–7.93 (m, 7H, CH_{naph}), 8.95 (s, br, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta = 11.1$, 13.9, 17.0, 20.2, 32.7, 43.8, 45.2, 69.8, 121.9, 122.8, 125.7, 126.4, 127.2, 128.4, 128.6, 129.0, 129.1, 129.3, 132.7, 133.7, 134.2, 136.4, 146.1, 147.3, 153.4, 156.9. MS (DCI/H_2O), *m/z* (%): 532 (10) $[C_{28}H_{31}ClN_7S]^+$. Anal. calcd for $C_{28}H_{30}ClN_7S$ (532.10): C, 63.20; H, 5.68; Cl, 6.66; N, 18.43; S, 6.03. Found: C, 62.95; H; 5.98; Cl, 6.76; N, 18.68; S, 6.42.

4.4.16. *N*-Benzyl-2-(2-hydroxyphenyl)-*N′*-(4-butyl-5-ethyl-4*H*-1,2,4-triazol-3-yl)-5-ethyl-1,3,4-thiadiazole-3(2*H*)-carboximidamide (8r), (SV B). Yield 41%; (determined by ^1H NMR analysis of the mixture **8r/9r**); mp 166 °C; crystals for X-ray from aqueous MeOH. IR (KBr) $\nu = 1626\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta =$ 0.75 (t, 3H, CH_3), 1.07 (m, 2H, CH_2), 1.19–1.37 (m, 8H, 2× CH_3, 1×CH_2), 2.49–2.65 (m, 4H, CH_2), 3.49–3.56 (m, 2H, CH_2), 4.73–4.92 (dd, 2H, CH_2), 6.22–7.32 (m, 9H, CH_{ph}) 7.51 (s, 1H, sp^3CH), 9.21 (s br, 1H, NH), 10.50 (s br, 1H, OH). ^{13}C NMR ($CDCl_3$): $\delta = 11.3$, 11.9, 13.8, 18.8, 19.8, 24.7, 31.5, 41.9, 48.7, 66.9, 116.3, 119.3, 126.0, 127.0, 127.3, 127.4, 128.4, 129.0 139.3, 151.9, 153.1, 153.9, 154.0, 156.4. MS (DCI/H_2O), *m/z* (%): 492 (42) $[C_{26}H_{34}N_7OS]^+$. Anal. calcd for $C_{26}H_{33}N_7OS$ (491.65): C, 63.52; H, 6.77; N, 19.94; O, 3.25; S, 6.52. Found: C, 63.03; H, 7.09; N, 20.31; S, 6.36.

4.4.17. *N*-(4-Methoxyphenyl)-2-(4-methylphenyl)-*N′*-(4-benzyl-5-methyl-4*H*-1,2,4-triazol-3-yl)-5-methyl-1,3,4-thiadiazole-3(2*H*)-carboximidamid (8s), (SV B). Yield 25%; mp 63 °C. IR (KBr) $\nu = 1627\ cm^{-1}$ (C=N, exocyclic). ^1H NMR ($CDCl_3$): $\delta = 1.92$ (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.55–4.76 (dd, 2H, CH_2), 6.71–7.19 (m, 13H, CH_{ph}), 7.22 (s, 1H, sp^3CH), 10.39 (s, br, 1H, NH). ^{13}C NMR ($CDCl_3$): $\delta = 11.3$, 16.6, 21.2, 45.2, 55.5, 72.9, 113.6, 124.6, 125.9, 126.9, 127.5, 128.4, 128.6, 129.4, 133.0, 135.8, 138.2, 138.3, 146.2, 147.9, 151.0, 156.5. MS (DCI/H_2O), *m/z* (%): 512 (9) $[C_{28}H_{30}N_7OS]^+$. Anal. calcd for $C_{28}H_{29}N_7OS$ (511.64): C, 65.73; H, 5.71; N, 19.16; O, 3.13; S, 6.27. Found: C, 65.42; H, 6.08; N, 18.95; S, 6.42.

4.4.18. 5-Benzyl-3-butyl-2,6-dimethyl-9-(4-methylphenyl)-3*H*,5*H*,9*H*-di[1,2,4]-triazolo[1,5-a:1′,5′-d][1,3,5]triazin-8-ium iodide (9c). Yield 75%; (determined by ^1H NMR analysis of the mixture **8c/9c**), mp 248 °C. ^1H NMR ($CDCl_3$): $\delta = 0.99$ (t, 3H, CH_3), 1.41 (m, 2H, CH_2), 1.78 (m, 2H, CH_2), 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.06 (t, 2H, CH_2), 5.32 (dd, 2H, $CH_{2(benzyl)}$), 7.27–7.42 (m, 9H, CH_{ph}), 7.49 (s, 1H, $sp^3CH_{triazinium}$). ^{13}C NMR ($CDCl_3$): $\delta = 11.6$, 12.1, 13.6, 19.9, 21.4, 44.0, 47.5, 77.2, 128.0, 128.2, 128.9, 129.3, 129.6, 130.2, 133.3, 133.3, 141.8, 149.9, 150.4, 150.7, 150.9. MS (DCI/H_2O), *m/z* (%): 428 (41) $[C_{25}H_{30}N_7]^+$. Anal. calcd for $C_{25}H_{30}IN_7$ (555.46): C, 54.06; H, 5.44; I, 22.85; N, 17.65. Found: C, 54.04; H, 5.64; I, 22.97; N, 17.78.

4.4.19. 5-Benzyl-3,9-di-(4-methylphenyl)-2,6-dimethyl-3*H*,5*H*,9*H*-di[1,2,4]-triazolo[1,5-a:1′,5′-d][1,3,5]triazin-8-ium iodide (9e), (modified reaction condition: 40 h at 60 °C, only 53% conversion). Yield 8%; mp 139 °C. IR (KBr) $\nu = 1587\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 2.26$ (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 7.32–7.58 (13H, CH_{ph}), 7.71 (s, 1H, $sp^3CH_{triazinium}$). ^{13}C NMR ($CDCl_3$): $\delta = 11.9$, 12.0, 21.4, 21.5, 47.2, 77.8, 126.9, 127.7, 127.8, 127.9, 128.5, 128.8, 129.2, 129.8, 130.2, 130.7, 133.1, 141.1, 141.8, 149.8, 150.2, 151.4. MS (DCI/H_2O), *m/z* (%): 462 (44) $[C_{28}H_{28}N_7]^+$. Anal. calcd for $C_{28}H_{28}IN_7$ (589.48): C, 57.05; H, 4.79; I, 21.53; N, 16.63. Found: C, 56.99; H, 5.06; I, 22.19; N, 17.05.

4.4.20. 3-Butyl-5-(4-chlorobenzyl)-2,6-dimethyl-9-(4-methylphenyl)-3*H*,5*H*,9*H*-di[1,2,4]-triazolo[1,5-a:1′,5′-d]-[1,3,5]triazin-8-ium iodide (9h). Yield 88% (determined by ^1H NMR analysis of the mixture **8h/9h**); mp 175 °C; IR (KBr) $\nu = 1560\ cm^{-1}$. ^1H NMR ($CDCl_3$): $\delta = 0.98$ (t, 3H, CH_3), 1.43 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 7.29–7.47 (m 8H, CH_{ph}), 7.52 (s, 1H, $sp^3CH_{triazinium}$). ^{13}C NMR ($CDCl_3$): $\delta = 11.5$, 12.1, 13.6, 19.9, 21.5, 30.7, 44.0, 46.8, 77.3, 128.2, 129.5, 130.2, 131.8, 2×134.9, 141.9, 149.8, 150.3, 150.7, 150.9. MS (FAB/dmab), *m/z* (%): 462 (100) $[C_{25}H_{29}ClN_7]^+$. Anal. calcd for $C_{25}H_{29}ClIN_7$ (589.90): C, 50.90; H, 4.96; Cl, 6.01; I, 21.51; N, 16.62. Found C, 50.53; H, 4.79; Cl/I, 26.08; N, 16.91.

4.4.21. 3,5-Dibutyl-2,6-diethyl-9-(2-hydroxyphenyl)-3*H*,5*H*,9*H*-di[1,2,4]triazolo[1,5-a:1′,5′-d][1,3,5]triazin-8-ium iodide (9k). Yield 57%; mp 190 °C. ^{1}H NMR ($CDCl_3$): δ=1.00 (t, 6H, CH_3), 1.26 (t, 6H, CH_3), 1.41 (m, 4H, CH_2), 1.82 (m, 4H, CH_2), 2.74 (m, 4H, CH_2), 3.95 (m, 4H, CH_2), 7.20 (s, 1H, $sp^3CH_{triazinium}$), 6.91 (t, 1H, CH_{ph}), 7.27 (t, 1H, CH_{ph}), 7.41 (d, 1H, CH_{ph}), 7.49 (d, 1H, CH_{ph}), 8.90 (s, br, 1H, OH). ^{13}C NMR ($CDCl_3$): δ=9.9, 13.6, 18.7, 19.7, 30.7, 43.2, 76.8, 118.2, 118.9, 119.2, 130.3, 132.9, 150.8, 153.3, 156.7. MS (DCI/H_2O), *m/z* (%): 424 (16) $[C_{23}H_{34}N_7O]^+$. Anal. calcd for $C_{23}H_{34}IN_7O$ (551.47): C, 50.09; H, 6.21; I, 23.01; N, 17.78; O, 2.90. Found C, 50.24; H, 6.15; I, 23.15; N, 17.67.

4.4.22. 3-Butyl-5-(4-chlorobenzyl)-2,6-diethyl-9-(2-hydroxyphenyl)-3*H*,5*H*,9*H*-di[1,2,4]triazolo[1,5-a:1′,5′-d]-[1,3,5]triazin-8-ium iodide (9l). Yield 80%; mp 121 °C (dec.); purified by column chromatography on silica gel 60 (0.063–0.200 mm), solvents 4:1:5 mixture of pentane, MeOH, ethyl acetate; IR (KBr) ν=1560 cm^{-1}. ^{1}H NMR (DMSO): δ=0.96 (t, 3H, CH_3), 1.07 (t, 3H, CH_3), 1.26 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.69 (m, 2H, CH_2), 2.53 (m, 2H, CH_2), 2.64 (m, 2H, CH_2), 4.02 (m, 2H, CH_2), 5.08 (s, 2H, CH_2), 6.82–7.50 (m, 8H, CH_{ph}), 7.65 (s, 1H, $sp^3CH_{triazinium}$). ^{13}C NMR (DMSO): δ=9.6, 9.7, 13.4, 17.7, 18.0, 18.9, 30.0, 42.2, 44.6, 74.7, 116.2, 119.5, 128.5, 2× 128.8, 129.4, 131.5, 132.5, 133.3, 150.1, 150.3, 153.2, 153.4, 156.4. MS (DCI/H_2O), *m/z* (%): 492 (11) $[C_{26}H_{31}ClN_7O]^+$. Anal. calcd for $C_{26}H_{31}ClIN_7O$ (619.93): C, 50.37; H, 5.04; Cl, 5.72; I, 20.47; N, 15.82; O, 2.56. Found C, 50.03; H, 4.88; Cl/I, 27.67; N, 15.79.

4.4.23. 5-Benzyl-3-(4-methoxyphenyl)-2,6-diethyl-9-(2-hydroxyphenyl)-3*H*,5*H*,9*H*-di[1,2,4]triazolo[1,5-a:1′,5′-d][1,3,5]triazin-8-ium iodide (9n). Yield 11% (purified by column chromatography on silica gel 60 (0.063–0.200 mm), solvens EtOAc/MeOH); mp 137–140 °C; IR (KBr) ν=1555 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.01–1.14 (m, 6H, CH_3), 2.45–2.57 (m, 4H, CH_2), 3.83 (s, 3H, CH_3), 4.96–5.16 (dd, 2H, CH_2), 6.90–7.57 (m, 13H, CH_{ph}), 7.36 (s, 1H, $sp^3CH_{triaziniun}$), 10.75 (s, br, 1H, OH). ^{13}C NMR ($CDCl_3$): δ=9.4, 10.1, 19.21, 19.24, 46.5, 55.7, 77.1, 115.4, 118.2, 119.1, 119.4, 122.5, 126.7, 127.5, 128.3, 129.1, 129.6, 130.5, 133.0 151.3, 151.9, 153.8, 154.1, 156.7, 161.1. MS (micro-ESI/MeOH), *m/z* (%): 508 (100) $[C_{29}H_{30}N_7O_2]^+$. Anal. calcd for $C_{29}H_{30}IN_7O_2\times H_2O$ (653.52): C, 53.30; H, 4.94; I, 19.42; N, 15.00; O, 7.34. Found C, 53.20; H, 4.72; I; 18.33; N, 14.43.

4.4.24. 3-Butyl-5-(4-chlorobenzyl)-2,6-dimethyl-9-(1-naphthyl)-3*H*,5*H*,9*H*-di[1,2,4]-triazolo[1,5-a:1′,5′-d]-[1,3,5]triazin-8-ium iodide (9q). Yield 80%; mp 127 °C (degr.); IR (KBr) ν=1560 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 0.93 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 2.06 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 7.07–7.96 (m, 11H, $CH_{napht,ph}$), 8.23 (s, br, 1H, $sp^3CH_{triazinium}$). ^{13}C NMR ($CDCl_3$): δ=11.5, 12.0, 13.6, 19.8, 30.7, 43.9, 46.7, 77.3, 125.3, 126.5, 127.6, 127.9, 128.2, 129.4, 129.5, 130.4, 131.8, 132.4, 132.5, 133.2, 134.1, 134.9, 149.7, 150.0, 150.9, 151.1. MS (DCI/H_2O), *m/z* (%): 498 (13) $[C_{28}H_{29}ClN_7]^+$. Anal. calcd for $C_{28}H_{29}ClIN_7$ (625.94): C, 53.73; H, 4.67; Cl, 5.66; I, 20.27; N, 15.66. Found C, 53.64; H, 4.83; Cl/I, 24.26; N, 15.26.

4.4.25. 5-Benzyl-3-butyl-2,6-diethyl-9-(2-hydroxyphenyl)-3*H*,5*H*,9*H*-di[1,2,4]triazolo[1,5-a:1′,5′d][1,3,5]triazin-8-ium iodide (9r). Yield 45% (determined by ^{1}H NMR analysis of the mixture **8r/9r**); mp 195 °C; IR (KBr) ν= 1592 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.97 (t, 3H, CH_3), 1.12 (t, 3H, CH_3), 1.26 (t, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.56 (m, 2H, CH_2), 3.86 (m, 2H, CH_2), 5.13–5.29 (dd, 2H, CH_2), 6.16 (s, br, 1H, OH), 7.37 (s, 1H, $sp^3CH_{triazinium}$), 6.88–7.56 (m, 9H, CH_{ph}), (s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ=9.5, 9.9, 13.6, 18.9, 19.0, 19.7, 30.8, 43.3, 46.6, 76.9, 118.4, 119.0, 119.4, 127.4, 128.8, 129.7, 130.4, 133.0, 133.1, 153.4, 153.7, 151.0, 151.1, 156.5. MS (FAB, dmba), *m/z* (%): 458 (100) $[C_{26}H_{32}N_7O]^+$. Anal. calcd for $C_{26}H_{32}IN_7O\times H_2O$ (603.50): C, 51.75; H, 5.68; I, 21.03; N, 16.25; O, 5.30. Found C, 51.98; H, 5.64; I, 21.20; N, 16.25.

4.4.26. 3-Benzyl-5-(4-methoxyphenyl)-2,6-dimethyl-9-(4-methylphenyl)-3*H*,5*H*,9*H*-di[1,2,4]triazolo[1,5-a:1′,5′-d][1,3,5]triazin-8-ium iodide (9s). Yield 26%; mp 154 °C; IR (KBr) ν=1587 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=2.20 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 5.6–5.11 (dd, 2H, CH_2), 7.02–7.60 (m, 13H, CH_{ph}), 7.65 (s, 1H, $sp^3CH_{triazinium}$). ^{13}C NMR ($CDCl_3$): δ=11.2, 11.8, 21.4, 47.1, 55.7, 77.8, 115.2, 122.8, 127.8, 128.0, 128.5, 128.7, 129.0, 129.2, 129.3, 130.1, 133.1, 141.7, 150.0, 150.1, 151.5, 161.0. MS (DCI/H_2O), *m/z* (%): 478 (30) $[C_{28}H_{28}N_7O]^+$. Anal. calcd for $C_{28}H_{28}IN_7O$ (605.48): C, 55.54; H, 4.66; I, 20.96; N, 16.19; O, 2.64. Found C, 56.02; H, 4.66; J, 19.43; N, 16.17.

4.4.27. 3-Benzyl-5-butylamino-6-[1-(ethylsulfanyl)ethylidene]amino-2-methyl-7-(4-methylphenyl)-3,7-dihydro-[1,2,4]triazolo[1,5-a][1,3,5]triazin-6-ium iodide (10c). A solution of iodoethane (0.05 mL, 0.6 mL) in THF (1 mL) was added to a solution of **7c** (0.23 g, 0.5 mmol) in THF (15 mL) at 5 °C. The reaction mixture was stirred 1 h at 5 °C, then evaporated also at 5 °C and dried in vacuo. The solid residue was extracted with EtOAc at room temperature and dried in vacuo. Yield 66% **10c**; mp 242 °C; IR (KBr) ν_{NH}=3243 cm^{-1}, ν_{Et}=2959, 2930 cm^{-1}, ν_{Ring}= 1599 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.94 (m, 3H, CH_3), 1.31–1.41 (m, 5H, CH_3/CH_2), 1.85 (m, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.09 (m, 2H, CH_2), 3.50 (s br, 1H, NH), 3.76 (m, 2H, CH_2), 5.22–5.36 (dd, 2H, CH_2), 6.60 (s, 1H, $sp^3CH_{triazinium}$), 7.10–7.41 (m, 9H, CH_{ph}). ^{13}C NMR ($CDCl_3$): δ=12.0, 14.1, 13.7, 19.9, 21.4, 24.7, 26.3, 31.7, 41.9, 46.3, 73.7, 127.0, 129.1, 129.3, 129.7, 129.8, 130.5, 133.3, 141.1, 149.6, 149.8, 153.6, 184.5. MS (FAB/dmba), *m/z* (%): 490 (100) $[C_{27}H_{36}N_7S]^+$. Anal. calcd for $C_{27}H_{36}IN_7S$ (617.59): C, 52.51; H, 5.88; I, 20.55; N, 15.88; S, 5.19. Found C, 52.60; H, 5.89; I, 21.07; N, 16.04; S, 5.05.

4.4.28. 5-Butylamino-3-(4-chlorobenzyl)-6-[1-(ethylsulfanyl)ethylidene]amino-2-methyl-7-(4-methylphenyl)-3,7-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin-6-ium iodide (10h). Analogous to **10c**. Yield **10h**: 65%; mp 198 °C; IR (KBr) ν_{NH}=3243 cm^{-1}, ν_{Et}=2958, 2929 cm^{-1}, ν_{Ring}= 1598 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=0.89 (m, 3H, CH_3),

1.23–1.35 (m, 5H, CH_3/CH_2), 1.60 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.00 (m, 2H, CH_2), 3.35 (s br, 1H, NH), 3.58 (m, 2H, CH_2), 5.24–5.32 (dd, 2H, CH_2), 6.53 (s, 1H, $sp^3CH_{triazinium}$), 7.05–7.42 (m, 8H, CH_{ph}). ^{13}C NMR ($CDCl_3$): δ=12.2, 13.7, 14.1, 19.9, 14.3, 21.5, 26.2, 31.7, 41.9, 46.4, 73.7, 127.0, 129.3, 129.5, 129.7, 129.9, 132.1, 135.1, 141.2, 149.7, 149.8, 153.2, 184.4. MS (FAB/dmba), *m/z* (%): 524 (100) $[C_{27}H_{35}ClN_7S]^+$. Anal. calcd for $C_{27}H_{35}CLIN_7S$ (652.03): C, 49.74; H, 5.41; Cl, 5.44; I, 19.46; N, 15.04; S, 4.92. Found C, 49.69; H, 4.93; Cl/I, 25.76; N, 14.92; S 4.61.

4.4.29. 5-Butylamino-3-(4-chlorobenzyl)-6-[1-(ethylsulfanyl)ethylidene]amino-2-methyl-7-(naphth-1-yl)-3,7-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin-6-ium iodide (10q). Analogous to **10c**. Yield 90%; mp 137–140 °C; IR (KBr) ν_{NH}=3205 cm^{-1}, ν_{Et}=2958, 2929 cm^{-1}, ν_{Ring}=1596 cm^{-1}. ^1H NMR ($CDCl_3$): δ=0.96 (m, 3H, CH_3), 1.31–1.46 (m, 5H, CH_3/CH_2), 1.72 (m, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.05 (m, 2H, CH_2), 3.72 (m, 2H, CH_2), 5.31–5.45 (dd, 2H, CH_2), 7.29 (s, 1H, $sp^3CH_{triazinium}$), 7.40–7.97 (m, 12H, NH, $CH_{ph/naphthyl}$). ^{13}C NMR ($CDCl_3$): δ=12.0, 13.4, 14.2, 19.8, 24.3, 26.5, 31.7, 41.9, 46.4, 68.0, 122.2, 125.3, 126.4, 127.3, 128.9, 129.2, 129.5, 131.0, 131.7, 131.8, 132.1, 133.9, 134.9, 135.1, 149.6, 149.8, 153.5, 184.0. MS (FAB/dmba), *m/z* (%): 560 (88) $[C_{30}H_{35}ClN_7S]^+$. Anal. calcd for $C_{30}H_{36}ClIN_7S$ (688.07): C, 52.37; H, 5.13; Cl, 5.15; I, 18.44; N, 14.25; S, 4.66. Found C, 52.01; H, 5.19; Cl/I, 24.12; N, 14.44; S, 4.78.

4.4.30. *N*-[3-Benzyl-2-methyl-5-oxo-7-(4-methylphenyl)-3,5-dihydro[1,2,4]triazolo[1,5-a][1,3,5]triazin-6(7*H*)-yl]ethanethioamide (11c). *n*-Butylamine (0.125 mL, 1.25 mmol) was added to a stirred suspension of **5a** in triethylamine (15 mL) at −10 °C. The mixture was stirred for 24 h at room temperature and then poured in ice water (30 g). After dropwise addition of acetic acid up to pH 6–7 the precipitate was filtered off and dried in vacuo. Crystallization from MeCN gave crystals for X-ray analysis. Yield 93% **11a**; mp 172 °C; IR (KBr) ν_{NH}=3172 cm^{-1}, ν_{CO}=1657 cm^{-1}, ν_{CS}=1178 cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.17 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.96–5.13 (dd, 2H, CH_2), 7.22–7.44 (m, 9H, CH_{ph}), 7.38 (s, 1H, $sp^3CH_{triazine}$), 10.27 (s, br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=11.6, 21.4, 31.1, 45.7, 73.8, 127.1, 127.8, 128.7, 129.2, 130.1, 132.4, 133.9, 140.7, 148.1, 152.2, 155.9, 199.7. MS (DCI/H_2O), *m/z* (%): 407 (56) $[C_{21}H_{23}N_6OS]^+$. Anal. calcd for $C_{21}H_{22}N_6OS$ (406.50): C, 62.05; H, 5.45; N, 20.67; O, 3.94; S, 7.89. Found C, 61.94; H, 5.77; N, 21.00; S 7.50.

4.4.31. *N*-[3-(4-Chlorobenzyl)-2-methyl-5-oxo-7-(4-methylphenyl)-3,5-dihydro[1,2,4]triazolo[1,5-a][1,3,5]-triazin-6(7*H*)-yl]ethanethioamide (11h). Analogous to **11c** from **5b** and *n*-butylamine; purifcation via column chromatography, elution with EtOAc/MeOH 9:1. Yield 86%; mp 170 °C; IR (KBr) ν_{NH}=3149 cm^{-1}, ν_{CO}=1653 cm^{-1}, ν_{CS}=1177 cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.18 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.93–5.08 (dd, 2H, CH_2), 7.22–7.39 (m, 8H, CH_{ph}), 7.31 (s, 1H, $sp^3CH_{triazine}$), 10.44 (s, br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=11.4, 21.4, 31.1, 45.1, 73.9, 127.1, 128.9, 129.2, 129.4, 130.1, 132.3, 140.8, 147.9, 152.1, 155.8, 198.8. MS (DCI/H_2O), *m/z* (%): 441 (20) $[C_{21}H_{22}ClN_6OS]^+$. Anal. calcd for $C_{21}H_{21}ClN_6OS$ (440.95): C, 57.20; H, 4.80; Cl, 8.04; N, 19.06; O, 3.63; S, 7.27. Found C; 56.90; H, 5.04; Cl; 8.30; N, 18.79; S, 6.98.

4.5. Crystal structure determination

The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[26,27]

The structures were solved by direct methods (SHELXS)[28] and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97).[29] The hydrogen atoms for the amino groups (N2 of **8r**, N6 of **11c**), for the chirale carbon atoms (C1 of **8i**, C1 of **8r**, C4 of **11c**), and for the hydroxyl groups (O1 of **8i**, O of **8r**) were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[29] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

4.5.1. Crystal data for 7c.[30] $C_{25}H_{31}N_7S$ * $1/4C_4H_8O_2$, Mr=483.65 g mol^{-1}, colourless prism, size 0.03×0.03×0.03 mm^3, monoclinic, space group *C*2/*c*, *a*=13.7683(3) Å, *b*=43.6678(14) Å, *c*=18.2513(4) Å, β=94.811(2)°, *V*=10934.6(5) $Å^3$, *T*=−90 °C, *Z*=16, ρ_{calcd}=1.175 g cm^{-3}, μ (Mo K_α)=1.47 cm^{-1}, *F*(000)=4128, 31678 reflections in *h*(−17/15), *k*(−56/55), *l*(−23/22), measured in the range 1.99°≤Θ≤27.47°, completeness Θ_{max}=98.6%, 12383 independent reflections, R_{int}=0.060, 7737 reflections with $F_o>4\sigma(F_o)$, 617 parameters, 0 restraints, $R1_{obs}$=0.066, wR^2_{obs}=0.152, $R1_{all}$=0.119, wR^2_{all}=0.182, GOOF=1.011, largest difference peak and hole: 1.002/−0.559 e $Å^{-3}$.

4.5.2. Crystal data for 8i.[30] $C_{24}H_{35}N_7O$ S, Mr=469.65 g mol^{-1}, colourless prism, size 0.04×0.04×0.03 mm^3, monoclinic, space group $P2_1/n$, *a*=11.2663(2) Å, *b*=20.0596(4) Å, *c*=12.0203(3) Å, β=112.392(1)°, *V*=2511.73(9) $Å^3$, *T*=−90 °C, *Z*=4, ρ_{calcd}=1.242 g cm^{-3}, μ (Mo K_α)=1.59 cm^{-1}, *F*(000)=1008, 9854 reflections in *h*(−14/14), *k*(−26/24), *l*(−15/15), measured in the range 2.34°≤Θ≤27.50°, completeness Θ_{max}=99.6%, 5741 independent reflections, R_{int}=0.033, 4010 reflections with $F_o>4\sigma(F_o)$, 306 parameters, 0 restraints, $R1_{obs}$=0.051, wR^2_{obs}=0.124, $R1_{all}$=0.083, wR^2_{all}=0.140, GOOF=1.028, largest difference peak and hole: 0.525/−0.315 e $Å^{-3}$.

4.5.3. Crystal data for 8r.[30] $C_{26}H_{33}N_7OS$, Mr=491.65 g mol^{-1}, colourless prism, size 0.03×0.03×0.02 mm^3, monoclinic, space group $P2_1/n$, *a*=14.4215(3) Å, *b*=10.4996(2) Å, *c*=18.0020(5) Å, β=106.548(1)°, *V*=2612.9(1) $Å^3$, *T*=−90 °C, *Z*=4, ρ_{calcd}=1.250 g cm^{-3}, μ (Mo K_α)=1.56 cm^{-1}, *F*(000)=1048, 11002 reflections in *h*(−18/18), *k*(−11/13), *l*(−23/23), measured in the range 2.44°≤Θ≤27.46°, completeness Θ_{max}=99.7%, 5955 independent reflections, R_{int}=0.044, 3911 reflections with $F_o>4\sigma(F_o)$, 328 parameters, 0 restraints, $R1_{obs}$=0.045, wR^2_{obs}=0.098, $R1_{all}$=0.0854,

$wR^2_{all}=0.111$, GOOF=0.997, largest difference peak and hole: 0.183/−0.293 e Å^{-3}.

4.5.4. Crystal data for 11c.[30] $C_{21}H_{22}N_6OS$, Mr=406.51 g mol^{-1}, colourless prism, size 0.02×0.02×0.01 mm^3, monoclinic, space group $C2/c$, a=24.0847(7) Å, b=9.5887(3) Å, c=19.2320(7) Å, β=113.316(1)°, V=4078.7(2) Å^3, T=−90 °C, Z=8, ρ_{calcd}=1.324 g cm^{-3}, μ (Mo K$_\alpha$)=1.84 cm^{-1}, $F(000)$=1712, 8301 reflections in h(−31/31), k(−12/12), l(−24/24), measured in the range $2.31° \le \Theta \le 27.51°$, completeness Θ_{max}=99.5%, 4671 independent reflections, R_{int}=0.036, 3060 reflections with $F_o > 4\sigma(F_o)$, 270 parameters, 0 restraints, $R1_{obs}$=0.053, wR^2_{obs}=0.125, $R1_{all}$=0.0941, wR^2_{all}=0.146, GOOF=1.033, largest difference peak and hole: 0.311/−0.274 e Å^{-3}.

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Improved synthesis of *N*-alkyl substituted dithieno[3,2-*b*:2′,3′-*d*]pyrroles

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Abstract—A new, convergent and improved synthetic method to prepare *N*-alkyl substituted dithienopyrroles is described. The procedure consists of a Pd-catalyzed amination of 3,3′-dibromo-2,2′-bithiophene. The reaction conditions were optimized, which makes this method applicable to prepare these molecules easily in high yields and on a large scale.

1. Introduction

N-Alkyl dithieno[3,2-*b*:2′,3′-*d*]pyrroles (DTPs) form an interesting class of molecules, especially since they are precursors for conducting polymers.[1] *N*-Alkyl DTPs can be considered as planar, fused-ring analogues of thiophene, which, upon polymerization, may show some advantages compared to poly(alkylthiophene)s, such as lower band gaps and oxidation potentials. Moreover, the electron donating nitrogen can increase the stability of the polymer in the oxidized state and further decrease the band gap of the polymers.

2. Results and discussion

Two routes have already been described to prepare *N*-alkyl DTPs. A first approach (Scheme 1(a)) consists of the synthesis of the parent DTP[2a] (**2**), followed by alkylation[2b] of **2** to produce the target molecules (**3**). Ogawa et al. developed a new, improved pathway, with higher overall yields, starting from 3-bromothiophene (Scheme 2(b)). Thus, 3-bromothiophene (**4**) was converted into the tertiary amine (**6**) using a Buchwald–Hartwig reaction.[3a] Since substantial amounts of mono-aminated product (**5**) are formed, it is usually necessary to carry out a second Buchwald–Hartwig reaction to prepare the tertiary amine in decent yields. Then, ring closure is performed by a one-pot two-step reaction, which consists of bromination with NBS, followed by Cu-mediated coupling.[3b]

Although the method described by Ogawa et al. represents an improved way compared to the previous one, a few drawbacks still remain. The starting compound, 3-bromothiophene (**4**), is quite expensive. Secondly, the shelf-life of the secondary and tertiary amine derivatives (**5** and **6**) is very limited. Moreover, scaling up the reaction from 10 to 100 mmol was cumbersome: in our hands, the overall yield dropped to 8%. Finally, Ogawa's way is a linear method, which implies that the whole reaction sequence must be repeated every time the alkyl substituent on DTP is varied.

Here, we represent a new, convergent and improved method to generate *N*-alkyl DTPs in high yields from inexpensive starting materials. The reaction sequence is presented in Scheme 2 and consists of a Buchwald–Hartwig reaction of the primary amine with 3,3′-dibromo-2,2′-bithiophene **7**.[4] This strategy has already been used for the synthesis of *N*-aryl substituted DTPs, but in different reaction conditions.[5] Compound **7** can be prepared in a high overall yield, starting from inexpensive 2-bromothiophene. All intermediary compounds and **7** are very stable and demand no purification.

In order to optimize the reaction conditions, the influence of different parameters, i.e. the catalyst's nature and its

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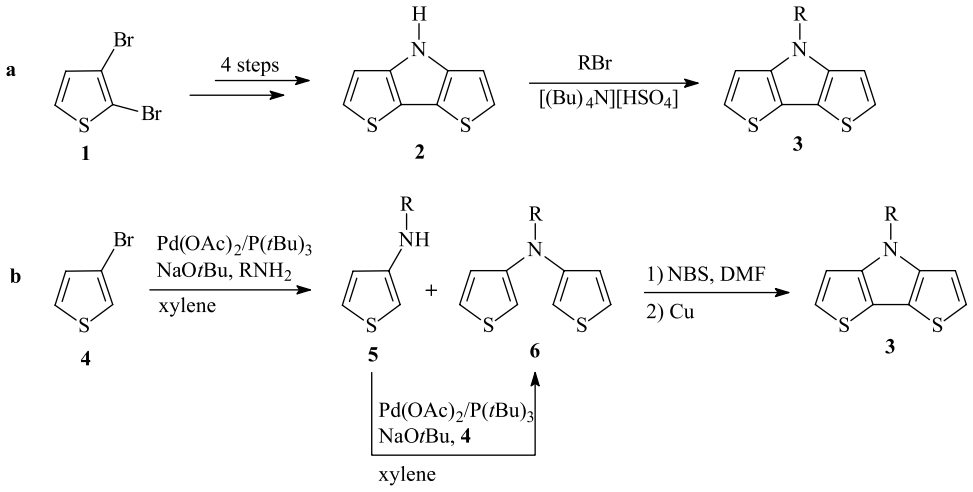
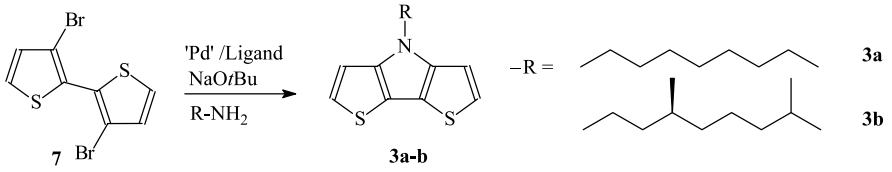


Scheme 1. Previous methods to synthesize *N*-alkyl DTPs.



Scheme 2. Synthesis of *N*-alkyl DTPs.

concentration, ligands, solvent, reaction time and upscaling were investigated. The results of the optimization of the reaction conditions are summarized in Table 1.

In entry 1–3 the monodentate ligand P(*t*-Bu)$_3$ was used and only bithiophene (**9**) was formed, regardless of the Pd-source. This is the by-product, resulting from a β-hydride elimination instead of a reductive elimination in the catalytic cycle (Fig. 1). Buchwald[6a] and Hartwig[6b,c] showed that this β-hydride elimination could be suppressed by the use of bidentate ligands. Therefore, DPPF and BINAP were used as ligands and Pd(DPPF)Cl$_2$ respectively Pd$_2$dba$_3$ as Pd-source (entries 4 and 5). This resulted in the exclusive formation of the target *N*-octyl DTP (**3a**). No trace of **9** was detected. In both cases, the reaction product could easily be purified by simple column chromatography. When BINAP was used, the yields were higher than in the case of DPPF. All these reactions were carried out in toluene at 110 °C until completion of the reaction, as judged by TLC control.

Subsequently, the solvent influence on the reaction was investigated. In entry 8, DMF was used as a polar solvent. In this case, no reaction took place and after 7 h, only starting material was isolated.

Furthermore, the influence of the temperature was examined. If the reaction was carried out at 90 °C, the outcome was unchanged, except that longer reaction times were needed to allow the reaction to reach completion and that the product was formed in lower yields (entry 6). Increasing the reaction temperature to 130 °C requires the use of *p*-xylene as solvent. The reaction time dropped, but no increase of the yield was observed.

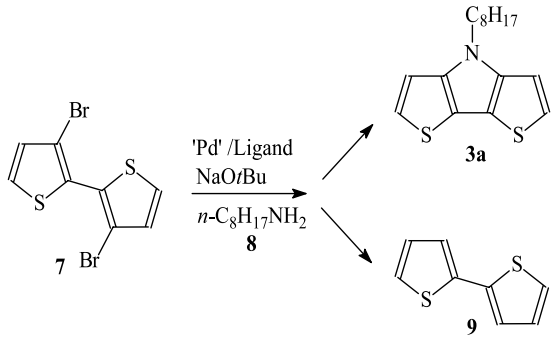
We also varied the catalyst and ligand concentration (entry 9). It was found that the catalyst concentration could be reduced from 5 to 1 mol%, without a reduction in yield, provided that longer reaction times were applied.

Finally, the reaction was scaled up to 15 mmol (entry 10). As follows from Table 1, this even leads to higher yields. Presumably, working on a larger scale reduces losses during work-up and purification, which might explain the higher isolated yields.

In order to obtain *N*-alkyl DTPs, the primary amine must react twice with **7**. At this point two unwanted side-reactions might occur. Firstly, the catalyst and ligands have shown to possess a rather strong tendency to mono-aminate.[6a] In order to produce tertiary amines from primary amines, it is usually necessary to perform a second, separate amination reaction. Secondly, the secondary amine can react intermolecularly with another bithiophene molecule, to produce polymeric structures. After completion of the reaction, neither of these side reactions were observed with our method, which indicates that the second, intramolecular amination step proceeds very smoothly. It is also worthwhile to note the intermediate mono-aminated compound (**10**[†]) can be observed with TLC and isolated. If the reaction is run to completion, this compound is not detected.

[†] 3-Bromo-3′-(*N*-octylamino)-2,2′-bithiophene: ^{1}H NMR ($CDCl_3$, ppm): δ=7.27 (d; J=5.9 Hz; 1H), 7.25 (d; J=5.9 Hz; 1H), 7.02 (d; J=5.9 Hz; 1H), 6.73 (d; J=5.9 Hz; 1H), 3.76 (s; 1H), 3.16 (t; 2H), 1.55 (qu; 2H), 1.2–1.4 (m; 10H), 0.87 (t; 3H). ^{13}C NMR ($CDCl_3$, ppm): δ=147.0, 131.2, 131.1, 126.4, 126.3, 118.2, 110.7, 103.3, 46.9, 31.9, 30.3, 29.5, 29.4, 27.1, 22.8, 14.2. MS: m/z=372 (M^+). $C_{16}H_{22}BrNS_2$: calcd: C 51.61%, H 5.95%, N 3.76%; found: C 51.24%, H 5.86%, N 3.61%.

Table 1. Pd-catalyzed amination of **7** with *n*-octylamine



Entry	Catalyst	Ligand added[a]	Reaction time (h)[b]	Solvent	Temperature (°C)	**9** (%)	**3a**[c] (%)	Catalyst concentration (mol%)
1[d]	$Pd(OAc)_2$	P(*t*-Bu)$_3$	3, 5	Toluene	110	Only	0	5
2[d]	$Pd(OAc)_2$	P(*o*-tol)$_3$	3, 5	Toluene	110	Only	0	5
3[d]	$PdCl_2$	P(*t*-Bu)$_3$	3, 5	Toluene	110	Only	0	5
4[d]	$Pd(DPPF)Cl_2$	DPPF	3, 5	Toluene	110	0	38	5
5[d]	$Pd_2dba_3 \cdot CH_2Cl_2$	BINAP	7	Toluene	110	0	67	5
6[d]	$Pd_2dba_3 \cdot CH_2Cl_2$	BINAP	31	Toluene	90	0	13	5
7[d]	$Pd_2dba_3 \cdot CH_2Cl_2$	BINAP	4, 75	*p*-Xylene	130	0	66	5
8[d]	$Pd_2dba_3 \cdot CH_2Cl_2$	BINAP	7	DMF	110	0	0	5
9[d]	$Pd_2dba_3 \cdot CH_2Cl_2$	BINAP	13, 5	Toluene	110	0	68	1
10[e]	$Pd_2dba_3 \cdot CH_2Cl_2$	BINAP	7	Toluene	110	0	80	5

[a] The ratio P/Pd=4 in all cases.
[b] Until **7** had completely reacted (TLC control).
[c] Isolated yields.
[d] On 1.5 mmol scale.
[e] On 15 mmol scale.

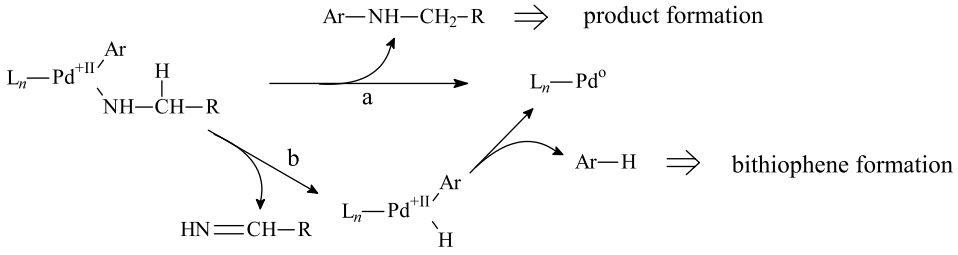
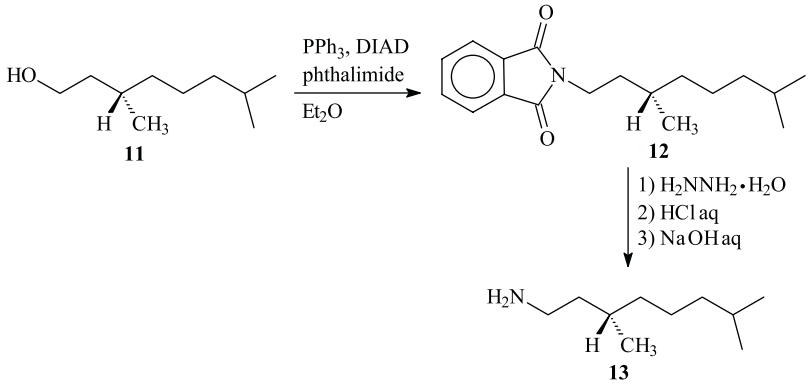


Figure 1. Reductive elimination (a) versus β-hydride elimination (b).

To prove that the reaction is not limited to one specific amine, i.e. *n*-octylamine, we also prepared a novel *N*-alkyl DTP. Since we are interested in chiral derivatives of DTP in order to prepare chiral poly(DTP)s, we prepared **3b**. The chiral amine (**13**) has previously been prepared[7] from (*S*)-citronellal in three steps in an overall yield of 46%. We designed an alternative strategy to synthesize **13** from chiral **11**,[8] which is obtained quantitatively from the commercially available and relatively inexpensive (*S*)-citronellol. The synthesis of **13** is presented in Scheme 3 and consists of the



Scheme 3. Synthesis of (*S*)-(−)-3,7-dimethyloctylamine (**13**).

preparation of phthalimide **12** from **11** by a Mitsunobu reaction[9] and subsequent hydrazinolysis of **12**. In this way, **13** was prepared in an overall yield of 77%. Finally, **3b** could easily be prepared in high yields using our new method.

3. Conclusion

We designed and optimized a new way to prepare *N*-alkyl substituted DTPs, which essentially consists of a Pd-catalyzed amination of 3,3′-dibromo-2,2′-bithiophene. The advantages of this new, convergent procedure are the very high yields, the possibility to work on large scale, the ease of purification and the inexpensive starting materials.

4. Experimental

4.1. General

All reagents were purchased from Aldrich Chemical Co., Acros Organics, Merck, Fluka and Avocado. Toluene and *p*-xylene were distilled over CaH_2 onto molecular sieve and diethyl ether was distilled from Na/K. ^1H and ^{13}C nuclear magnetic resonance (NMR) measurements were carried out with a Bruker Avance 300 MHz. The optical rotations were measured with an Analis Optical Activity Polaar 20.

4.1.1. Synthesis of (*S*)-*N*-3,7-dimethyloctylphthalimide 12. A solution of triphenylphosphine (26.2 g, 100 mmol), phthalimide (14.7 g, 100 mmol) and **11** (16.0 g, 100 mmol) in dry diethyl ether (100 mL) was purged with argon and a solution of DIAD (20.0 mL, 100 mmol) in dry diethyl ether (40 mL) was slowly added. After stirring overnight, the precipitate was filtered off and washed thoroughly with diethyl ether. The filtrate was concentrated in vacuo, yielding a yellow oil, which was used without further purification.

Yield: 25.9 g (89%); ^1H NMR ($CDCl_3$, ppm): $\delta=7.83$ (dd; $J=5.9$ Hz, $J=2.9$ Hz; 2H), 7.70 (dd; $J=5.9$ Hz, $J=2.9$ Hz; 2H), 3.70 (t; 2H), 1.70 (m; 1H), 1.4–1.5 (m; 3H), 1.0–1.4 (m; 6H), 0.98 (d; 3H), 0.86 (d; 6H). ^{13}C NMR ($CDCl_3$, ppm): $\delta=168.4$, 133.8, 132.3, 123.1, 39.3, 37.0, 36.4, 35.5, 30.8, 27.9, 24.6, 22.7, 19.5. MS: $m/z=287$ (M^+), 174 ($M^+-C_8H_{17}$), 160 ($M^+-C_9H_{19}$), 148 ($M^+-C_{10}H_{19}$). $C_{18}H_{25}NO_2$: calcd: C 75.22%, H 8.77%, N 4.87%; found: C 74.89%, H 8.59%, N 4.67%.

4.1.2. Synthesis of (*S*)-(−)-3,7-dimethyloctylamine 13. A solution of **12** (25.8 g, 90.0 mmol) in absolute ethanol (50 mL) was purged with argon and hydrazine monohydrate (4.37 mL, 90.0 mmol) was added drop wise. The mixture was heated to reflux for 2 h. Then, excess HCl-solution (5 M) was added and the mixture was refluxed for an additional 10 min and cooled. The precipitate was filtered off and washed with water. The filtrate was concentrated in vacuo and excess NaOH-solution (2 M) was added. The crude compound was extracted twice with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvents were removed via rotary evaporation. Amine **13** was isolated as a viscous, colorless oil by vacuum distillation.

Yield: 12.3 g (86%); bp 117 °C/15 mmHg; ^1H NMR ($CDCl_3$, ppm): $\delta=2.70$ (m; 2H), 1.50 (m; 3H), 1.35–1.05 (m; 9H), 0.87 (d; 3H), 0.86 (d; 6H). $[\alpha]_D^{20}=-2.6$ ($c=56$ in CH_2Cl_2).

4.2. General procedure for the synthesis of *N*-functionalized dithieno[3,2-*b*:2′,3′-*d*]pyrroles 3a–b

A solution of **7** (4.92 g, 15.3 mmol), NaO*t*-Bu (3.54 g, 36.8 mmol), Pd_2dba_3 (0.350 g, 0.382 mmol) and BINAP (0.950 g, 1.53 mmol) in dry toluene (30 mL) was purged with argon for 20 min. The appropriate amine (15.3 mmol) was added and the mixture was stirred for 7 h at 110 °C under an argon atmosphere. After cooling down, water (20 mL) was added and the layers were separated. The water phase was extracted twice with diethyl ether. The combined organic layers were dried over $MgSO_4$ and the solvents were removed via rotary evaporation. Finally, the crude compound was purified by column chromatography (silica gel; eluent: hexane/dichloromethane 90/10 (v/v)).

4.2.1. *N*-Octyldithieno[3,2-*b*:2′,3′-*d*]pyrrole 3a. The product was collected as a colorless oil, which crystallized upon standing. Yield: 3.64 g (80%); mp 34.9–35.4 °C (lit.[3b] 34.6–35.2); ^1H NMR ($CDCl_3$, ppm): $\delta=7.12$ (d; $J=5.5$ Hz; 2H), 7.00 (d; $J=5.5$ Hz; 2H), 4.19 (t; 2H), 1.86 (qu; 2H), 1.2–1.4 (m; 10H), 0.86 (t; 3H).

4.2.2. (*S*)-(+)-*N*-(3,7-Dimethyloctyl)dithieno[3,2-*b*:2′,3′-*d*]pyrrole 3b. The product was collected as a yellow oil, which did not crystallize. Yield: 3.19 g (65%); ^1H NMR ($CDCl_3$, ppm): $\delta=7.12$ (d; $J=5.5$ Hz; 2H), 7.00 (d; $J=5.5$ Hz; 2H), 4.20 (m; 2H), 1.88 (m; 1H), 1.67 (m; 1H), 1.49 (m; 2H), 1.0–1.4 (m; 6H), 0.96 (d; 3H), 0.84 (d; 6H). ^{13}C NMR ($CDCl_3$, ppm): $\delta=144.8$, 122.8, 114.7, 110.9, 45.5, 39.2, 37.2, 37.0, 30.4, 27.9, 25.3, 22.6, 19.6. MS: $m/z=319$ (M^+), 192 ($M^+-C_9H_{19}$). $C_{18}H_{25}NS_2$: calcd: C 67.66%, H 7.89%, N 4.38%; found: C 67.28%, H 7.74%, N 4.19%. $[\alpha]_D^{20}=+0.56$ ($c=51$, CH_2Cl_2).

Acknowledgements

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Effect of substituent on the enantioselectivity for lipase-catalyzed kinetic resolution of glycerol derivatives

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Abstract—The lipase-catalyzed transesterifications of various substituted diphenyl 1,2-ketals of glycerol have been investigated. Efficient modification of the substrate structure with bis(4-bromophenyl) ketal was found to enhance the enantioselectivity up to $E=57$ at 0 °C.

1. Introduction

Chiral glycerol derivatives are useful as chiral building blocks for the syntheses of biologically active chiral compounds such as β-blockers[1] and PAF antagonists.[2] Although the efficient asymmetric syntheses of glycerol derivatives were achieved by the lipase-catalyzed transesterification of racemic 3-(aryloxy)-1,2-propanediols with lipase PS from *Pseudomonas cepacia* (PCL) and vinyl acetate,[3] the esterification of various 1,2-ketals of glycerol with succinic anhydride[4] and the hydrolysis of carboxylic esters of the 1,2-ketals of glycerol[5] were reported to proceed with low enantioselectivities. These results are consistent with the reported finding that the enantioselectivity of PCL toward primary alcohols is much lower than toward secondary alcohols.[6] However, Sakai et al. described that the *E* value for the kinetic resolution of 2,2-dimethyl-1,3-dioxolane-4-methanol **1** using lipase AK from *Pseudomonas fluorescens* (PFL) increased up to 55 (9 at 30 °C) by lowering the reaction temperature to −40 °C in *i*-Pr_2O,[7] although it needed a large amount of lipase and longer reaction time. As an alternative approach, we investigated the optimization of the structures of the glycerol derivatives by altering the protecting group because we recently found that the enantioselectivity during transesterification catalyzed by the immobilized PCL significantly depended on the position of the substituent on the aromatic ring, and the *N*-3,5-dimethylbenzyl group was found to transform the *trans*-2,5-substituted pyrrolidine derivative into an efficiently-resolved substrate.[8] Thus, we expected that 1,3-dioxolane-4-methanol with a variety of 4-substituted phenyl groups in place of the methyl group could improve the enantioselectivity (Fig. 1).

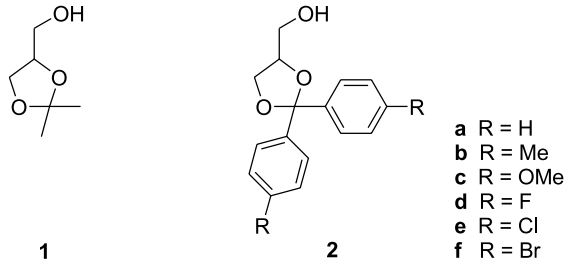

Figure 1.

In this paper, we describe the study of the substituent effect on the enantioselectivity for the lipase-catalyzed transesterification of various 2,2-bis(4-substituted phenyl)-1,3-dioxolane-4-methanols **2a**–**f**.

2. Results and discussion

The substrates **2a**–**f** were prepared by the cyclic ketal formation of glycerol and the corresponding 4-substituted benzophenones in the presence of *p*-toluenesufonic acid at reflux using a Dean–Stark apparatus as previously described[5] (Scheme 1). To investigate the solvent effect, the substrate **2e** was selected as a suitable substrate and the transesterifications catalyzed by lipase PS (PCL) and AK (PFL) were carried out in various solvents at 25 °C (Scheme 2). The enantiomeric excess (ee) values of alcohols **2e** and the resulting acetates **3e** were determined by an

Keywords: Lipase; Transesterification; Kinetic resolution; Glycerol; Substituent effect.
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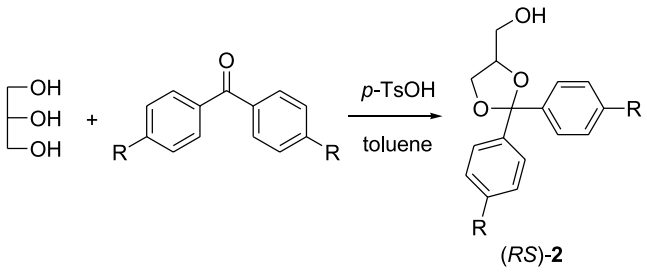


Scheme 1. Preparation of glycerol derivatives.

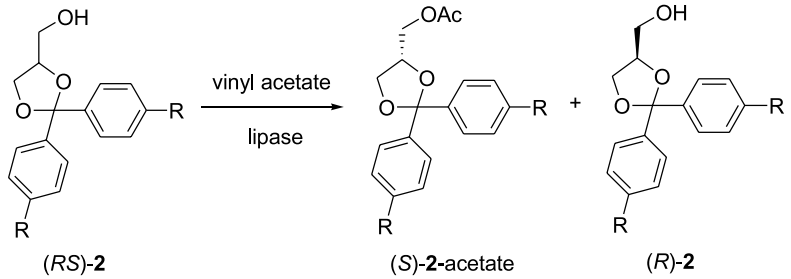
HPLC analysis using a chiral column. The absolute configurations of the remaining alcohols were determined to be *R*-form by comparison of the optical rotations, which were consistent with the empirical rule for chiral primary alcohols.[6] These results are summarized in Table 1.

Acylation of substrate **2e** with vinyl butyrate and lipase AK in *i*-Pr_2O afforded a slightly higher enantioselectivity ($E=11$) than that of **1** ($E=9$)[7] under the similar reaction conditions. Use of vinyl acetate as an acylating agent slightly increased the enantioselectivity ($E=18$). Dry hexane was found to be a better solvent ($E=18$) than wet-hexane for the kinetic resolution of the substrate **2e** using lipase AK. In the case of lipase PS, the similar solvent effect was observed and dry hexane was also proved to be the optimal solvent ($E=21$) among the solvents examined.

Next, the substituent effect on the enantioselectivity was examined using a series of substrates **2a–f** and vinyl acetate in dry hexane at 25 °C (Table 2).

Although the enantioselectivity of lipase AK for the substrates **2a–c** decreased as the size of the electron-donating group increased (Entries 1–3), those of the substrates **2d–f** increased as the size of the electron-withdrawing halogen group on the benzene ring far from the stereocenter increased (Entries 4–6). On the other hand, the enantioselectivity of lipase PS for the substrates **2a–c** and **2d–f** increased as the size of both substituent groups increased (Entries 7–12). Among them, the substrate **2f** (R=Br) showed the highest enantioselectivity ($E=36$). Thus, bis(4-bromophenyl) ketal as the protecting group was found to transform glycerol into an efficiently-resolved substrate.

Finally, the temperature effect on the enantioselectivity was examined using lipase PS in dry hexane at 0 °C as shown in Figure 2. Although the *E* values of the substrates **2a**, **2b**, and **2d** (R=H, Me, F) did not change at 0 °C, those of substrates **2e** and **2f** bearing an electron-withdrawing group (R=Cl, Br) increased from 21 to 25 and from 36 to 57, respectively. On the other hand, the *E* value decreased for substrate **2c** (R=OMe). This result suggests that the inversion of the temperature effect might be due to the strong electron-donating character of the methoxy group in the diphenyl ketals **2c**. It is noted that this effect of the substituent and temperature is quite opposite to that of the esterification of 2-(4-substituted phenoxy)propionic acids catalyzed by lipase MY from *Candida rugosa* ($E=120$, the substrate



Scheme 2. Lipase-catalyzed transesterification of glycerol derivatives.

Table 1. Solvent effect on the enantioselectivity in lipase-catalyzed acylations of **2e**[a]

Entry	Solvent	Lipase	Time (h)	ee_s(%)[b]	ee_p(%)[b]	Convn.(%)[c]	*E* value[c]
1	*i*-Pr_2O[d]	AK	8	61	71	46	11
2	*i*-Pr_2O	AK	3.5	71	79	47	18
3	THF	AK	7	63	63	30	6.0
4	Toluene	AK	6	48	61	44	7.0
5	Wet-hexane[e]	AK	2	48	44	65	7.0
6	Dry-hexane[f]	AK	2	69	94	58	18
7	*i*-Pr_2O	PS	5	33	62	35	5.9
8	THF	PS	8	15	56	21	4.1
9	Toluene	PS	8.5	35	70	33	8.0
10	Wet-hexane[e]	PS	1.5	76	69	52	10
11	Dry-hexane[f]	PS	4	67	83	45	21

[a] Reaction conditions: substrate (0.2 mmol), vinyl acetate (0.8 mmol), lipase (60 mg), solvent (2 ml), 25 °C.
[b] Determined by HPLC analysis using chiralcel OD column. ee_s; (*R*)-**2**, ee_p; (*S*)-**2**-acetate.
[c] Calculated using the equation in Ref. [9].
[d] Vinyl butyrate was used.
[e] Water-saturated hexane.
[f] Distilled from sodium.

Table 2. Subustituent effect on the enantioselectivity in lipase-catalyzed acylations of glycerol derivatives **2a**–**f**[a]

Entry	Substrate, R	Lipase	Time (h)	ee_s(%)[b]	ee_p(%)[b]	Convn. (%)[c]	*E* value[c]
1	**2a**, H	AK	1.5	95	68	58	20
2	**2b**, 4-Me	AK	2	49	69	41	9.1
3	**2c**, 4-OMe	AK	4	65	60	52	7.8
4	**2d**, 4-F	AK	2	83	42	66	5.9
5	**2e**, 4-Cl	AK	2	69	94	58	18
6	**2f**, 4-Br	AK	2	86	77	53	22
7	**2a**, H	PS	6	49	58	46	6.0
8	**2b**, 4-Me	PS	4	41	74	36	10
9	**2c**, 4-OMe	PS	4	67	83	45	21
10	**2d**, 4-F	PS	4	53	72	42	10
11	**2e**, 4-Cl	PS	4	67	83	45	21
12	**2f**, 4-Br	PS	2	81	87	48	36

[a] Reaction conditions: substrate (0.2 mmol), vinyl acetate (0.8 mmol), lipase (60 mg), dry-hexane (2 ml), 25 °C.
[b] Determined by HPLC analysis using chiralcel OD or OD-H column. ee_s; (*R*)-**2**, ee_p; (*S*)-**3**.
[c] Calculated using the equation in Ref. 9.

bearing a methoxy group, 57 °C).[10] Figure 3 shows the correlation between the enantioselectivity of **2a**–**f** and the Hammett σ_p value,[11] implying that the electron-withdrawing character might be the main factor to enhance the enantioselectivity. Figure 4 shows the correlation between the enantioselectivity and van der Waals radius.[12] The enantioselectivity of **2b** bearing the larger methyl group was much lower than that of **2e**,**f** (R = Cl, Br), which suggests that the electronic factor play a more important role than the steric factor in this PCL-catalyzed transesterification of the glycerol derivatives. On the other hand, a good correlation between the enantioselectivity and reactivity was observed as shown in Figure 5. These results suggest that the hydrophobic interaction between the bromo group and the active site of PCL allowed the fast-reacting substrate to strongly bind, leading to the enhancement of both the reactivity and enantioselectivity.

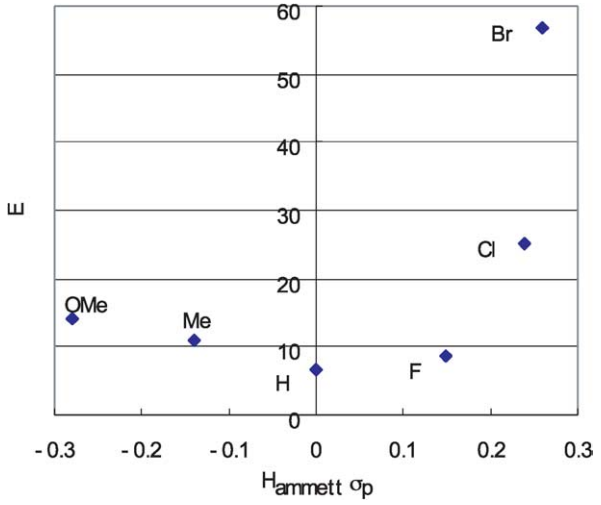


Figure 3. Relation between the enantioselectivity and Hammett σ_p.

Schrag et al. reported that the active-site cleft of PCL based on an X-ray structure analysis was ovoid (10 Å×25 Å across) and was about 15 Å deep and 4 Å wide at the bottom.[12] Figure 6 shows a cutaway view of the active-site cleft (Figure 2(d) in the literature[12]) and the supposed transition-state model for the fast-reacting (*S*)-bis(4-bromophenyl) ketal of glycerol. Although the detailed computer modeling of the X-ray crystal structure of PCL and conformations of the ketal have not yet been performed, the methylene group of dioxalane seems to nestle into the smaller hydrophobic pocket and one of the 4-bromophenyl groups seems to point toward the alternate hydrophobic pocket.[6] Therefore, this overlapping also supported the previous proposition that the additional hydrophobic interaction between the bromo group and the active-site cleft might enhance the reactivity and enantioselectivity.

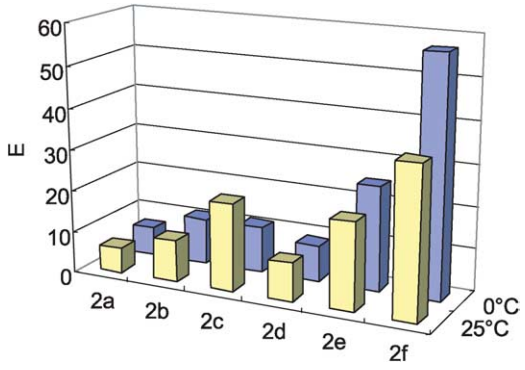


Figure 2. Temperature effect.

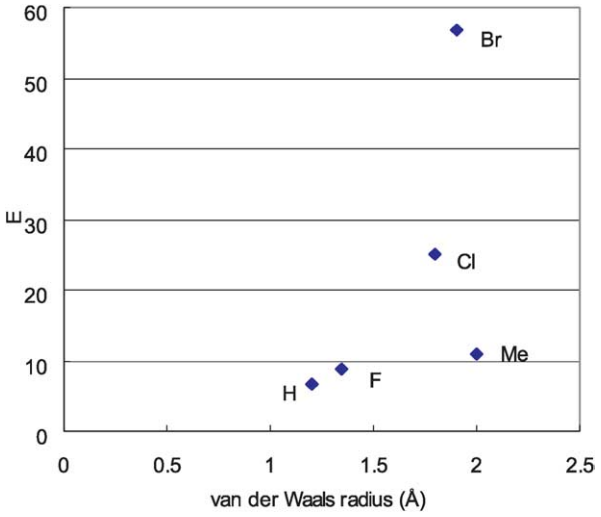


Figure 4. Relation between the enatioselectivity and van der Waals radius.

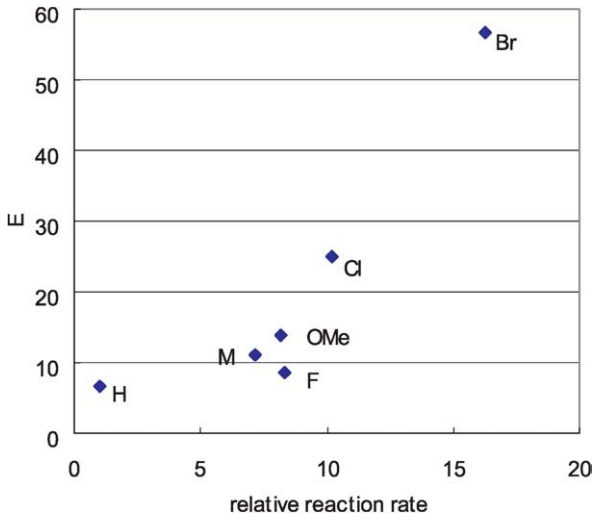


Figure 5. Relation between the enatioselectivity and reactivity. Relative reaction rate was calculated by comparing each (convn./time) of **2b–f** with that of **2a** (R=H).

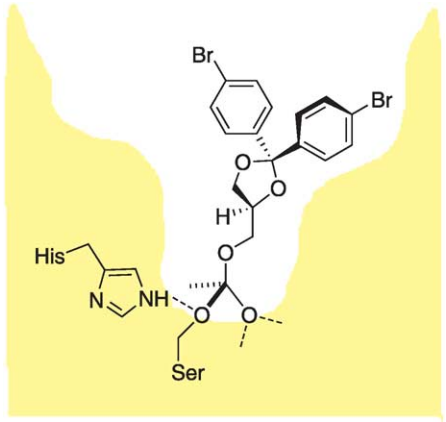


Figure 6. Supposed model of the fast-reacting (*S*)-enantiomer for PCL and the cutaway view of the active-site cleft of PCL. Larger hydrophobic pocket is located far away from the cutaway view and alternate hydrophobic pocket points toward this side.

3. Conclusion

In summary, we have demonstrated that the efficient modification of the substrate structure with bis(4-bromophenyl) ketal as the protecting group enhanced the enantioselectivity of the lipase-catalyzed kinetic resolution of glycerol derivatives at 0 °C. This substrate-tuning method by a protecting group would provide an alternative approach to improve the lipase-catalyzed kinetic resolution of primary alcohols.

4. Experimental

4.1. General

The IR spectra were determined using a JASCO A 302 FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using a JNM-A400 spectrometer, respectively. The mass spectra were recorded using a JEOL JMS-SX102A mass spectrometer. The optical rotations were determined using a JASCO P-1010 polarimeter. The HPLC analysis was carried out using DAICEL Chiralcel OD and OD-H columns (0.46×25 cm) with a Shimadzu LC6A. TLC was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25 mm) and the column chromatography was performed using Merck 23-400 mesh silica gel. All reagents were purchased from Wako Chemical Co., Tokyo Kasei Kogyo Co., Lancaster Synthesis, Ltd. or Aldrich Chemical.

4.2. Typical procedure for the synthesis of 1,2-ketal of glycerols

4.2.1. 2,2-Bis(4-methylphenyl)-1,3-dioxolane-4-methanol (2b). A mixture of glycerol (0.759 g, 8 mmol), 4,4′-dimethylbenzophenone (1.75 g, 8.2 mmol), and *p*-toluenesulfonic acid (18.2 mg) in toluene (5 ml) was refluxed for 24 h. After cooling, the reaction mixture was quenched with 0.1 M NaOH and extracted with ether. The combined organic layer was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. The residue was washed with hexane and chromatographed (hexane/ethyl acetate, 3:1) to give a viscous oil (1.52 g, 64%); IR (neat) 3465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80 (1H, br s), 2.30 (3H, s), 2.32 (3H, s), 3.62 (1H, dd, J=5.1, 11.7 Hz), 3.78 (1H, dd, J=3.4, 11.7 Hz), 3.95 (1H, dd, J=6.1, 8.1 Hz), 4.00 (1H, t, J=8.1 Hz), 4.29 (1H, m), 7.10 (2H, d, J=8.0 Hz), 7.13 (2H, d, J=7.8 Hz), 7.34 (2H, d, J=8.0 Hz), 7.40 (2H, d, J=7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.1, 63.2, 66.1, 76.8, 110.2, 125.9, 126.1, 128.8, 137.7, 137.9, 139.1, 139.2; EI HRMS $C_{18}H_{20}O_3$ (M^+) 284.1412. Found 284.1452.

4.2.2. 2,2-Bis(4-methoxyphenyl)-1,3-dioxolane-4-methanol (2c). Yield 36%; IR (neat) 3460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80 (1H, br s), 3.76–3.82 (2H, m), 3.78 (3H, s), 3.80 (3H, s), 3.96 (1H, dd, J=6.4, 8.0 Hz), 4.00 (1H, t, J=8.0 Hz), 4.30 (1H, m), 6.83 (2H, d, J=8.4 Hz), 6.87 (2H, d, J=8.4 Hz), 7.36 (2H, d, J=8.4 Hz), 7.42 (2H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 55.3, 63.3, 66.1, 76.7, 110.2, 113.5, 127.7, 134.4, 159.4; EI HRMS $C_{18}H_{20}O_5$ (M^+) 316.1311. Found 316.1325.

4.2.3. 2,2-Bis(4-fluorophenyl)-1,3-dioxolane-4-methanol (2d). Yield 38%; IR (neat) 3455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81 (1H, dd, J=5.8, 6.8 Hz), 3.66 (1H, ddd, J=5.1, 6.8, 12.0 Hz), 3.81 (1H, ddd, J=3.6, 5.8, 11.7 Hz), 3.98 (1H, dd, J=6.1, 8.0 Hz), 4.02 (1H, t, J=8.3 Hz), 4.31 (1H, m), 6.98–7.10 (4H, m), 7.40–7.51 (4H, m); ^{13}C NMR ($CDCl_3$) δ 63.1, 66.3, 76.7, 109.5, 115.1, 115.3, 128.1, 128.2, 161.4, 163.9; EI HRMS $C_{16}H_{14}F_2O_3$ (M^+) 292.0911. Found 292.0870.

4.2.4. 2,2-Bis(4-chlorophenyl)-1,3-dioxolane-4-methanol (2e). Yield 42%; IR (neat) 3460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (1H, dd, J=5.2, 6.4 Hz), 3.65 (1H, ddd, J=5.6, 6.4, 12.0 Hz), 3.80 (1H, ddd, J=4.0, 5.2, 11.6 Hz), 3.98 (1H, dd, J=6.1, 8.1 Hz), 4.02 (1H, dd, J=7.1, 8.1 Hz), 4.31 (1H, m), 7.34–7.25 (4H, m), 7.47–7.37 (4H, m); ^{13}C NMR ($CDCl_3$) δ 62.6, 65.9, 76.7, 108.9, 127.0, 128.1, 133.9, 139.8; EI HRMS $C_{16}H_{14}Cl_2O_3$ (M^+) 324.0320. Found 324.0304.

4.2.5. 2,2-Bis(4-bromophenyl)-1,3-dioxolane-4-methanol (2f). Yield 43%; IR (neat) 3460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ

1.70 (1H, dd, $J=5.8$, 6.8 Hz), 3.65 (1H, ddd, $J=5.1$, 6.8, 12.0 Hz), 3.80 (1H, ddd, $J=3.6$, 5.8, 12.0 Hz), 3.98 (1H, dd, $J=6.4$, 8.3 Hz), 4.02 (1H, dd, $J=7.6$, 8.3 Hz), 4.31 (1H, m), 7.40–7.31 (4H, m), 7.49–7.43 (4H, m); ^{13}C NMR ($CDCl_3$) δ 63.1, 66.4, 77.2, 109.4, 122.7, 127.8, 128.0, 131.6, 131.7, 140.8; EI HRMS $C_{16}H_{14}Br_2O_3$ (M^+) 413.9310. Found 413.9329.

4.3. Typical procedure for lipase-catalyzed tranesterification of 2a with vinyl acetate

Vinyl acetate (74 μl, 0.8 mmol) was added to a suspension of the 1,2-ketal of glycerol **2a** (25.6 mg, 0.1 mmol) and lipase (60 mg) in hexane (2 ml) and the mixture was stirred at 25 °C for 6 h. The reaction was monitored by TLC. The reaction mixture was filtered off on celite and washed with dichloromethane. The filtrate was evaporated under reduced pressure. Flash column chromatography (hexane/ethyl acetate 3:2) of the residue afforded the **2a**-acetate (HPLC with Chiralcel OD, hexane/*i*-PrOH 97:3, 0.7 ml/min^{-1}, retention time; 14 and 16 min for (*R*)- and (*S*)-enantiomer) and the alcohol **2a** (HPLC with Chiralcel OD, hexane/*i*-PrOH 97:3, 0.7 ml/min^{-1}, retention time; 32 and 37 min for (*R*)- and (*S*)-enantiomer). To establish the absolute configuration of the remaining alcohol **2a**, its optical rotation sign was compared with the reported value; (*R*)-(−)-**2a**; $[\alpha]_D^{21}$ −11.5 (*c*, 0.52, MeOH) (lit.,[5] $[\alpha]_D^{20}$ +22.5 (*c*, 0.36, MeOH) for (*S*)-isomer). The other absolute configurations of the remaining alcohols **2b-f** were assigned as (*R*) by comparison of the sign of the optical rotations and the order of retention times on an HPLC chiral column with that of (*R*)-(−)-**2a**. Moreover, those of the acetates were confirmed by transformation (10% acetic acid) into (*S*)-(+)-1-*O*-acetylglycerol.[13]

For **2b** and **2b**-acetate, HPLC with Chiralcel OD, hexane/*i*-PrOH 97:3, 0.7 ml/min^{-1}; **2c**, OD, hexane/*i*-PrOH 97:3, 0.6 ml/min; **2c**-acetate, OD-H, hexane/*i*-PrOH 97:3, 0.7 ml/min^{-1}; **2d**, OD, hexane/*i*-PrOH 96:4, 0.5 ml/min^{-1}; **2d**-acetate, OD-H, hexane/*i*-PrOH 200:1, 0.4 ml/min^{-1}; **2e**, OD, hexane/*i*-PrOH 96:4, 0.6 ml/min^{-1}; **2e**-acetate, OD-H, hexane/*i*-PrOH 200:1, 0.8 ml/min^{-1}; **2f**, OD, hexane/*i*-PrOH 98:2, 0.6 ml/min^{-1}; **2f**-acetate, OD-H, hexane/*i*-PrOH 200:1, 0.4 ml/min^{-1}.

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Chemistry of vinyl sulfones. Approach to novel conformationally restricted analogues of glutamic acid

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Abstract—A totally different approach to conformationally restricted glutamic acid analogues is described, in which one of the acid functions is replaced by a cyclopropanol. The reactivity of cyclopropanol vinyl sulfones toward addition of lithiated Schöllkopf bislactim ether provides a facile synthesis of α-amino acid diastereoisomers. Conformational analysis of these analogues, incorporating solvation effects, and docking to a glutamate receptor model, are used to show the relevance of the conformational restrictions employed.

1. Introduction

S-Glutamic acid (Glu) is the major excitatory neurotransmitter in the central nervous system of vertebrates.[1] Many strategies have been devised to reduce or eliminate the conformational flexibility of the natural ligand. Among these, the most widely used technique is ring insertion. There has been a vast body of work in this area, with the synthesis of three to six-membered carbocyclic analogues, bicyclo[1.1.1]pentane,[2] spiro[2.2]pentane,[3] bicyclo[2.1.1]-hexane,[4] and compounds built upon the bicyclo[2.2.1]heptane,[5] 7-azanorbornane[6] and 2-azanorbornane[7] skeletons. Among all these analogues, the carboxycyclopropylglycines (CCGs) represent the most important source of active analogues for the Glu receptors.[8] The vast majority of analogues described up to the present time have two carboxylic acids, so in order to obtain a totally new approach, we decided to replace one of the carboxylic acids with a cyclopropanol group. This change may also be justified on the basis that the delta carboxylate of glutamate is known to interact with at least some of its ionotropic receptors via a hydrogen bond to an uncharged alcohol sidechain of serine, in contrast to the alpha carboxylate which interacts via a salt bridge with an arginine residue and would probably be more difficult to replace with an uncharged group. We also planned to provide greater conformational rigidity via inclusion of a methyl group, suggesting that amino acids such as **1** or **2** could be of interest (Fig. 1).

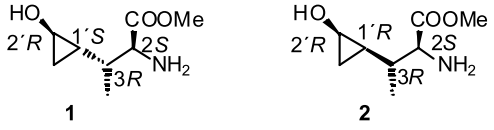

Figure 1. Novel conformationally restricted analogues of glutamic acid.

2. Results and discussion

Recently, we have described a new methodology for the synthesis of cyclopropanols[9] that leads, by choice of the appropriate protecting group and double bond stereochemistry of the allyl sulfone, to *trans* or *cis* 2-substituted cyclopropanols (Scheme 1).[10,11]

The synthesis of amino acid **1** has been described recently[10] following Schöllkopf's methodology,[12] starting from the vinyl sulfone **5**, which in turn is obtained stereoselectively from allyl sulfones **3** or **4**. In this paper we communicate the study of the addition of the lithiated bislactim ether to the vinyl sulfone **6** which presents the *cis* stereochemistry in the cyclopropane ring, and describe how following the same methodology leads to various potential analogues of glutamate.

Keywords: Cyclopropanes; Allyl and vinyl sulfones; Aminoacids.
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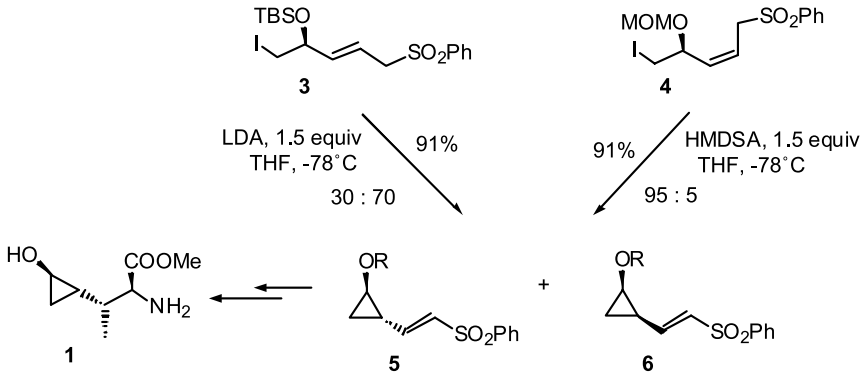


Scheme 1.

The initial coupling of lithiated Schöllkopf's bislactim ether with the vinyl sulfone **6** proceeds in the same way as for the corresponding *trans* diastereoisomer **5**, to give (in this case with complete diastereoselectivity) only one diastereoisomer **8**. This stereoselectivity can be understood by reference to transition states similar to those proposed by Schöllkopf for the addition of the lithiated bislactim ether to α-β unsaturated ester or nitro compounds.[12] The stereochemistry of the addition product **8** was established by examination of the NMR spectra and by means of NOE experiments (Scheme 2).

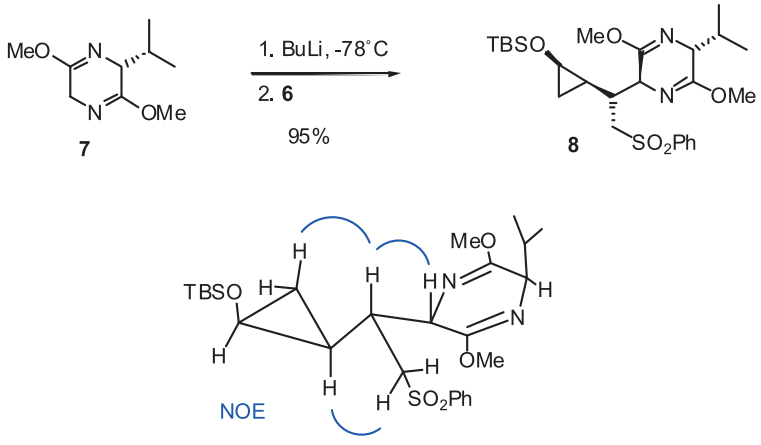
Deprotection of the auxiliary was more problematic than expected. Hydrolysis of compound **8** under the usual conditions gives the required compound **9** in low yield. When compound **8** was treated with TBAF in THF the unstable cyclopropanol **10** was obtained. If, after deprotection of the TBS group, the resulting crude mixture is treated in situ under hydrolytic conditions, compound **11** was obtained as the major component in 84% yield. When shorter reaction times were used, **11** was obtained in 30% yield along with **12** (60% yield). In order to purify **11**, it was submitted to acetylation. Acetate **13** was isolated (Scheme 3). The structures of both compounds (**12** and **13**) were determined by extensive NMR studies.

Due to the problems encountered in the hydrolysis of compound **8** we decided to desulfonylate first. Desulfonylation of **8** under the usual conditions gave **14** (Scheme 4).

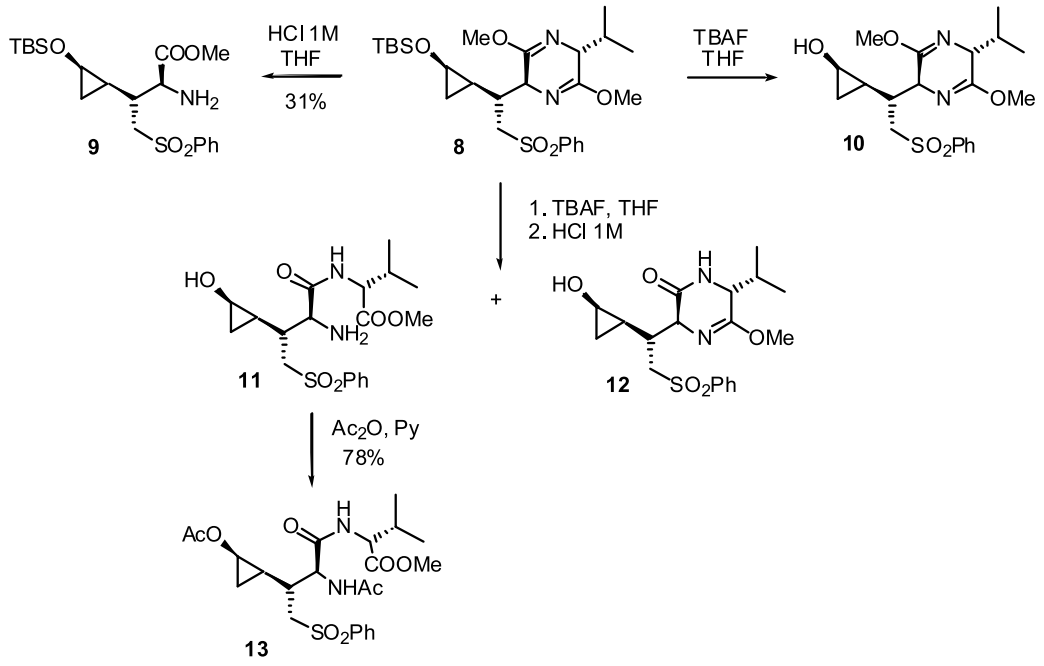
The hydrolysis of the auxiliary was again found to be difficult. Problems with the deprotection of this auxiliary have already been reported by Undheim et al.[13] When compound **14** was deprotected with TBAF the cyclopropanol **15** was obtained, although in low yield, but if the crude mixture was treated with MOM chloride the yield of protected material **16** rose to 88%. Deprotection of the auxiliary in this case takes place smoothly to give the amino ester **17**, but this could not be deprotected under any conditions.

In order to circumvent this problem, the strategy for deprotection was changed. We decided to replace the TBS group by something that could be hydrolyzed in the organism but which would be stable to deprotection under mild acidic conditions, and selected the acetoxy group as an appropriate example. Compound **14** was deprotected and acetylated to give acetate **18** in one step. This compound was submitted to the usual hydrolysis conditions giving the corresponding amino ester **19** in excellent yield. Transformation to compound **20** is observed in the NMR tube where the acetoxy group migrates to the neighbouring amino group. Column chromatography of the mixture gives a small amount of urethane **21** (Scheme 4).

We have already described our work[10] on a comparative conformational analysis of *trans*-**1** with the conformation of glutamic acid proposed to be required for activity at group II metabotropic glutamate receptors (based upon the activities



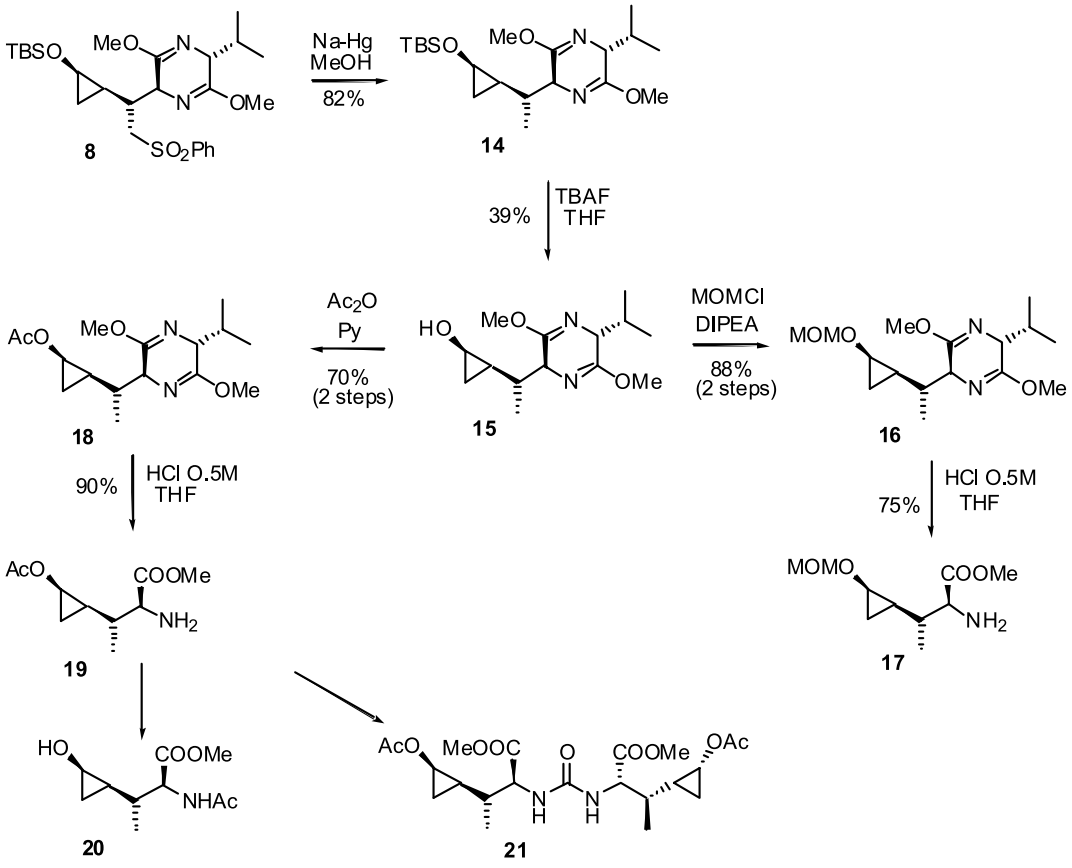
Scheme 2.



Scheme 3.

of conformationally restricted analogues as discussed above), showing that the cyclopropanol OH group is almost perfectly superimposed on the δ acid oxygen of glutamate.

We have carried out a similar study to that performed previously to confirm that the amino acid *cis*-**2** would superimpose well on the conformation of glutamic acid found in the crystal structures of model proteins for the ionotropic glutamate receptors, such as the 1LBC structure from the protein databank.[14] The conformational preference



Scheme 4.

of both *trans*-**1** and *cis*-**2** was determined using macromodel[15] with the MMFFs forcefield,[16] TNCG minimization with up to 5000 interactions and default convergence criteria and torsion driving about the C1–CA–CB–CG and CA–CB–CG–HG torsions (torsion1 and torsion2, respectively) through a full circle with a 15° increment. The GB/SA water solvation model[17] was used and the zwitterionic form of the amino acid was modeled. The solvation model was essential, since otherwise the conformational energy landscape was dominated by intramolecularly hydrogen-bonded species, in agreement with literature precedent on Kainate.[18] Using this method, a clear energy minimum was located at the (torsion1, torsion2) value of (165°, 75°) for both compounds. While this means that the alpha and beta carbons occupy the same locations relative to the α-aminoacid function, the alcohol on the cyclopropane occupies markedly different space (Fig. 2).

The structures shown below each graph represent (with black carbons) the lowest-energy conformation found for the cyclopropane in question and (with green carbons) a reference compound with the α-amino acid in the same orientation. For the *trans* cyclopropane the conformationally rigid group II metabotropic glutamate receptor ligand LY 354740 is shown. For the *cis* cyclopropane glutamic acid as observed in the crystal structure 1LBC[19] from the protein databank is shown.

Given the clear similarity between the *cis* cyclopropanol and glutamate in the conformation found in the 1LBC structure (a model for the ionotropic glutamate receptor type 2, iGluR2), we also examined how well the ligand would fit to the glutamate site of the protein. Thus, the cyclopropanol in its lowest-energy conformation was superimposed using the carboxylate and alpha carbons and the amino nitrogen on the Glu326 glutamate ligand in 1LBC, using Sybyl version 6.9.[20] Glu326 was then excised from the structure and the cyclopropanol *cis*-**2** merged into the structure in its place. Hydrogen atoms were added to the entire system in idealized positions and a short molecular dynamics simulation in which only the hydrogen atoms were allowed to move, and only the zone of 8 Å around the cyclopropanol *cis*-**2** was considered of interest, was used to remove strain in the active site. The simulation ran for 500 fs at a temperature of 10 K with 10 fs coupling, momentum removal and nonbonded reset times, with velocity scaling. A further 500 fs of simulation was then done with all atoms within 5 Å of the ligand permitted to move, but the remainder held rigid. Energy minimization to default convergence, using MMFF94S as the forcefield, was then used to produce a model in which the ligand was docked into the glutamate site. This docking is shown in Figure 3 as a relaxed-eye stereoview. The pocket is shown as a separated surface calculated with Molcad in Sybyl, based upon the ligand atoms and non-water atoms within 5 Å of the ligand. Glutamic acid as observed in the 1LBC crystal structure is shown with orange carbon atoms, while *cis*-**2** is shown with green carbon atoms. All the interactions of the amino acid portion of glutamate with the protein appear to be reproduced by this ligand, along with a hydrogen bond from the cyclopropanol OH group to a serine sidechain that forms an interaction with the delta carboxylate of glutamic acid in the crystal structure 1LBC.

Based on these observations, we believe that it is likely that compounds such as *cis*-**2** may have activity against certain glutamate receptors, and that they may show selectivity as between different classes of receptor.

3. Conclusions

In this manner we have opened a new way for the synthesis of amino acid analogues of glutamic acid using a totally

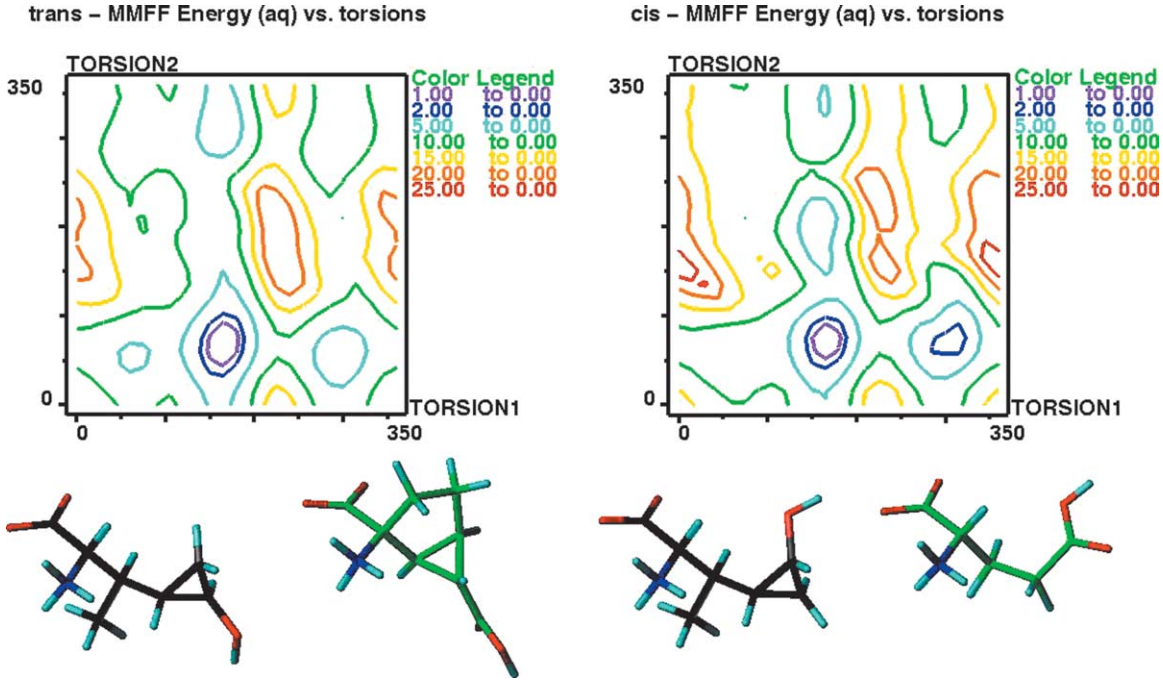


Figure 2. Conformational preferences of *trans*-**1** and *cis*-**2** energies in kcal/mol.

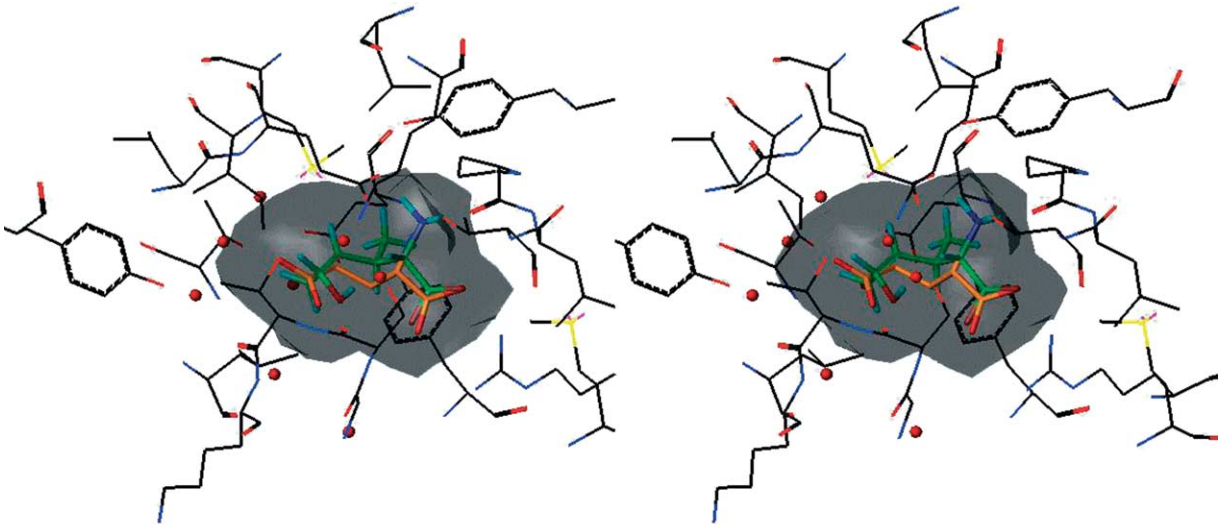


Figure 3. Docking of cyclopropanol *cis*-**2** into the glutamate site of the protein.

different approach, and have devised methods for overcoming the more difficult deprotection of the *cis* as compared to the *trans* cyclopropane intermediates. While the molecular modeling studies do not show conclusively that the ligands we have designed will be ligands for the glutamate receptors, they do suggest that it may be possible to develop such ligands using the synthetic technology that has been discussed here. Both docking of the ligand to the active site of a relevant protein model and conformational search support the view that these ligands may be able to act selectively on subgroups of the glutamate receptors, and the method used for the conformational analysis demonstrates the importance of incorporating solvent effects in the study of such polar systems.

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ using Varian 200 VX and Bruker DRX 400 instruments. IR spectra were registered on a BOMEM 100 FT IR spectrophotometer. Optical rotations were determined in a Perkin-Elmer 241 polarimeter in 1 dm cells. The electron impact (EI) mass spectra were run on a VG-TS 250 spectrometer at 70 eV ionising voltage. HRMS were recorded in a VG Platform (Fisons) spectrometer using Chemical Ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. THF was distilled over Na/benzophenone.

4.1.1. (2*S*,5*R*,1′*R*,1″*R*,2″*R*)-2-{2-Benzenesulfonyl-1-[2-(*tert*-butyl-dimethyl-silanyloxy)-cyclopropyl]-ethyl}-5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazine (8). BuLi 1.6 M in hexane (0.78 mL, 1.25 mmol) was added to a −78 °C solution of *R*-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine **7** (220 mg, 1.19 mmol) in dry THF (4 mL). After 20 min, a solution of **6** (200 mg, 0.59 mmol) in dry THF (3 mL) was added. After 30 min at −78 °C the reaction mixture was quenched with saturated NH_4Cl solution (2 mL). The product was then extracted into EtOAc. The organic extracts were combined, washed with H_2O and saturated brine, then dried over anhydrous Na_2SO_4, filtered and the solvent removed. The crude was purified by flash silica column chromatography (hexane–EtOAc 90:10) to yield 293 mg (0.56 mmol, 95%) of **8** as a white solid. $[\alpha]_D^{22} = +8.8$ (*c* 1.04, $CHCl_3$); TLC (7:3 hexane/EtOAc) $R_f = 0.45$; IR: 2955, 2859, 1692, 1464, 1445, 1310, 1235, 150, 1040, 1011, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 and 0.08 (2s, 3H each, CH_3–Si), 0.52 (dt, $J=3.2$, 6.2, 6.2 Hz, 1H, H_β-3″), 0.68 and 0.99 (2d, $J=6.8$ Hz, 3H each, $(CH_3)_2CH$–), 0.75 (dt, $J=9.2$, 6.2, 6.2 Hz, 1H, H_α-3″), 0.84 (s, 9H, *t*Bu–Si), 1.16 (m, 1H, H-1″), 2.19 (dhep, $J=3.6$, 6.8 Hz, 1H, $(CH_3)_2CH$–), 2.60 (m, 1H, H-1′), 2.89 (dd, $J=3.2$, 14.6 Hz, 1H, H_A-2′), 3.15 (dd, $J=9.2$, 14.6 Hz, 1H, H_B-2′), 3.44 (dt, $J=3.2$, 6.2, 6.2 Hz, 1H, H-2″), 3.48 and 3.67 (2s, 3H each, MeO–), 3.93 (t, $J=3.6$ Hz, 1H, H-5), 4.27 (t, $J=3.6$ Hz, 1H, H-2), 7.53 (m, 2H, H_{meta} –SO_2Ph), 7.62 (m, 1H, H_{para} –SO_2Ph), 7.87 (m, 2H, H_{ortho} –SO_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4 and −4.9 (CH_3–Si), 14.5 (C-3″), 16.8 and 18.8 [$(CH_3)_2CH$–], 17.7 [$(CH_3)_3CSi$], 18.2 (C-1″), 25.4 [$(CH_3)_3CSi$], 32.4 [$(CH_3)_2CH$–], 36.2 (C-1′), 50.0 (C-2″), 52.2 and 52.3 (MeO–), 57.6 (C-2′), 58.9 (C-2), 61.0 (C-5), 127.9 (C_{ortho}, –SO_2Ph), 129.0 (C_{meta}, –SO_2Ph), 133.1 (C_{para}, –SO_2Ph), 140.2 (C_{ipso}, –SO_2Ph), 162.4 (C-6), 164.5 (C-3); MS: *m*/*z* (%) 523 (25) $[M+1]^+$, 141 (70), 73 (100); HRMS: calcd for $C_{26}H_{43}N_2O_5SSi$ $[M+1]^+$: 523.2662, found 523.2622.

4.1.2. (2*S*,3*R*,1′*R*,2′*R*)-2-Amino-4-benzenesulfonyl-3-[2′-(*tert*-butyl-dimethyl-silanyloxy)-cyclopropyl]-butyric acid methyl ester (9). To a solution of **8** (63.4 mg, 0.121 mmol) in THF (1 mL) was added HCl 1 M (0.3 mL, 0.30 mmol). The mixture was left to stir for 15 h at room temperature. Concentrated ammonia was then added to the stirred mixture until a pH of 9 was reached. The product was extracted into CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and the solvent removed. The crude product was purified by flash silica column chromatography (hexane–EtOAc 50:50) to yield 16 mg (0.037 mmol, 31%) of **9** as a colourless oil. TLC (EtOAc) $R_f = 0.43$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 and 0.09 (2s, 3H each, CH_3–Si), 0.12 (dt, $J=$ 3.2, 6.2, 6.2 Hz, 1H, H_β-3′), 0.61 (m, 1H, H_α-3′), 0.88 (s,

9H, *t*Bu–Si), 1.17 (m, 1H, H-1′), 2.23 (m, 1H, H-3), 3.22 (dd, $J=5.2$, 14.8 Hz, 1H, H_A-4), 3.36 (dt, $J=3.2$, 6.2, 6.2 Hz, 1H, H-2′), 3.46 (dd, $J=6.2$, 14.8 Hz, 1H, H_B-4), 3.69 (s, 3H, –COOMe), 3.84 (m, 1H, H-2), 7.50 (m, 3H, H_{meta} and H_{para} –SO_2Ph), 7.84 (m, 2H, H_{ortho} –SO_2Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.0 and −4.7 (CH_3–Si), 13.7 (C-3′), 18.1 [$(CH_3)_3C$Si], 19.4 (C-1′), 25.8 [$(CH_3)_3$CSi], 37.1 (C-3), 51.2 (C-2′), 52.3 (–COO*Me*), 56.7 (C-2), 57.6 (C-4), 128.3 (C_{ortho}, –SO_2Ph), 129.4 (C_{meta}, –SO_2Ph), 133.7 (C_{para}, –SO_2Ph), 140.1 (C_{ipso}, –SO_2Ph), 176.0 (–*C*OOMe).

4.1.3. (2*S*,5*R*,1′*R*,1″*R*,2″*R*)-2-{2′-Benzenesulfonyl-1′-[2″-hydroxy-cyclopropyl]-ethyl}-5-isopropyl-3,6-dimethoxy-2,5-dihydro-pyrazine (10). To a solution of **8** (44.8 mg, 0.068 mmol) in THF (0.75 mL) was added tetrabutylammonium fluoride 1.0 M solution in THF (130 μL, 0.13 mmol). The mixture was left to stir for 2 h. It was then diluted with EtOAc, washed with H_2O and saturated brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Attempts were made to purify the crude product by flash column chromatography on silica gel, but cyclopropanol **10** proved unstable and could not be isolated.

4.1.4. (2*S*,3*R*,2′*R*,1″*R*,2″*R*)-2′-[2-Amino-4-benzenesulfonyl-3-(2″-hydroxy-cyclopropyl)-butyryl amino]-3′-methyl-butyric acid methyl ester (11). To a solution of **8** (23.6 mg, 0.045 mmol) in THF (0.75 mL) was added tetrabutylammonium fluoride 1.0 M solution in THF (60 μL, 0.60 mmol). The mixture was left to stir for 1 h. The reaction was quenched with H_2O (0.2 mL) and HCl 1 M solution (0.13 mL, 0.13 mmol) was then added. It was left to stir for 3 h at room temperature. Concentrated ammonia was then added to the stirred mixture until a pH of 9 was reached. The product was extracted into CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and the solvent removed. The crude product was purified by flash column chromatography on silica (hexane–EtOAc 30:70) to yield 15.6 mg (0.038 mmol, 84%) of slightly impure compound **11**. TLC (EtOAc) $R_f=0.14$; IR: 3600–3100, 2965, 1742, 1669, 1516, 1447, 1306, 1148; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.10 (m, 1H, H_β-3″), 0.67 (m, 1H, H_α-3″), 0.94 (m, 1H, H-1″), 1.02 (d, $J=6.9$ Hz, 6H, (CH_3)$_2$CH–), 2.26 (m, 1H, (CH_3)$_2$C*H*–), 3.23 (m, 1H, H-3), 3.36 (dd, $J=3.2$, 14.6 Hz, 1H, H_A-4), 3.43 (m, 1H, H-2′), 3.59 (dd, $J=11.0$, 14.6 Hz, 1H, H_B-4), 3.76 (s, 3H, –COOMe), 3.75 (m, 1H, H-2), 4.14 (d, $J=$ 4.8 Hz, 1H, –NH), 4.53 (dd, $J=4.8$, 8.0 Hz, 1H, H-2′), 7.60 (m, 3H, H_{meta} and H_{para} –SO_2Ph), 7.93 (m, 2H, H_{ortho} –SO_2Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4 (C-3″), 18.2 and 19.6 [(CH_3)$_2$CH–], 18.8 (C-1″), 31.0 [(CH_3)$_2$*C*H–], 39.0 (C-3), 49.6 (C-2″), 52.5 (–COO*Me*), 54.6 (C-2′), 58.0 (C-2), 58.5 (C-4), 127.9 (C_{ortho}, –SO_2Ph), 129.8 (C_{meta}, –SO_2Ph), 134.3 (C_{para}, –SO_2Ph), 139.4 (C_{ipso}, –SO_2Ph), 172.2 and 173.0 (CO).

4.1.5. (2*S*,5*R*,1′*R*,1″*R*,2″*R*)-2-[2′-Benzenesulfonyl-1′-(2″-hydroxy-cyclopropyl)-ethyl]-5-isopropyl-6-methoxy-2,5-dihydro-1*H*-pyrazin-3-one (12). To a solution of **8** (56.3 mg, 0.108 mmol) in THF (1 mL) was added tetrabutylammonium fluoride 1.0 M solution in THF (140 μL, 0.14 mmol). The mixture was left to stir for 1 h. The reaction was quenched with H_2O (0.2 mL) and HCl 1 M solution (0.35 mL, 0.35 mmol) was then added. It was left to stir for 1 h at room temperature. Concentrated ammonia was then added to the stirred mixture until a pH of 9 was reached. The product was extracted into CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and the solvent removed. Compounds were separated by flash column chromatography on silica (hexane–EtOAc 50:50) to yield 25.6 mg (0.065 mmol, 60%) of **12** and 15.5 mg (0.038 mmol, 35%) of **11**. Compound **12**: $[\alpha]_D^{22}=-8.0$ (*c* 1.00, $CHCl_3$); TLC (EtOAc) $R_f=0.40$; IR: 3600–3100, 2959, 2930, 1672, 1466, 1447, 1306, 1231, 1148; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (dt, $J=3.2$, 6.0, 6.0 Hz, 1H, H_β-3″), 0.61 (dt, $J=9.2$, 6.0, 6.0 Hz, 1H, H_α-3″), 0.93 and 1.00 (2d, $J=6.9$ Hz, 3H each, (CH_3)$_2$CH–), 0.96 (m, 1H, H-1″), 2.16 (m, 1H, (CH_3)$_2$C*H*–), 2.60 (tt, $J=2.8$, 2.8, 10.4, 10.4 Hz, 1H, H-1′), 3.30 (dt, $J=$ 3.2, 6.2, 6.2 Hz, 1H, H-2″), 3.36 (dd, $J=2.8$, 14.6 Hz, 1H, H_A-2′), 3.76 (m, 1H, H-5), 3.78 (s, 3H, MeO–), 4.51 (dd, $J=10.0$, 14.6 Hz, 1H, H_B-2′), 4.56 (t, $J=2.8$ Hz, 1H, H-2), 4.66 (br s, 1H, –OH), 6.45 (d, $J=2.6$ Hz, 1H, –NH), 7.56 (m, 2H, H_{meta} –SO_2Ph), 7.64 (m, 1H, H_{para} –SO_2Ph), 7.94 (m, 2H, H_{ortho} –SO_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (C-3″), 17.6 and 18.8 [(CH_3)$_2$CH–], 19.4 (C-1″), 32.4 [(CH_3)$_2$*C*H–], 37.2 (C-1′), 49.4 (C-2″), 53.9 (MeO–), 57.1 (C-2), 58.4 (C-2′), 59.6 (C-5), 127.9 (C_{ortho}, –SO_2Ph), 129.2 (C_{meta}, –SO_2Ph), 133.5 (C_{para} –SO_2Ph), 139.9 (C_{ipso}, –SO_2Ph), 163.9 (C-6), 171.0 (C-3); MS: *m*/*z* (%) 395 (10) $[M+1]^+$, 186 (5); HRMS: calcd for $C_{19}H_{27}N_2O_5S$ $[M+1]^+$: 395.1641, found 395.1632.

4.1.6. (2*S*,3*R*,2′*R*,1″*R*,2″*R*)-2′-[3-(2″-Acetoxy-cyclopropyl)-2-acetylamino-4-benzenesulfonyl-butyryl amino]-3′-methyl-butyric acid methyl ester (13). To a solution of **11** (30 mg, 0.073 mmol) in pyridine (1 mL) was added Ac_2O (0.5 mL). The solution was allowed to stir for 21 h. Ice was then added and the mixture was poured into a separating funnel and extracted with EtOAc. The organic extracts were combined, washed with a solution of 2 N HCl, a solution of $NaHCO_3$ (5%), H_2O, and brine, and then dried over anhydrous Na_2SO_4, filtered and the solvent removed. The product was purified by column chromatography (hexane–EtOAc 50:50) to yield 25.3 mg of **13** (0.057 mmol, 78%). $[\alpha]_D^{22}=+6.2$ (*c* 1.17, $CHCl_3$); TLC (EtOAc) $R_f=0.20$; IR: 3500–3200, 2967, 1744, 1663, 1632, 1447, 1375, 1306, 1236, 1148; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (dt, $J=3.5$, 7.1, 7.1 Hz, 1H, H_β-3″), 0.95 (m, 1H, H_α-3″), 0.97 and 1.00 (2d, $J=6.8$ Hz, 3H each, (CH_3)$_2$CH–), 1.30 (m, 1H, H-1″), 2.01 and 2.02 (2s, 3H each, CH_3CO–), 2.23 (m, 2H, H-3 and (CH_3)$_2$C*H*–), 3.30 (dd, $J=3.6$, 14.7 Hz, 1H, H_A-4), 3.59 (dd, $J=9.2$, 14.7 Hz, 1H, H_B-4), 3.73 (s, 3H, –COOMe), 4.24 (dt, $J=3.4$, 6.6, 6.6 Hz, 1H, H-2″), 4.44 (dd, $J=4.8$, 8.3 Hz, 1H, H-2′), 5.08 (dd, $J=4.5$, 7.7 Hz, 1H, H-2), 6.71 (d, $J=7.6$ Hz, N*H*Ac), 7.12 (d, $J=$ 8.2 Hz, 1H, NHCO), 7.59 (m, 2H, H_{meta} –SO_2Ph), 7.67 (m, 1H, H_{para} –SO_2Ph), 7.98 (m, 2H, H_{ortho} –SO_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 (C-3″), 17.2 (C-1″), 17.8 and 19.1 [(CH_3)$_2$CH–], 20.7 and 23.1 (CH_3CO–), 30.7 [(CH_3)$_2$*C*H–], 34.7 (C-3), 52.1 (–COO*Me*), 53.4 (C-2″), 54.0 (C-2), 57.6 (C-2′), 58.3 (C-4), 128.1 (C_{ortho}, –SO_2Ph), 129.4 (C_{meta}, –SO_2Ph), 134.0 (C_{para}, –SO_2Ph), 138.8 (C_{ipso}, –SO_2Ph), 169.6 (CONH), 170.2 (NH*C*OCH$_3$), 171.2 (O*C*OCH$_3$), 171.6 (–*C*OOMe); MS: *m*/*z* (%) 497 (10) $[M+1]^+$, 366 (10), 196 (10); HRMS: calcd for $C_{23}H_{33}N_2O_8S$ $[M+1]^+$: 497.1958, found 497.1954.

4.1.7. (2*S*,5*R*,1′*R*,1″*R*,2″*R*)-2-{1′-[2″-(*tert*-Butyl-dimethyl-silanyloxy)-cyclopropyl]-ethyl}-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (14). A solution of **8** (163 mg, 0.312 mmol) in dry MeOH (4 mL) was added to Na–Hg 5% amalgam (1 g) via cannula. The reaction mixture was left to stir for 1 h 30 min at room temperature under Ar. The residue was filtered and diluted with EtOAc. The mixture was washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed. The crude product was purified by flash column chromatography on silica (hexane–EtOAc 95:5) to yield 98 mg (0.256 mmol, 82%) of **14** as a white solid. $[\alpha]_D^{22}=-21.8$ (*c* 0.93, $CHCl_3$); TLC (7:3 hexane–EtOAc) $R_f=0.63$; IR: 2959, 2859, 1699, 1462, 1366, 1235, 1152, 1045, 1015, 839, 775; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 6H, CH_3–Si), 0.12 (m, 1H, H_β-3″), 0.62 (dt, $J=9.6$, 5.8, 5.8 Hz, 1H, H_α-3″), 0.70 and 1.04 (2d, $J=7.0$ Hz, 3H each, (CH_3)$_2$CH–), 0.74 (d, $J=6.8$ Hz, 3H, H-2′), 0.89 (s, 9H, *t*Bu–Si), 1.05 (m, 1H, H-1″), 2.06 (m, 1H, (CH_3)$_2$C*H*–), 2.25 (m, 1H, H-1′), 3.49 (dt, $J=3.2$, 6.2, 6.2 Hz, 1H, H-2″), 3.64 and 3.70 (2s, 3H each, MeO–), 3.93 (t, $J=3.2$ Hz, 1H, H-5), 4.21 (t, $J=3.2$ Hz, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.0 and −4.7 (CH_3–Si), 12.9 (C-3″), 14.0 (C-2′), 16.8 and 19.2 [(*C*H$_3$)$_2$CH–], 18.1 [(CH$_3$)$_3$*C*Si–], 19.8 (C-1″), 25.8 [(*C*H$_3$)$_3$CSi–], 32.1 [(CH$_3$)$_2$*C*H–], 35.6 (C-1′), 50.9 (C-2″), 52.3 and 52.4 (MeO–), 59.4 (C-2), 60.8 (C-5), 163.6 (C-6), 164.2 (C-3); MS: *m*/*z* (%) 383 (10) $[M+1]^+$, 199 (15), 141 (35), 73 (100); HRMS: calcd for $C_{20}H_{39}N_2O_3Si$ $[M+1]^+$: 383.2730, found 383.2701.

4.1.8. (2*S*,5*R*,1′*R*,1″*R*,2″*R*)-2-[1′-(2″-Hydroxy-cyclopropyl)-ethyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (15). To a solution of **14** (56.2 mg, 0.147 mmol) in THF (1 mL) was added tetrabutylammonium fluoride 1.0 M solution in THF (190 μL, 0.19 mmol). The mixture was left to stir for 30 min. It was then diluted with EtOAc, washed with H_2O and saturated brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography on silica (hexane–EtOAc 80:20) to yield 15.3 mg (0.057 mmol, 39%) of **15** as a colourless oil. $[\alpha]_D^{22}=+14.6$ (*c* 1.12, $CHCl_3$); TLC (7:3 hexane–EtOAc) $R_f=0.38$; IR: 3600–3100, 2961, 1694, 1462, 1308, 1236, 1015, 774; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.24 (dt, $J=3.2$, 6.2, 6.2 Hz, 1H, H_β-3″), 0.70 (m, 1H, H_α-3″), 0.72 and 1.05 (2d, $J=6.6$, 7.2 Hz, respectively, 3H each, (CH_3)$_2$CH–), 0.84 (m, 1H, H-1″), 1.04 (d, $J=7.0$ Hz, 3H, H-2′), 2.12 (m, 1H, (CH_3)$_2$C*H*–), 2.24 (m, 1H, H-1′), 3.43 (dt, $J=3.0$, 6.6, 6.6 Hz, 1H, H-2″), 3.71 (s, 6H, MeO–), 3.97 (t, $J=3.6$ Hz, 1H, H-5), 4.02 (t, $J=3.6$ Hz, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.8 (C-3″), 16.6 (C-2′), 17.1 and 19.3 [(*C*H$_3$)$_2$CH–], 20.9 (C-1″), 32.1 [(CH$_3$)$_2$*C*H–], 36.4 (C-1′), 50.0 (C-2″), 52.6 and 52.8 (MeO–), 59.5 (C-5), 61.3 (C-2), 163.8 (C-6), and 165 (C-3).

4.1.9. (2*S*,5*R*,1′*R*,1″*R*,2″*R*)-5-Isopropyl-3,6-dimethoxy-2-[1′-(2″-methoxymethoxy-cyclopropyl)-ethyl]-2,5-dihydro-pyrazine (16). To a solution of **14** (34.7 mg, 0.091 mmol) in THF (1 mL) was added tetrabutylammonium fluoride 1.0 M solution in THF (100 μL, 0.10 mmol). The mixture was left to stir for 45 min. Then, it was diluted with EtOAc, washed with H_2O and saturated brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was submitted for MOM protection. It was dissolved in dry CH_2Cl_2 (1 mL). To the ice-cooled solution, diisopropylethyl amine (20 μL, 0.109 mmol) and MOMCl (30 μL, 0.40 mmol) were added. After 1 h 30 min the reaction mixture was quenched with H_2O (0.5 mL). The product was extracted into Et_2O. The organic extracts were combined, washed with H_2O and saturated brine, then dried over anhydrous Na_2SO_4, filtered and the solvent removed. The crude was purified by flash column chromatography on silica (hexane–EtOAc 90:10) to yield 24.8 mg (0.079 mmol, 88%) of **16** as a colourless oil. $[\alpha]_D^{22}=-49.0$ (*c* 1.20, $CHCl_3$); TLC (7:3 hexane–EtOAc) $R_f=0.49$; IR: 2961, 1697, 1458, 1236, 1047; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.26 (dt, $J=3.2$, 6.0, 6.0 Hz, 1H, H_β-3″), 0.70 and 1.04 (2d, $J=7.0$, 6.6 Hz, respectively, 3H each, (CH_3)$_2$CH–), 0.75 (m, 1H, H_α-3″), 0.77 (d, $J=7.2$ Hz, 3H, H-2′), 1.22 (m, 1H, H-1″), 2.02 (m, 1H, (CH_3)$_2$C*H*–), 2.25 (m, 1H, H-1′), 3.42 (s, 3H, –CH_2OCH_3), 3.57 (dt, $J=3.2$, 6.6, 6.6 Hz, 1H, H-2″), 3.67 and 3.70 (2s, 3H each, MeO–), 3.94 (t, $J=3.2$ Hz, 1H, H-5), 4.17 (t, $J=3.2$ Hz, 1H, H-2), 4.70 (m, 2H, –CH_2OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.6 (C-3″), 14.4 (C-2′), 16.9 and 19.3 [(*C*H$_3$)$_2$CH–], 20.7 (C-1″), 32.1 [(CH$_3$)$_2$*C*H–], 35.5 (C-1′), 52.4 and 52.5 (MeO–), 55.4 (C-2″), 55.9 (–CH_2OCH_3), 59.4 (C-2), 60.9 (C-5), 97.1 (–CH_2OCH_3), 163.7 (C-6 and C-3); MS: *m*/*z* (%) 313 (75) $[M+1]^+$, 281 (30), 183 (25), 141 (100); HRMS: calcd for $C_{16}H_{29}N_2O_4$ $[M+1]^+$: 313.2127, found 313.2143.

4.1.10. (2*S*,3*R*,1′*R*,2′*R*)-2-Amino-3-(2′-methoxymethoxy-cyclopropyl)-butyric acid methyl ester (17). To a solution of **16** (24.8 mg, 0.079 mmol) in THF (1.5 mL) was added HCl 0.5 M (0.5 mL, 0.25 mmol). The mixture was left to stir for 14 h at room temperature. Concentrated ammonia was then added to the stirred mixture until a pH of 9 was reached. The product was extracted into CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and the solvent removed. The crude product was purified by flash column chromatography on silica ($CHCl_3$–MeOH 98:2) to yield 13 mg (0.059 mmol, 75%) of **17**. $[\alpha]_D^{22}=-52.3$ (*c* 0.73, $CHCl_3$); TLC (9:1 $CHCl_3$–MeOH) $R_f=0.45$; IR: 3385, 3320, 2959, 1746, 1441, 1225, 1159, 1045; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.26 (dt, $J=3.2$, 6.2, 6.2 Hz, 1H, H_β-3′), 0.72 (m, 1H, H_α-3′), 0.93 (m, 1H, H-1′), 1.03 (d, $J=7.4$ Hz, 3H, H-4), 1.82 (m, 1H, H-3), 3.30 (br s, 2H, –NH_2), 3.40 (–CH_2OCH_3), 3.54 (dt, $J=3.4$, 6.2, 6.2 Hz, 1H, H-2′), 3.72 (m, 1H, H-2), 3.74 (s, 3H, –COOMe), 4.68 (s, 2H, –CH_2OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.8 (C-3′), 15.5 (C-4), 20.7 (C-1′), 36.2 (C-3), 52.1 (–COO*Me*), 54.9 (C-2′), 56.0 (–CH_2OCH_3), 58.5 (C-2), 97.0 (–CH_2OCH_3), 176 (–*C*OOMe); MS: *m*/*z* (%) 218 (60) $[M+1]^+$, 186 (15); HRMS: calcd for $C_{10}H_{20}NO_4$ $[M+1]^+$: 218.1392, found 218.1378.

4.1.11. (2*S*,5*R*,1′*R*,1″*R*,2″*R*)-2-[1′-(2″-Acetoxy-cyclopropyl)-ethyl]-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (18). To a solution of **14** (27.3 mg, 0.071 mmol) in THF (0.75 mL) was added tetrabutylammonium fluoride 1.0 M solution in THF (80 μL, 0.08 mmol). The mixture was left to stir for 1 h. It was then diluted with EtOAc, and washed with H_2O and saturated brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was submitted for acetylation. It was

dissolved in pyridine (1 mL) and Ac_2O (0.5 mL) was added. The solution was allowed to stir for 6 h. Ice was then added and the mixture was poured into a separating funnel and extracted with EtOAc. The organic extracts were combined, washed with a solution of 2 N HCl, a solution of $NaHCO_3$ (5%), H_2O, and brine, and then dried over anhydrous Na_2SO_4, filtered and the solvent removed. The product was purified by column chromatography (hexane–EtOAc 90:10) to yield 15.4 mg (0.050 mmol, 70%) of **18**. $[\alpha]_D^{22}=+27.3$ (*c* 1.24, $CHCl_3$); TLC (7:3 hexane–EtOAc) $R_f=0.55$; IR: 2965, 1748, 1697, 1236; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.42 (dt, $J=3.4$, 6.2, 6.2 Hz, 1H, H_β-3″), 0.68 and 1.04 (2d, $J=7.0$ Hz, 3H each, $(CH_3)_2CH$–), 0.76 (d, $J=7.0$ Hz, 3H, H-2′), 0.95 (dt, $J=9.6$, 6.6, 6.6 Hz, 1H, H_α-3″), 1.42 (m, 1H, H-1″), 1.89 (m, 1H, $(CH_3)_2CH$–), 2.08 (CH_3CO), 2.26 (m, 1H, H-1′), 3.67 and 3.69 (s, 3H each, MeO–), 3.94 (t, $J=3.6$ Hz, H-5), 4.05 (t, $J=3.8$ Hz, H-2), 4.24 (dt, $J=3.4$, 6.6, 6.6 Hz, 1H, H-2″); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.7 (C-3″), 14.1 (C-2′), 16.8 and 19.3 [$(CH_3)_2CH$–], 20.0 (C-1″), 21.1 (CH_3CO–), 32.0 [$(CH_3)_2CH$–], 35.5 (C-1′), 52.4 and 52.5 (MeO–), 53.5 (C-2″), 59.2 (C-2), 60.8 (C-5), 163.4 (C-6), 163.6 (C-3), 172.5 (CH_3CO–); MS: *m*/*z* (%) 311 (100) $[M+1]^+$, 267 (25), 183 (25), 141 (80); HRMS: calcd for $C_{16}H_{27}N_2O_4$ $[M+1]^+$: 311.1971, found 311.1962.

4.1.12. (2*S*,3*R*,1′*R*, 2′*R*)-3-(2′-Acetoxy-cyclopropyl)-2-amino-butyric acid methyl ester (19). To a solution of **18** (13 mg, 0.042 mmol) in THF (1 mL) was added HCl 0.5 M (0.2 mL, 0.10 mmol). The mixture was left to stir for 7 h at room temperature. Concentrated ammonia was then added to the stirred mixture until a pH of 9 was reached. The product was extracted into CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and the solvent removed. Compound **19** [8.1 mg (0.038 mmol, 90%)] was obtained. TLC (9:1 $CHCl_3$–MeOH) $R_f=0.35$; IR: 3300, 2961, 1744, 1373, 1236; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.44 (dt, $J=3.4$, 6.6, 6.6 Hz, 1H, H_β-3′), 0.90 (m, 1H, H_α-3′), 1.05 (d, $J=7.0$ Hz, 3H, H-4), 1.13 (m, 2H, H-1′), 1.13 (m, 2H, H-1′ and H-3), 2.07 (s, 3H, CH_3CO), 3.36 (br s, 2H, $-NH_2$), 3.70 (m, 1H, H-2), 3.73 (s, 3H, –COOMe), 4.22 (dt, $J=3.4$, 6.6, 6.6 Hz, 1H, H-2′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.97 (C-3′), 14.8 (C-4), 20.1 (C-1′), 21.0 (CH_3CO), 35.3 (C-3), 52.5 (–COO*Me*), 53.1 (C-2′), 56.8 (C-2), 172.3 (–*C*OOMe and CH_3CO); MS: *m*/*z* (%) 216 (10) $[M+1]^+$, 91 (35); HRMS: calcd for $C_{10}H_{18}NO_4$ $[M+1]^+$: 216.1236, found 216.1262.

4.1.13. (2*S*,3*R*,1′*R*, 2′*R*)-2-Acetylamino-3-(2′-hydroxy-cyclopropyl)-butyric acid methyl ester (20). Compound **20** was isolated during attempts to purify compound **19**. $[\alpha]_D^{22}=+4.3$ (*c* 0.14, $CHCl_3$); TLC (9:1 $CHCl_3$–MeOH) $R_f=0.23$; IR: 3600–3100, 2969, 1744, 1659, 1377; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.26 (dt, $J=3.4$, 6.2, 6.2 Hz, 1H, H_β-3′), 0.51 (dt, $J=9.6$, 6.6, 6.6 Hz, 1H, H_α-3′), 0.79 (m, 1H, H-1′), 1.13 (d, $J=7.4$ Hz, 3H, H-4), 1.64 (br s, 1H, –OH), 1.84 (m, 1H, H-3), 2.02 (s, 3H, CH_3CO), 3.52 (dt, $J=3.4$, 6.6, 6.6 Hz, 1H, H-2′), 3.75 (s, 3H, –COOMe), 4.58 (dd, $J=5.2$, 7.8 Hz, 1H, H-2), 6.60 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.3 (C-3′), 17.6 (C-4), 21.0 (C-1′), 23.3 (CH_3CO), 35.4 (C-3), 50.7 (C-2′), 52.4 (–COO*Me*), 56.8 (C-2), 170.4 (CH_3CO), 173.1 (–*C*OOMe); MS: *m*/*z* (%) 216 (10) $[M+1]^+$, 178 (10), 95 (40), 69 (80); HRMS: calcd for $C_{10}H_{18}NO_4$ $[M+1]^+$: 216.1236, found 216.1232.

4.1.14. (2*S*,3*R*,1′*R*,2′*R*)-3-(2′-Acetoxy-cyclopropyl)-2-[3-(2′-acetoxy-cyclopropyl)-2-methoxycarbonyl-propyl]-ureido}-butyric acid methyl ester (21). Compound **21** was isolated during attempts to purify compound **19**. TLC (9:1 $CHCl_3$–MeOH) $R_f=0.35$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (m, 2×1H, H_β-3′), 0.96 (m, 2×2H, H_α-3′ and H-1′), 1.06 (d, $J=7.1$ Hz, 2×3H, H-4), 1.73 (m, 2×1H, H-3), 2.09 (s, 2×3H, CH_3CO), 3.69 (s, 2×3H, –COOMe), 4.25 (dt, $J=3.5$, 6.7, 6.7 Hz, 2×1H, H-2′), 4.50 (dd, $J=4.4$, 9.2 Hz, 2×1H, H-2), 5.31 (d, $J=9.2$ Hz, 2×1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9 (C-3′), 16.3 (C-4), 19.0 (C-1′), 20.9 (CH_3CO), 34.5 (C-3), 51.9 (–COO*Me*), 53.2 (C-2′), 56.5 (C-2), 157.1 (–NHCONH–), 172.7 (CH_3CO), 173.1 (–*C*OOMe); MS: *m*/*z* (%) 479 (30) $[M+Na]^+$, 457 (15) $[M+1]^+$, 216 (15); HRMS: calcd for $C_{21}H_{33}N_2O_9$ $[M+1]^+$: 457.2186, found 457.2203.

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A polystyrene-supported triflating reagent for the synthesis of aryl triflates

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Abstract—An insoluble polystyrene-supported triflating reagent has been prepared by suspension co-polymerization of *N*-(4-vinylphenyl)trifluoromethanesulphonimide, styrene and the *J*anda*J*el® cross-linker. This reagent, in the presence of triethylamine, allows for the efficient synthesis of aryl triflates from a wide range of phenols in a process that permits the desired product to be isolated from the reaction mixture in essentially pure form via several filtration and concentration operations. Adding to the utility of this reagent is its ability to be easily recovered, regenerated and reused. Both soluble and insoluble bifunctional polymers containing trialkylamine moieties in addition to triflimide groups were also prepared and examined as triflating reagents. Unfortunately these reagents afforded only modest yields of the desired products in representative reactions.

1. Introduction

The use of polymer-supported reagents and catalysts in polymer-assisted organic synthesis has become commonplace since they can reduce product purification to simple filtration and concentration operations and are potentially easily recycled.[1] A vast array of such reagents and catalysts have been reported that use both insoluble[2] and soluble[3] polymers as their carriers and new ones are continually being developed in order to broaden the range of reactions in which they are applicable. In this regard, we have a long-standing interest in the development of both soluble and insoluble polymer-supported amine,[4] fluorinated ketone,[5] phosphine,[6] sulfide[7] and sulfoxide[8] reagents. Thus, in our research we have noticed that a missing tool from the polymeric reagent toolbox is a readily accessible and easy to use heterogeneous polymer-supported reagent that allows for the conversion of phenols to aryl triflates and isolation of the products via simple filtration and concentration operations.

Aryl triflates are versatile building blocks in organic synthesis since they participate in a variety of metal catalyzed carbonylation and coupling reactions.[9,10] Thus, methods and reagents for the synthesis of aryl (an enol) triflates are constantly being developed and refined. Recent developments for their preparation include the use of triflic anhydride in an aqueous biphasic reaction system,[11] and the use of *N*-phenyltrifluoromethanesulfonimide (**1**)[12] (Fig. 1) in conjunction with controlled microwave heating.[13] One drawback associated with the use of reagent **1** is that it and its by-products can be difficult to separate from the triflate product. Therefore, both polar analog **2**, which not only aids in product purification but also accelerates its formation,[14] and soluble poly(ethylene glycol)-supported analog **3**,[15] which can facilitate product isolation, have been reported. While the former has seen widespread use, the latter has not. Perhaps, one reason for the lack of use of **3** is that it requires a precipitation operation before it and its by-products can be removed by filtration, and thus, it is not very amenable to use in parallel synthesis or with automation equipment. Therefore, an insoluble polymer-supported reagent that does not require a precipitation step prior to filtration might find broader acceptance and utilization. Herein, we wish to report the synthesis and use of such a reagent.

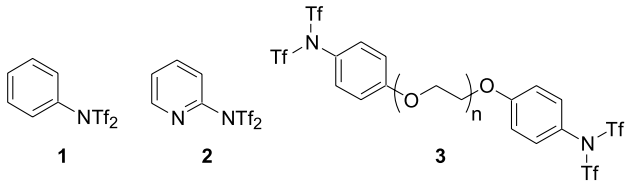

Figure 1. Current triflimide reagents.

2. Results and discussion

The preparation of a polymer-supported triflating reagent requires an aniline polymer as the base material and many

Keywords: Aryl triflates; *J*anda*J*el; Triflimide groups.
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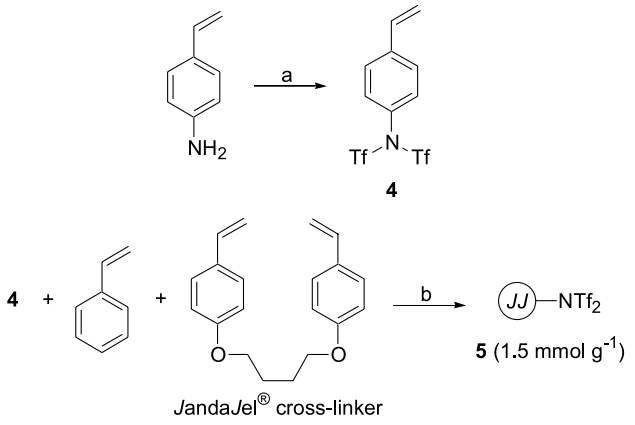


Scheme 1. Synthesis of reagents **5**. Reagents and conditions: (a) Et_3N (3 equiv), Tf_2O (2 equiv), anhydrous CH_2Cl_2, 0 °C. (b) PhCl, AIBN, water, acacia gum, NaCl, 85 °C.

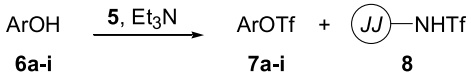
preparations of such polymers have been reported. These methods include Schmidt rearrangement of a benzyl azide resin,[16] attachment of an aniline derivative to a preformed polymer,[17] and the incorporation of either 4-vinylaniline[18] or *N*-Boc-4-vinylaniline[19] in the polymerization process. While any of these methods could have provided us with a suitable polymeric starting material, we choose a more direct route by preparing a functional monomer[20] containing the desired triflimide functional group and incorporating it into the polymer during the polymerization process.

Thus, functional monomer **4** was prepared in 90% yield by reaction of 4-vinylaniline with 2 equiv of Tf_2O in the presence of excess Et_3N. After determining the stability of **4** to the polymerization reaction conditions, it was used to prepare an insoluble polystyrene reagent. Thus, it was suspension co-polymerized[21] with styrene and the flexible *J*anda*J*el® cross-linker[22,23] to afford insoluble **5** (*J*anda*J*el®-NTf_2) (Scheme 1). Elemental analysis was used to determine the loading level of **5** to be 1.6 mmol NTf_2 g^{-1} based on the average analysis results for nitrogen and sulphur content.

Next, we examined the use of **5** in the preparation of a variety of aryl triflates derived from phenols (**6a–i**) substituted with both electron donating and withdrawing substituents (Table 1). These reactions were performed in dichloromethane at room temperature using 2 equiv of both **5** and Et_3N. Upon the complete disappearance of **6a–i** according to TLC analysis (4–16 h), the reactions were filtered to remove the insoluble polymer, concentrated in vacuo and filtered through a short plug of silica gel. Finally, removal of the solvent afforded triflates **7a–i** in essentially pure form, as determined by ^1H NMR analysis. As can be seen in Table 1, all substrates were isolated in good to excellent yield.[24]

With our success in synthesizing aryl triflates containing carbonyl functional groups (**7h–i**), we were interested to see if aryl triflates containing aliphatic alcohols could also be prepared. Gratifyingly, diols **6j–l** afforded the corresponding monotriflates **7j–l** in moderate to good yield (Table 2) when the reactions were performed at 50 °C. The structures of **7j–k** were confirmed by their oxidation to the corresponding aldehyde and ketone (**7h**), respectively. It should be noted that these reactions were quite sluggish

Table 1. Aryl triflate synthesis



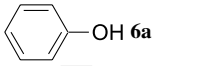
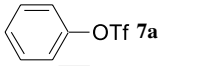
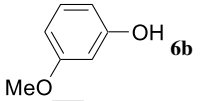
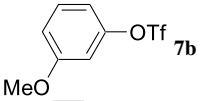
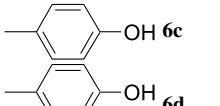
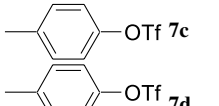
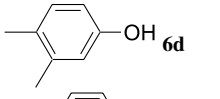
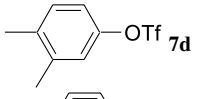
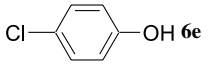
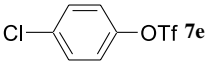
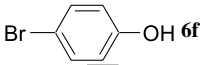
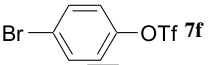
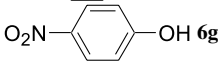
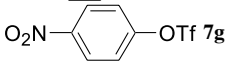
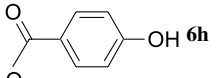
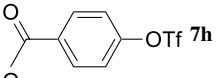
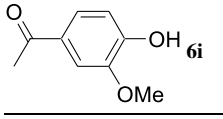
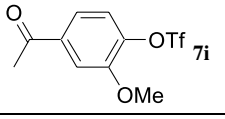
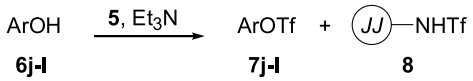
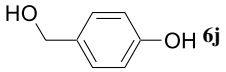
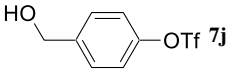
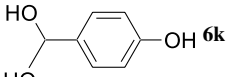
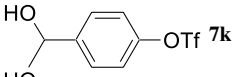
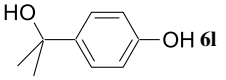
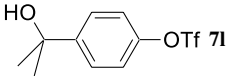
Phenol	Triflate	Yield (%)
		74
		82
		81
		91
		82
		81
		99
		100
		99

Table 2. Synthesis of aryl triflates containing aliphatic alcohol groups



Phenol	Triflate	Yield (%)
 **6j**	 **7j**	48
 **6k**	 **7k**	90
 **6l**	 **7l**	63

even at elevated temperature and 2–5 days and 4 equiv of **5** were required for the complete consumption of the starting diol. Furthermore, the formation of **7j–l** was accompanied by numerous uncharacterized impurities and these products required chromatographic purification. One possible explanation for the requirement of a larger excess of **5** for the synthesis of **7j–l** is that the isolated products may have been formed by hydrolysis of initially generated ditriflate molecules. Such a reaction pathway would also explain the complex crude product mixtures obtained for **7j–l**.

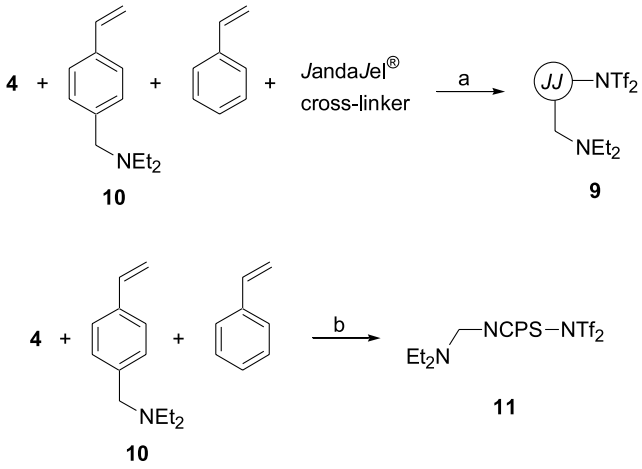
Having established that **5** is effective and efficient in converting a broad range of aryl alcohols into the corresponding triflates, we next examined its recyclability. Thus, we recovered the polymer (a mixture of **5** and **8**) at the end of the reactions and treated it with Tf_2O and Et_3N. As can be seen in Table 3, the same sample of **5** can be reused at least three times for the conversion of **6h** to **7h**, with only modest decrease in efficiency. Considering the small scale of the reactions performed, we consider the reported yields to be approximately equivalent. However, the reactions of the later cycles were somewhat sluggish compared to the initial reaction and required slightly longer reaction times. Nevertheless, it is important to note that the reactions were efficient in all cases and only the desired product was observed.

Table 3. Recycling of **5**

6h **7h**

Cycle	Yield (%)
1	100
2	88
3	95
4	92

Lastly, we examined the possibility of incorporating basic amine moieties into **5** so that the triflation reactions might be performed without the requirement for a base to be added and thereby possibly eliminate the need for the filtration through silica gel to obtain pure product. Thus, bifunctional polymer **9**, which contains not only triflimide moieties, but also basic trialkylamine groups was prepared by the inclusion of monomer **10**[4] in a 3:2 ratio compared to **4**, in the polymerization process (Scheme 2). The loading levels



Scheme 2. Synthesis of bifunctional polymers **9** and **11**. Reagents and conditions: (a) PhCl, AIBN, water, acacia gum, NaCl, 85 °C. (b) PhMe, AIBN, 85 °C.

of both the amine and triflimide functional groups were determined by elemental analysis to be 1.3 and 0.8 mmol g^{-1}, respectively, based on nitrogen and sulfur content. To our knowledge only one other such bifunctional polymer has been reported in the literature and it contains both basic pyridine moieties and catalytic 4-dimethylaminopyridine groups and it was used in esterification reactions.[25] Unfortunately, when **9** was used to convert **6h** to **7h**, only trace amounts (<5%) of the desired product were observed by GC analysis, even after extended reaction times at elevated temperature.

In order to gain insight into the failure of **9** to be an efficient triflating reagent, we prepared the soluble, non-cross-linked polystyrene (NCPS) reagent **11** by co-polymerization of **4**, **10**, and styrene (Scheme 2), since it would be easier to characterize spectroscopically and be a homogeneous reagent. Analysis of **11** by IR, and ^1H and ^{19}F NMR spectroscopy and comparison of this data with that of **4** indicated that the amine and triflimide groups are compatible with one other in the polystyrene matrix. Even when both **9** and **11** were subjected to the aqueous suspension polymerization reaction conditions, only minor signals indicating N–H bonds were observed in the IR spectra. Thus, premature cleavage of the triflimide groups was probably not responsible for the poor results with **9**. Reaction of **6h** with **11** also only afforded low yield of **7h**

(ca. 8%), indicating that the heterogeneous nature of **9** was also not responsible for its inefficiency. Thus, some unknown interaction between the amine and triflimide functional groups must be responsible for the failure of the bifunctional polymers **9** and **11** to be useful triflating reagents.

3. Conclusions

We have prepared the new, insoluble polystyrene-supported triflimide reagent **5** and demonstrated its usefulness in the synthesis of a range of aryl triflates, including ones that contain aliphatic hydroxyl groups. This reagent is recyclable at least three times with no significant decrease in its efficiency. Finally, we report the synthesis of bifunctional polymeric reagents **9** and **11**. Unfortunately, these are not as efficient as **5** is in the preparation of aryl triflates, which may be due to micro-environmental factors that arise from bringing the amine and triflimide moieties together in the same polymer matrix.[25]

Finally, we have attempted to use **5** in the synthesis of enol triflates from ketones, and in sample reactions the products formed required chromatographic purification, as is the case when **1** and **2** are used. Thus, considering the heterogeneity of **5** and the prolonged reaction times required compared to homogeneous small molecule reagents, we found no advantages to using **5** in enol triflate synthesis and therefore limited our study to the preparation of aryl triflates. Significantly, when **5** is used in such applications, the work-up and isolation of the aryl triflate product is simple, amenable to being performed in parallel in an automated fashion and can be completed in a matter of minutes. Thus, it should be a useful tool in parallel synthesis, where the ability to simply isolate products with high purity is essential.

4. Experimental

4.1. General

All reagents were obtained from the Aldrich, Lancaster or Acros chemical companies and were used without further purification. All moisture sensitive reactions were carried out in dried glassware under a N_2 atmosphere. Tetrahydrofuran was distilled under a N_2 atmosphere over sodium and benzophenone. Dichloromethane was distilled under a N_2 atmosphere over calcium hydride. Merck silica gel 60 (230–400 mesh) was used for chromatography. Thin layer chromatography analysis was performed using glass plates coated with silica gel 60 F_{254}. Gas chromatographic analyses were performed using an RTX-5 column with a Thermo Finnigan Focus chromatograph. NMR spectra were recorded using either a Bruker DRX 300 or an AV400 spectrometer. Chemical shift data is expressed in ppm with reference to TMS. HR EI-MS data was recorded on a Finnigan MAT 96 mass spectrometer.

4.1.1. *N*-(4-Vinylphenyl)trifluoromethanesulfonimide (4). To a solution of 4-aminostyrene (5.40 g, 45.2 mmol) and Et_3N (18.8 mL, 135.5 mmol) in anhydrous CH_2Cl_2 (100 mL) at −78 °C was added triflic anhydride (15.2 mL, 90.3 mmol). The reaction mixture was stirred at this temperature for 1 h and then warmed to rt and stirred for 1 h more. At this time, the reaction mixture was diluted with CH_2Cl_2 (400 mL) and then washed sequentially with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (5% EtOAc/hexanes) to afford **4** as white solid (15.58 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (d, 1H, J=10.9 Hz), 5.85 (d, 1H, J=17.6 Hz), 6.73 (dd, 1H, J=17.6, 10.9 Hz), 7.35 (d, 2H, J=8.5 Hz), 7.51 (d, 2H, J=8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.3, 113.3–123.3 (J_{CF}=323.2 Hz), 127.9, 131.1, 131.5, 135.3, 141.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.1. IR (KBr, cm^{-1}): 3073, 1633, 1507, 1122, 741, 661. HR EI-MS: calcd for $C_{10}H_7NS_2O_4F_6$, 382.9720; found 382.9713.

The stability of **4** to the suspension polymerization conditions was examined by placing it in the acacia solution described below. This was heated to 85 °C for 20 h. At this time, TLC analysis indicated only the presence of unchanged **4**. No more highly polar compounds were observed.

4.1.2. *Janda*Jel®-NTf$_2$ (5). A solution of acacia gum (6.0 g) and NaCl (3.8 g) in warm deionized water (45 °C, 150 mL) was placed in a 150 mL flanged reaction vessel equipped with a mechanical stirrer and deoxygenated by purging with N_2 for 2 h.[26] A solution of **4** (5.74 g, 15.0 mmol), styrene (4.26 g, 41.0 mmol), 1,4-bis(4-vinylphenoxy)butane[22d] (0.33 g, 1.1 mmol), and AIBN (0.2 g, 1.3 mmol) in chlorobenzene (10 mL) was injected into the rapidly stirred aqueous solution. The resulting suspension was heated at 85 °C for 20 h. At this time the crude polymer was collected and washed with hot water (3×100 mL) and then placed in a Soxhlet extractor and washed with THF for 24 h. The beads were then washed sequentially with diethyl ether (250 mL), and hexane (250 mL), and then dried in vacuo for 24 h to afford **5** (8.5 g, 85%). IR (KBr, cm^{-1}): 3068, 3029, 1603, 1501, 1128, 760, 701. Elemental analysis was used to determine the nitrogen content (2.3%) and the sulfur content (9.6%), and thus the loading level of **5** was 1.6 mmol g^{-1}.

4.1.3. *Janda*Jel®-(CH$_2$NEt$_2$)NTf$_2$ (9). A solution of acacia gum (6.0 g) and NaCl (3.8 g) in warm deionized water (45 °C, 150 mL) was placed in a 150 mL flanged reaction vessel equipped with a mechanical stirrer and deoxygenated by purging with N_2 for 2 h. A solution of **4** (3.83 g, 10.0 mmol), **10**[4] (2.84 g, 15 mmol), styrene (3.33 g, 32.0 mmol), 1,4-bis(4-vinylphenoxy)butane[22d] (0.34 g, 1.1 mmol), and AIBN (0.2 g, 1.3 mmol) in chlorobenzene (10 mL) was injected into the rapidly stirred aqueous solution. The resulting suspension was heated at 85 °C for 20 h. At this time the crude polymer was collected and washed with hot water (3×100 mL) and then placed in a Soxhlet extractor and washed with THF for 24 h. The beads were then washed sequentially with diethyl ether (250 mL), and hexane (250 mL), and then dried in vacuo for 24 h to afford **9** (5.4 g, 54%). IR (KBr, cm^{-1}): 3498, 3027, 1606, 1510, 1145, 761, 700. Elemental analysis was used to determine the nitrogen content (2.9%) and the sulfur content (5.0%), and thus the loading levels of the amine and

triflimide groups in **9** were 1.3, and 0.8 mmol g^{-1}, respectively.

4.1.4. NCPS-(CH_2NEt_2)NTf_2 (11). To a solution of styrene (1.67 g, 16.0 mmol), **10** (1.42 g, 7.5 mmol) and **4** (1.79 g, 5.0 mmol) in toluene (20 mL) was added AIBN (0.024 g, 0.14 mmol). The mixture was purged with N_2 for 30 min and the solution was stirred at 85 °C for 24 h. The solution was concentrated in vacuo and the residue was taken up in 2 mL of THF. This solution was added dropwise to a vigorously stirred cold Et_2O (0 °C, 200 mL). The white precipitate was filtered and dried to afford **11** as a white powder (1.6 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.60 (br, 10H), 1.63–2.41 (br, 36H), 2.82–3.32 (br, 4H), 3.81–4.38 (br, 1H), 6.12–7.75 (br, 20H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.1. IR (KBr, cm^{-1}): 3504, 3028, 1603, 1506, 1129, 762, 702.

4.2. General procedure for aryl triflate synthesis using 5

Reagent **5** (0.47 g, 0.75 mmol) and Et_3N (0.1 mL, 0.75 mmol) were added to a solution of **6** (0.375 mmol) in anhydrous CH_2Cl_2 (5 mL). The reaction mixture was shaken at rt until TLC analysis indicated the complete disappearance of **6** (4–16 h). At this time, the resin was filtered off and the filtrate was concentrated in vacuo. The resulting residue was then filtered through a plug of silica gel using CH_2Cl_2. Removal of the solvent afforded **7** that was determined to be essentially pure by ^{1}H NMR.

The syntheses of **7j–l** were performed at 50 °C and required 4, 5, and 2 days, respectively, for the complete disappearance of starting material. These products were purified by silica gel chromatography.

4.2.1. Characterization data for 7a.[11] Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.29 (m, 2H), 7.34–7.49 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.8–125.6 (J_{CF}=318.7 Hz), 121.7, 128.8, 130.7, 150.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.9. HR EI-MS: calcd for $C_7H_5SO_3F_3$, 225.9911; found 225.9913.

4.2.2. Characterization data for 7b.[27] Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.80 (t, 1H, J=2.3 Hz), 6.85–6.94 (m, 2H), 7.33 (t, 1H, J=8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 107.5, 113.3, 114.2, 114.0–123.5 (J_{CF}=319.0 Hz), 130.6, 150.3, 160.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.9. HR EI-MS: calcd for $C_8H_7SO_4F_3$, 256.0017; found 256.0019.

4.2.3. Characterization data for 7c.[11] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.15 (d, 2H, J=8.6 Hz), 7.23 (d, 2H, J=8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 114.0–123.6 (J_{CF}=318.8 Hz), 121.0, 130.7, 138.5, 147.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.9. HR EI-MS: calcd for $C_8H_7SO_3F_3$, 240.0068; found 240.0071.

4.2.4. Characterization data for 7d.[28] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.28 (s, 3H), 6.99 (dd, 1H, J=8.3, 2.6 Hz), 7.03 (d, 1H, J=2.4 Hz), 7.17 (d, 1H, J=8.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.2, 112.8–125.6 (J_{CF}=318.7 Hz), 118.7, 122.4, 131.3, 137.5, 139.5, 148.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.0. HR EI-MS: calcd for $C_9H_9SO_3F_3$, 254.0224; found 254.0226.

4.2.5. Characterization data for 7e.[10e] Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, 2H, J=9.0 Hz), 7.43 (d, 2H, J=9.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.7–125.5 (J_{CF}=318.9 Hz), 123.1, 130.8, 134.7, 148.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.8. HR EI-MS: calcd for $C_7H_4SClO_3F_3$, 259.9522; found 259.9526.

4.2.6. Characterization data for 7f.[11] Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, 2H, J=8.8 Hz), 7.56 (d, 2H, J=8.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.5–123.9 (J_{CF}=318.9 Hz), 122.4, 123.4, 133.8, 148.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.8. HREI-MS: calcd for $C_7H_4SBrF_3O_3$, 303.9017; found 303.9014.

4.2.7. Characterization data for 7g.[11] Yellow solid (mp 52–56 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 2H, J=8.9 Hz), 8.37 (d, 2H, J=8.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.7–125.4 (J_{CF}=318.9 Hz), 122.9, 126.4, 147.5, 153.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.0. HR EI-MS: calcd for $C_7H_4NSF_3O_5$, 270.9762; found 270.9760.

4.2.8. Characterization data for 7h.[29] Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H), 7.39 (d, 2H, J=8.8 Hz), 8.07 (d, 2H, J=8.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 112.7–125.4 (J_{CF}=318.8 Hz), 122.0, 130.9, 137.3, 152.8, 196.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.8. HR EI-MS: calcd for $C_9H_7SO_4F_3$, 268.0017; found 268.0015.

4.2.9. Characterization data for 7i.[30] White solid (mp 100–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.98 (s, 3H), 7.32 (d, 1H, J=8.4 Hz), 7.57 (dd, 1H, J=8.4, 2.0 Hz), 7.65 (d, 1H, J=1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 56.4, 112.3, 114.0–123.5 (J_{CF}=318.5 Hz), 122.6, 122.5, 137.8, 141.9, 151.7, 196.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.8. HR EI-MS: calcd for $C_{10}H_9SO_5F_3$, 298.0123; found 298.0116.

4.2.10. Characterization data for 7j. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (br, 1H), 4.70 (s, 2H), 7.25 (dd, 2H, J=6.8, 2.2 Hz), 7.43 (d, 2H, J=8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.0, 114.0–123.5 (J_{CF}=318.8 Hz), 121.4, 128.5, 141.4, 148.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.9. HR EI-MS: calcd for $C_8H_7SO_4F_3$, 256.0017; found 256.0019.

For structural proof, **7j** was oxidized to the corresponding aldehyde using PDC (2.5 equiv) in CH_2Cl_2 at rt for 2 h (83% yield). Characterization data for this aldehyde: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2H, J=8.6 Hz), 8.01 (d 2H, J=8.6 Hz), 10.05 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.9–122.5 (J_{CF}=318.9 Hz), 122.3, 131.8, 136.0, 153.2, 190.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.7. HR EI-MS: calcd for $C_8H_5SO_4F_3$, 253.9861; found 253.9860.

4.2.11. Characterization data for 7k. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, 3H, J=6.5 Hz), 2.07 (br, 1H), 4.93 (q, 1H, J=6.5 Hz), 7.24 (dd, 2H, J=6.8, 2.0 Hz), 7.45 (dd, 2H, J=6.8, 1.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 69.4, 114.0–123.5 (J_{CF}=318.8 Hz), 121.3, 127.2,

146.3, 148.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.0. HR EI-MS: calcd for $C_9H_9SO_4F_3$, 270.0174; found 270.0168.

For structural proof **7k** was oxidized to **7h** using PDC (2.5 equiv) in CH_2Cl_2 at rt for 3 h (87% yield). Characterization data for this product agreed with that which was previously observed.

4.2.12. Characterization data for 7l. White solid (mp 32–35 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 6H), 7.22 (d, 2H, J=8.9 Hz), 7.56 (d, 2H, J=8.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.1, 72.6, 112.8–125.5 (J_{CF}= 318.7 Hz), 121.3, 126.9, 148.6, 150.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.9. HR EI-MS: calcd for $C_{10}H_{11}SO_4F_3$, 284.0330; found 284.0363.

4.3. Procedure for regeneration and reuse of polymer 5

The polymeric reagent recovered from the aryl triflate synthesis reactions (a mixture of **5** and **8**) was treated with triflic anhydride (3 equiv) and Et_3N (3 equiv) in anhydrous CH_2Cl_2 at −78 °C for 1 h and then warmed to room temperature and stirred for 18 h more. The polymer **5** was filtered and washed as before.

The same sample of **5** was used four times to prepare **7h**. For each triflation cycle, the reaction was monitored by TLC analysis and the product was purified and characterized as before.

4.4. Use of polymers 9 and 11 for aryl triflate synthesis

Reagent **9** (2 equiv of $-NTf_2$, 3 equiv of $-CH_2NEt_2$) was used in CH_2Cl_2, DMF, 1,4-dioxane at rt (70 °C for the later two solvents) for the conversion of **6h** to **7h**. Samples of the reaction solutions were intermittently analyzed by gas chromatography to determine the extent of reaction. After up to 5 days, **7h** was formed in less than 5% yield under all reaction conditions.

Reagent **11** (2 equiv of $-NTf_2$, 3 equiv of $-CH_2NEt_2$) was used in CH_2Cl_2 at rt. After 3 days, analysis by gas chromatography indicated that **7h** was formed in only 8% yield.

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Metalation/functionalization sequences applied to 2-bromo-3-fluoroquinolines

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Abstract—Mono- and disubstituted 2-bromo-3-fluoroquinolines **3** are readily accessible. They can be converted into the 3-fluoroquinoline-2-carboxylic acids **5** by consecutive halogen/metal permutation and into the 2-bromo-3-fluoroquinoline-4-carboxylic acids **6** by consecutive deprotonation and carboxylation. The latter compounds can be reduced to afford the 3-fluoroquinoline-4-carboxylic acids **7**. The yields are excellent throughout. Rather than to introduce one functional group alternatively at the 2- or 4-position, one may also attach two different functional groups sequentially to both sites.

1. Introduction

2-Fluoro-3-methoxy-2-propenoic acid, generally employed as its methyl ester[1,2] or acyl chloride,[3] is an extremely versatile building block for the construction of a variety of heterocyclic compounds.[3] The condensation with anilines provides 2-fluoro-3-methoxy-prop-2-enanilides and, after acid catalyzed cyclization, 3-fluoroquinolin-2(1*H*)-ones. The latter react with phosphoric trichloride (phosphorus oxychloride) to give 2-chloro-3-fluoro-quinolines which can be reduced to the 3-fluoroquinolines.[1]

2. Results

We wish now to report on an extension of these earlier studies. As key intermediates serve 2-bromo-3-fluoroquinolines **3** which were readily obtained by the treatment of 3-fluoroquinolin-2(1*H*)-ones **2** with phosphoric tribromide. The immediate precursors to the fluoroquinolinones **2** were the open-chain anilides **1** which in turn were made from the ultimate starting materials, aniline itself and four monosubstituted and one disubstituted congeners (Scheme 1).

Unlike chlorine, bromine atoms can be displaced against lithium in butyllithium-mediated halogen/metal permutation processes, which can be performed in tetrahydrofuran, diethyl ether or, often more cleanly, in toluene. The organometallic intermediates thus generated may be trapped with any electrophile. Reaction with dry ice afforded the 3-fluoroquinoline-2-carboxylic acids **5** in an average yield of 75%. To accomplish a site-selective displacement of the nitrogen-adjacent bromine atom at the 2-position of the dibromo compound **3e**, the interconversion reaction had to be conducted in toluene at −100 °C as at −75 °C a 9:1 mixture of 2- and 8-lithiated intermediates was produced. When lithium diisopropylamide was employed as the base instead, deprotonation occurred at the vacant 4-position and subsequent carboxylation afforded the 2-bromo-3-fluoroquinoline-4-carboxylic acids **6** in 84% average yield. Pyridine being, particularly at the 4-position, far more acidic than benzene, the 3,7-difluorinated substrate **3c** underwent deprotonation and subsequent functionalization selectively in the heterocyclic part. Reductive removal of the heavy halogen from the acids **6** (by either catalytic hydrogenation or with tin dichloride[4]) gave the 3-fluoroquinoline-4-carboxylic acids **7**, yields averaging 79% this time. The same compounds **7** are accessible by an operational inversion of the carboxylation and reduction steps. Debromination of the 2-bromo-3-fluoroquinolines **3** leads to the 3-fluoroquinolines **4** which, as demonstrated previously,[1] can be deprotonated effectively with lithium diisopropylamide in the presence of potassium *tert*-butoxide ('Mordini mixture') in order to be carboxylated subsequently (Scheme 2).

Keywords: Bromine replacement by hydrogen; Carboxylation; Formylation; 3-Fluoroquinoline-2- and -4-carboxylic acids; Halogen/metal permutation ('halogen exchange') reactions; Hydrogen/metal permutation ('metalation') reactions.
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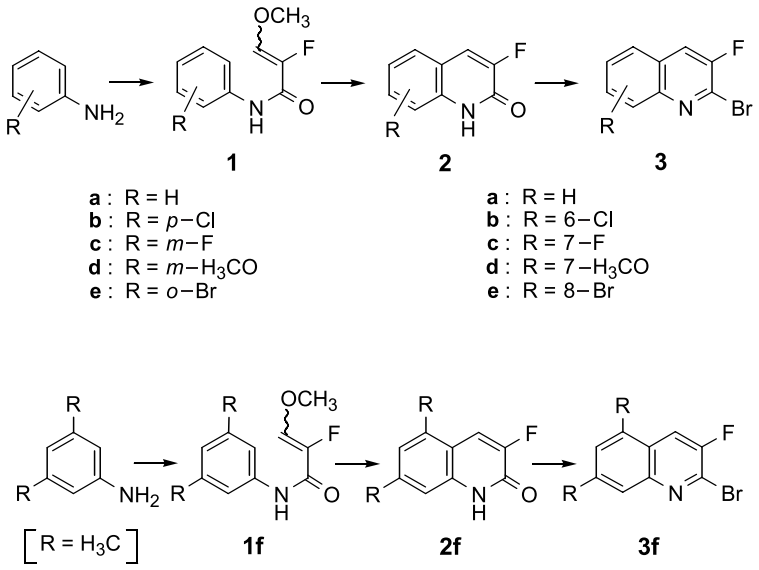


Scheme 1.

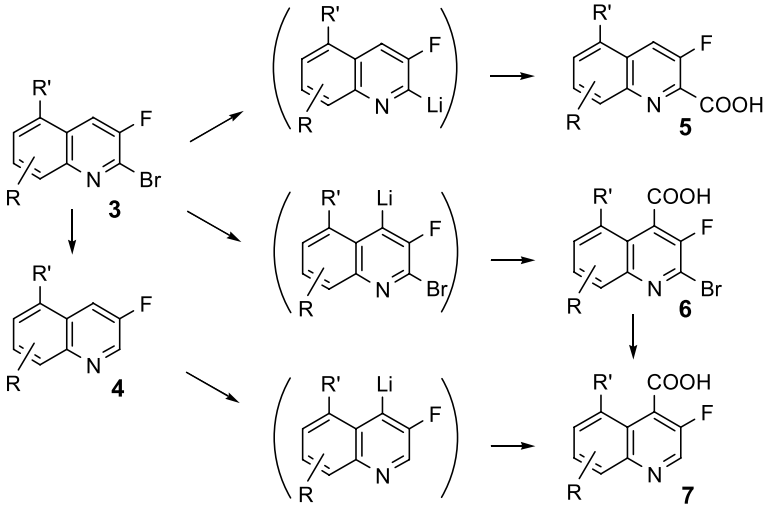
Carboxy groups or another functionality may not only be introduced alternatively into either the 2- or the 4-position of 2-bromo-3-fluoroquinolines **3** but also sequentially in both sites. Two series of reactions have been performed to illustrate this possibility.

2-Bromo-3-fluoro-5,7-dimethylquinoline **3f** was converted into the quinoline-4-carboxylic acid **6f**, as described above, before being subjected to a halogen/metal permutation with lithium tributylmagnesate[5] followed by trapping with dimethylformamide. The formylacid **8a** thus formed was isolated as the crystalline thiosemicarbazone **8b** (78%) (Scheme 3).

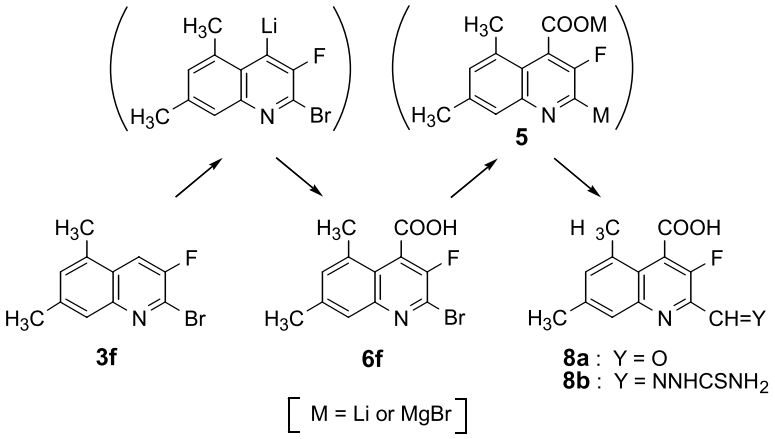
When dimethylformamide was added to the 4-lithiated 2-bromo-3-fluoroquinoline (**3a**) and thus the formyl entity was introduced as the first functional group, the aldehyde **9a** (98%) had to be protected by acetalization with ethylene glycol, thus producing the 1,3-dioxole **9b** (97%). Ensuing halogen/metal permutation, carboxylation and acetal hydrolysis gave the formylcarboxylic acid **10b** (74%) (Scheme 4).

3. Conclusions

The present investigation features methods designed to install flexibility into the derivatization and, in particular, functionalization of quinolines. This class of compounds represents a key segment of heterocyclic chemistry. As



Scheme 2.



Scheme 3.

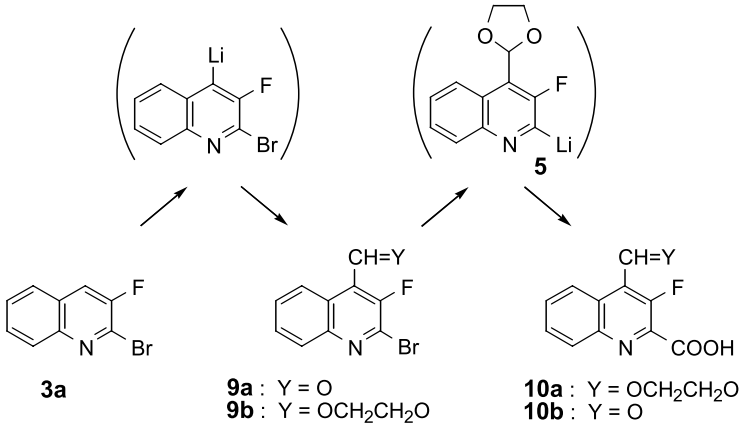
demonstrated, the elaborated procedures tolerate the presence of a great variety of substituents located in the benzo ring.

Notwithstanding such general statements, it deems appropriate to examine in detail to what extent this work is novel and significant. Neither bromofluoroquinolines, readily accessible on our route, nor organometallic derivatives thereof have ever been reported. These compounds offer a manifold of possibilities for further elaboration. Whereas 3-fluoroquinoline itself and its 2-butoxy congener require mixed-metal reagents to undergo metalation efficaciously,[1] lithium diisopropylamide suffices to deprotonate 2-bromo-3-fluoroquinolines cleanly at the 4-position. The menacing nucleophilic bromide/amide displacement can be perfectly controlled and avoided. The lithiated species resulting from 4-deprotonation can be trapped by standard electrophilic reagents such as carbon dioxide. Alternatively, 2-lithio species may be generated by permutational halogen/metal interconversion and subsequently be intercepted again with dry ice or another electrophile.

So far without precedent is the combination of both processes, the metalation followed by functionalization and the halogen/metal permutation followed by another functionalization. The feasibility of such a sequence has been demonstrated in two model cases.

We have previously investigated the functionalization of 4-bromo-2-(trifluoromethyl)quinolines[6,7] and 2-bromo-4-(trifluoromethyl)quinolines.[8,9] They differ in two respects from the present substrates. On one hand they contain a doubly acidified 3-position and on the other hand, the trifluoromethyl entity provides relatively little neighboring group assistance to the deprotonation of *ortho* positions but has a long-ranging effect whereas the fluorine atom is an excellent *ortho*-metalation-promoting substituent the activating effect of which, however, rapidly levels off with distance.[10]

The preparation and subsequent transformations of 2-bromo-3-fluoroquinolines **3** deserves attention even if the outcome might have been anticipated on the basis of earlier work. The metal was cleanly introduced in the 4-position when lithium dialkylamide-type bases were employed. Remarkably, these deprotonations were not accompanied by any bromine migration.[11,12] In comparison with chlorine, trifluoromethyl and alkoxy, bromine disposes of additional reaction modes. It can be easily and selectively replaced by hydrogen through metal-mediated reduction or catalytic hydrogenation;[12] it can participate in permutational halogen/metal interconversions to leave its place to lithium; and it can undergo carbon–carbon linking Suzuki couplings.[13–16]



Scheme 4.

4. Experimental

4.1. General

Details concerning standard operations and abbreviations have been given in previous publications from this laboratory.[17,18] ^{1}H and (^{1}H-decoupled) ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively. If not specified otherwise the samples were dissolved in deuteriochloroform or, if marked by an asterisk, in dimethylsulfoxide-d_6. Mass spectra were obtained at 70 eV ionization potential while a source temperature of 200 °C was maintained. Whenever no molecular peak was observed under such conditions, chemical ionization ('c.i.') in an ammonia atmosphere at 100 °C source temperature was applied. To avoid redundancy, in all cases only the [^{35}Cl] and [^{79}Br] fragments and not the [^{37}Cl] and [^{81}Br] isotopomers are listed.

The anilides **1a**, **1c** and **1d** have been isolated and characterized previously.[2] In the present work, all anilides were collected as crude products and cyclized by heating in 70% sulfuric acid without prior purification. The preparation of the quinolinones **2a**,[1] **2c**,[2] and **2d**[2] has already been reported.

4.1.1. 6-Chloro-3-fluoroquinol-2(1*H*)-one (2b). Butyllithium (0.50 mol) in hexanes (0.33 L) and methyl 2-fluoro-3-methoxyprop-2-enoate[1] (*Z*/*E*∼1:1; 27 mL, 34 g, 0.25 mol) were added consecutively to 4-chloroaniline (45 mL, 47 g, 0.50 mol) in tetrahydrofuran (2.7 L) at 0 °C. After 1 h at 25 °C, the mixture was poured into 2.0 M hydrochloric acid (0.70 L). The two phases were separated and the aqueous one extracted with diethyl ether (3×0.25 L). The combined organic layers were washed with a saturated aqueous solution (0.25 L) of sodium hydrogen carbonate, brine (0.25 L) and dried with anhydrous sodium sulfate. After evaporation, a brownish-yellow solid residue was left behind. It was heated in 96% sulfuric acid (2.0 L) to 50 °C for 5 h. The mixture was poured on crushed ice. The precipitate was collected by filtration and washed with water (2×0.10 L); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 306–308 °C (reprod.); yield: 89.9 g (88%). ^{1}H NMR: δ=11.29 (s, broad, 1H), 7.75 (d, J=2.4 Hz, 1H), 7.71 (d, J=10.1 Hz, 1H), 7.52 (dd, J=8.9, 2.4 Hz, 1H), 7.46 (d, J=8.8 Hz, 1H) ppm. ^{13}C NMR*: δ=155.4 (d, J=27 Hz), 151.2 (d, J=253 Hz), 134.5 (s), 129.2 (s), 126.5 (d, J=6 Hz), 126.4 (s), 119.4 (d, J=8 Hz), 118.3 (d, J=18 Hz), 117.0 (s) ppm. MS: *m*/*z* (%)=199 (41) [M$^+$+2], 198 (44) [M$^+$+1], 197 (100) [M$^+$], 164 (14), 134 (11), 107 (10). Anal. Calcd for C_9H_5ClFNO (197.60): C, 54.71; H, 2.55. Found: C, 54.51; H, 2.61.

4.1.2. 8-Bromo-3-fluoroquinol-2(1*H*)-one (2e). Prepared analogously from 2-bromoaniline (0.10 kg, 0.60 mol) with 96% aqueous sulfuric acid at 50 °C for 5 h; tiny colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 202–204 °C (reprod.); yield: 71.4 g (64%). ^{1}H NMR: δ=9.30 (s, broad, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.51 (dd, J=8.0, 1.3 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR*: δ=155.7 (d, J=27 Hz), 150.7 (d, J=252 Hz), 133.4 (s), 133.0 (s), 127.7 (d, J=6 Hz), 123.8 (s), 119.8 (d, J=8 Hz), 119.3 (dd, J=18, 4 Hz), 108.0 (s) ppm. MS: *m*/*z* (%)=242 (32) [M$^+$+1], 241 (100) [M$^+$], 215 (15), 134 (21), 107 (28), 81 (21). Anal. Calcd for C_9H_5BrFNO (242.05): C, 44.66; H, 2.08. Found: C, 44.66; H, 2.03.

4.1.3. 3-Fluoro-5,7-dimethyquinol-2(1*H*)-one (2f). Prepared analogously from 3,5-dimethylaniline (0.14 L, 0.14 kg, 1.2 mol) using 32% hydrochloric acid at 50 °C for 5 h; colorless platelets (from *N*,*N*-dimethylformamide); mp 278–280 °C (reprod.); yield: 81.8 g (72%). ^{1}H NMR: δ=7.70 (d, J=10.9 Hz, 1H), 7.13 (s, 1H), 6.95 (s, 1H), 2.50 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR*: δ=155.4 (d, J=27 Hz), 149.8 (d, J=249 Hz), 139.0 (s), 136.3 (s), 134.9 (d, J=6 Hz), 125.1 (s), 116.5 (d, J=17 Hz), 114.5 (d, J=6 Hz), 113.0 (s), 21.1 (s), 18.3 (s) ppm. MS: *m*/*z* (%)=208 (19%), 192 (24) [M$^+$+1], 191 (100) [M$^+$], 190 (27), 175 (7). Anal. Calcd for $C_{11}H_{10}FNO$ (191.20): C, 69.10; H, 5.27. Found: C, 68.88; H, 5.10.

4.1.4. 2-Bromo-3-fluoroquinoline (3a). 3-Fluoroquinol-2(1*H*)-one (**2a**; 33 g, 0.20 mol) and phosphoric tribromide (0.12 kg, 0.40 mol) were heated together for 30 min to 150 °C before the mixture was poured on crushed ice (0.50 kg), neutralized with a 5.0 M aqueous solution of sodium hydroxide (0.30 L) and subjected to a steam distillation; colorless needles (from hexanes); mp 82–83 °C (reprod.); yield: 40.8 g (90%). ^{1}H NMR: δ=8.07 (d, J=8.6 Hz, 1H), 7.80 (d, J=8.1 Hz, 2H), 7.71 (t, J=7.5 Hz, 1H), 7.61 (t, J=7.3 Hz, 1H) ppm. ^{13}C NMR: δ=151.9 (d, J=260 Hz), 145.3 (s), 132.1 (d, J=26 Hz), 129.6 (s), 128.7 (s), 128.1 (s), 127.1 (d, J=5 Hz), 119.7 (d, J=18 Hz) ppm. ^{19}F NMR: δ=−115.5 (d, J=8.2 Hz) ppm. MS: *m*/*z* (%)=242 (30), 226 (62) [M$^+$+1], 225 (100) [M$^+$], 162 (42), 146 (14). Anal. Calcd for C_9H_5BrFN (226.04): C, 47.82; H, 2.23. Found: C, 47.78; H, 2.26.

4.1.5. 2-Bromo-6-chloro-3-fluoroquinoline (3b). Prepared analogously from 6-chloro-3-fluoroquinol-2(1*H*)-one (**2b**; 59 g, 0.30 mol). The reaction mixture was kept for 30 min at 190 °C; colorless needles (from ethanol); mp 139–141 °C (reprod.); yield: 61.1 g (78%). ^{1}H NMR: δ=7.97 (d, J=9.3 Hz, 1H), 7.76 (d, J=2.3 Hz, 1H), 7.69 (d, J=7.5 Hz, 1H), 7.62 (dd, J=9.3, 2.3 Hz, 1H) ppm. ^{13}C NMR: δ=153.0 (d, J=263 Hz), 143.5 (s), 134.2 (s), 132.4 (d, J=27 Hz), 130.6 (s), 130.1 (s), 128.8 (d, J=4 Hz), 125.8 (d, J=5 Hz), 118.7 (d, J=19 Hz) ppm. MS: *m*/*z* (%)=260 (52) [M$^+$+1], 259 (100) [M$^+$], 196 (11), 181 (5), 144 (9). Anal. Calcd for $C_9H_5BrClFNO$ (260.49): C, 41.50; H, 1.55. Found: C, 41.50; H, 1.51.

4.1.6. 2-Bromo-3,7-difluoroquinoline (3c). Prepared analogously as described for quinoline **3a** from the 5:95 mixture of 3,5- and 3,7-difluoroquinol-2(1*H*)-one (**2c**; 47 g, 0.26 mol); colorless needles (from hexanes); mp 105–107 °C (reprod.); yield: 47.6 g (75%). ^{1}H NMR: δ=7.8 (m, 2H), 7.70 (dd, J=8.5, 2.4 Hz, 1H), 7.42 (dt, J=8.5, 2.4 Hz, 1H) ppm. ^{13}C NMR: δ=162.4 (d, J=252 Hz), 151.7 (d, J=258 Hz), 145.4 (s), 133.3 (dd, J=26, 7 Hz), 129.0 (dm, J=164 Hz), 124.6 (s), 119.4 (ddd, J=165, 20, 5 Hz), 118.4 (ddd, J=165, 26, 5 Hz), 112.4 (dd, J=165, 22 Hz) ppm. ^{19}F NMR: δ=−116.3 (t, J=7.6 Hz), −109.5 (quint, J=7.6 Hz) ppm. MS: *m*/*z* (%)=244 (62) [M$^+$+1],

243 (100) [M^+], 242 (45), 180 (7), 163 (8). Anal. Calcd for $C_9H_4BrF_2N$ (244.04): C, 44.30; H, 1.65. Found: C, 44.32; H, 1.82.

4.1.7. 2-Bromo-3-fluoro-7-methoxyquinoline (3d). The 1:4 mixture of 3-fluoro-5- and 3-fluoro-7-methoxyquinol-2(1*H*)-one (**2d**; 28 g, 0.15 mol) was heated together with phosphoric tribromide (84 g, 0.29 mol) in anhydrous propionitrile (0.30 L) under reflux for 4 h. After evaporation of the solvent, the residue was poured on ice (0.30 kg). A 5.0 M aqueous solution (0.20 L) of sodium hydroxide was added. The precipitate was collected by filtration and washed with water (4×50 mL). The crude product was dissolved in ethyl acetate, filtered through a pad of silica gel and crystallized from a mixture of ethyl acetate and hexanes; colorless needles; mp 136–138 °C (reprod.); yield: 24.5 g (62%). ^{1}H NMR: δ=7.73 (d, J=7.7 Hz, 1H), 7.66 (d, J=9.1 Hz, 1H), 7.38 (d, J=2.5 Hz, 1H), 7.25 (dd, J=9.1, 2.5 Hz, 1H), 3.93 (s, 3H) ppm. ^{13}C NMR: δ=160.8 (s), 151.4 (d, J=256 Hz), 146.3 (s), 131.9 (d, J=26 Hz), 127.9 (d, J=4 Hz), 122.9 (d, J=3 Hz), 121.4 (s), 119.9 (d, J=19 Hz), 106.9 (s), 55.7 (s) ppm. MS: *m/z* (%)=256 (62) [M^++1], 255 (100) [M^+], 254 (48), 211 (6), 175 (7), 132 (6). Anal. Calcd for $C_{10}H_7BrFNO$ (256.07): C, 46.90; H, 2.76. Found: C, 46.90; H, 2.71.

4.1.8. 2,8-Dibromo-3-fluoroquinoline (3e). Prepared analogously as described for quinoline **3a** from 8-bromo-3-fluoroquinol-2(1*H*)-one (**2e**; 58 g, 0.24 mol); colorless needles (from ethanol); mp 129–131 °C (reprod.); yield: 56.5 g (77%). ^{1}H NMR: δ=7.99 (d, J=7.5 Hz, 1H), 7.77 (d, J=7.5 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H) ppm. ^{13}C NMR: δ=153.0 (d, J=263 Hz), 142.4 (s), 133 (m), 129.2 (d, J=4 Hz), 128.5 (s), 126.9 (d, J=5 Hz), 123.6 (s), 119.9 (d, J=19 Hz) ppm. MS: *m/z* (%)=304 (56) [M^++1], 303 (100) [M^+], 224 (42), 145 (76), 118 (16). Anal. Calcd for $C_9H_4Br_2FN$ (304.94): C, 35.45; H, 1.32. Found: C, 35.64; H, 1.17.

4.1.9. 2-Bromo-3-fluoro-5,7-dimethylquinoline (3f). 3-Fluoro-5,7-dimethylquinol-2(1*H*)-one (**2f**; 4.8 g, 25 mmol) and phosphoric tribromide (14 g, 50 mmol) were heated in anhydrous propionitrile (50 mL) under reflux for 2 h. After evaporation of the volatiles, the residue was poured on ice (50 g). A 2.0 M aqueous solution (84 mL) of sodium hydroxide was added. The precipitate was collected by filtration, and washed with water (4×10 mL). The crude product was dissolved in ethyl acetate, filtered through a pad of silica gel and recrystallized from ethanol; colorless needles; mp 126–128 °C (reprod.); yield: 5.21 g (82%). ^{1}H NMR: δ=7.86 (d, J=8.3 Hz, 1H), 7.68 (s, 1H), 7.27 (s, 1H), 2.60 (s, 3H), 2.50 (s, 3H) ppm. ^{13}C NMR: δ=151.7 (d, J=258 Hz), 145.8 (s), 139.6 (s), 133.7 (d, J=5 Hz), 131.0 (d, J=26 Hz), 130.7 (s), 125.7 (s), 125.5 (s), 116.5 (d, J=19 Hz), 21.7 (s), 18.6 (s) ppm. MS: *m/z* (%)=254 (93) [M^++1], 253 (100) [M^+], 252 (18), 240 (22), 238 (27). Anal. Calcd for $C_{11}H_9BrFN$ (254.10): C, 51.99; H, 3.57. Found: C, 52.16; H, 3.59.

4.1.10. 3-Fluoroquinoline[1] (4a). Palladium (10% on charcoal, 0.20 g) was added to a solution of 2-bromo-3-fluoroquinoline (**3a**; 7.9 g, 35 mmol) and triethylamine (9.8 mL, 7.1 g, 70 mmol) in methanol (60 mL), stirred under an atmosphere of hydrogen (1 atm) at 25 °C. After 2 h, the required amount of hydrogen had been taken up. Distillation afforded a colorless oil; bp 47–48 °C/1.9 mmHg; mp 4–5 °C (reprod.); yield: 4.34 g (87%). ^{1}H NMR: δ=8.82 (d, J=2.6 Hz, 1H), 8.13 (d, J=8.3 Hz, 1H), 7.79 (d, J=8.6 Hz, 1H), 7.76 (dd, J=9.0, 2.9 Hz, 1H), 7.68 (t, J=8.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR: δ=156.2 (d, J=256 Hz), 145.4 (s), 141.5 (d, J=27 Hz), 129.5 (s), 128.5 (s), 127.6 (s), 127.2 (s), 118.2 (d, J=16 Hz) ppm. MS: *m/z* (%)=148 (19) [M^++1], 147 (100) [M^+], 120 (9).

4.1.11. 8-Bromo-3-fluoroquinoline (4e). A solution containing 2,8-dibromo-3-fluoroquinoline (**3e**; 7.6 g, 25 mol) and butyllithium (25 mmol) in toluene (0.10 L) and hexanes (20 mL) was kept for 45 min at −100 °C, before being treated with methanol (10 mL, 8.0 g, 0.25 mol). Afterwards the solvents were stripped off and the residue was crystallized; colorless needles (aqueous methanol); mp 67–68 °C (reprod.); yield: 5.09 g (90%). ^{1}H NMR: δ=8.94 (d, J=2.9 Hz, 1H), 8.04 (dd, J=7.4, 1.3 Hz, 1H), 7.81 (dd, J=8.3, 2.9 Hz, 1H), 7.78 (dd, J=8.3, 1.3 Hz, 1H), 7.44 (t, J=8.0 Hz, 1H) ppm. ^{13}C NMR: δ=156.7 (d, J=259 Hz), 142.4 (s), 142.1 (s), 132.4 (s), 129.8 (d, J=5 Hz), 128.2 (s), 127.3 (d, J=4 Hz), 124.9 (s), 118.9 (d, J=17 Hz) ppm. MS: *m/z* (%)=226 (22) [M^++1], 225 (49) [M^+], 146 (100), 126 (35), 119 (30), 100 (20). Anal. Calcd for C_9H_5BrFN (226.05): C, 47.82; H, 2.23. Found: C, 47.54; H, 2.07.

4.1.12. 3-Fluoroquinoline-2-carboxylic acid (5a). A solution containing 2-bromo-3-fluoroquinoline (**3a**; 10 g, 45 mol) and butyllithium (45 mmol) in diethyl ether (0.20 L) and hexanes (20 mL) was kept for 45 min at −75 °C before being poured onto an excess of freshly crushed dry ice. After addition of water (0.10 L), the reaction mixture was extracted with diethyl ether (3×45 mL) and the aqueous layer was acidified with 2.0 M aqueous solution of hydrochloric acid (10 mL) to pH 1. The precipitate was collected by filtration and washed with water (2×10 mL); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 129–130 °C (decomp.); yield: 6.19 g (72%). ^{1}H NMR: δ=8.17 (d, J=8.6 Hz, 1H), 8.06 (d, J=10.2 Hz, 1H), 7.91 (d, J=8.3 Hz, 1H), 7.83 (td, J=7.8, 1.4 Hz, 1H), 7.75 (t, J=7.5 Hz, 1H) ppm. ^{13}C NMR: δ=161.0 (s), 155.9 (d, J=271 Hz), 143.0 (s), 136.0 (d, J=11 Hz), 131.9 (d, J=6 Hz), 130.5 (m), 129.6 (s), 127.4 (d, J=4 Hz), 123.4 (d, J=18 Hz) ppm. MS: *m/z* (%)=208 (31), 193 (10) [M^++2], 192 (45) [M^++1], 191 (100) [M^+], 147 (78). Anal. Calcd for $C_{10}H_6FNO_2$ (191.16): C, 62.83; H, 3.16. Found: C, 63.18; H, 3.29.

4.1.13. 6-Chloro-3-fluoroquinoline-2-carboxylic acid (5b). Prepared analogously from 2-bromo-6-chloro-3-fluoroquinoline (**3b**; 6.5 g, 25 mmol) but, to improve the yield, using toluene (0.11 L) rather than diethyl ether as the solvent; colorless needles (from acetone) mp 147–149 °C (decomp.); yield: 4.60 g (82%). ^{1}H NMR: δ=8.11 (d, J=9.1 Hz, 1H), 7.97 (d, J=10.2 Hz, 1H), 7.90 (d, J=2.3 Hz, 1H), 7.75 (dd, J=9.1, 2.3 Hz, 1H) ppm. ^{13}C NMR (D_3CCOCD_3): δ=163.4 (d, J=6 Hz), 156.4 (d, J=267 Hz), 143.0 (s), 140.9 (d, J=14 Hz), 135.8 (s), 132.3 (s), 132.1 (d, J=6 Hz), 131.4 (s), 126.9 (d, J=4 Hz), 121.8

(d, $J=19$ Hz) ppm. MS: m/z (%)=226 (24) [$M^+ +1$], 225 (7) [M^+], 208 (24), 181 (100), 146 (21). Anal. Calcd for $C_{10}H_5ClFNO_2$ (225.60): C, 53.24; H, 2.32. Found: C, 53.13; H, 1.91.

4.1.14. 3,7-Difluoroquinoline-2-carboxylic acid (5c). Analogously as described in the preceding paragraph from 2-bromo-3,7-difluoroquinoline (**3c**; 4.9 g, 20 mmol); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 136–137 °C (decomp.); yield: 2.80 g (67%). ^{1}H NMR: $\delta=$ 8.09 (d, $J=9.9$ Hz, 1H), 7.93 (dd, $J=9.1$, 5.6 Hz, 1H), 7.81 (dd, $J=9.1$, 2.7 Hz, 1H), 7.56 (tm, $J=8.6$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=164.8$ (d, $J=5$ Hz), 162.8 (dm, $J=247$ Hz), 154.1 (d, $J=259$ Hz), 144.9 (s), 143.0 (dd, $J=17$, 4 Hz), 130.8 (dm, $J=166$ Hz), 127.3 (d, $J=7$ Hz), 122.4 (ddd, $J=$ 169, 19, 5 Hz), 120.4 (dd, $J=166$, 26 Hz), 113.4 (dd, $J=$ 167, 20 Hz) ppm. MS: m/z %=210 (22) [$M^+ +1$], 209 (20) [M^+], 192 (14), 165 (100). Anal. Calcd for $C_{10}H_5F_2NO_2$ (209.15): C, 57.43; H, 2.41. Found: C, 57.38; H, 2.68.

4.1.15. 3-Fluoro-7-methoxyquinoline-2-carboxylic acid (5d). Prepared analogously as described for acid **5a**, from 2-bromo-3-fluoro-7-methoxyquinoline (**3d**; 6.40 g, 25 mmol); pale yellow prisms (from aqueous *N*,*N*-dimethylformamide); mp 135–136 °C (decomp.); yield: 4.52 g (82%). ^{1}H NMR: $\delta=7.98$ (d, $J=10.2$ Hz, 1H), 7.77 (d, $J=9.0$ Hz, 1H), 7.4 (m, 2H), 3.99 (s, 3H) ppm. ^{13}C NMR: $\delta=161.7$ (s), 161.4 (d, $J=6$ Hz), 155.3 (d, $J=267$ Hz), 144.9 (s), 135.5 (d, $J=10$ Hz), 128.1 (d, $J=3$ Hz), 127.3 (d, $J=5$ Hz), 124.7 (s), 123.6 (d, $J=18$ Hz), 106.7 (s), 56 (m) ppm. MS: m/z (%)=223 (5) [$M^+ +2$], 222 (31) [$M^+ +1$], 221 (45) [M^+], 204 (25), 177 (100). Anal. Calcd for $C_{11}H_8FNO_3$ (221.19): C, 59.73; H, 3.65. Found: C, 59.66; H, 3.72.

4.1.16. 8-Bromo-3-fluoroquinoline-2-carboxylic acid (5e). Prepared from 2,8-dibromo-3-fluoroquinoline (**3e**; 7.6 g, 25 mmol) in the same way as described for acid **5b** but starting the reaction at −100 °C; colorless tiny prisms (from diethyl ether); mp 137–138 °C (decomp.); yield: 4.57 g (79%). ^{1}H NMR: $\delta=8.15$ (d, $J=7.5$ Hz, 1H), 8.12 (d, $J=9.8$ Hz, 1H), 7.89 (dd, $J=8.3$, 1.1 Hz, 1H), 7.60 (t, $J=7.9$ Hz, 1H) ppm. ^{13}C NMR (D_3CCOCD_3): $\delta=163.3$ (d, $J=6$ Hz), 156.3 (d, $J=267$ Hz), 141.5 (s), 141.3 (d, $J=$ 15 Hz), 134.4 (s), 132.7 (d, $J=6$ Hz), 131.0 (s), 128.5 (d, $J=4$ Hz), 125.3 (s), 123.3 (d, $J=18$ Hz) ppm. MS: m/z (%)=270 (48) [$M^+ +1$], 269 (100) [M^+], 251 (20), 225 (40), 191 (8). Anal. Calcd for $C_{10}H_5BrFNO_2$ (270.05): C, 44.48; H, 1.87. Found: C, 44.41; H, 2.11.

4.1.17. 3-Fluoro-5,7-dimethylquinoline-2-carboxylic acid (5f). Prepared analogously from 2-bromo-5,7-dimethyl-3-fluoroquinoline (**3f**; 6.4 g, 25 mmol) as described for acid **5b**; colorless needles (from aqueous methanol); mp 125–126 °C (decomp.); yield: 3.67 g (67%). ^{1}H NMR: $\delta=$ 8.11 (d, $J=11.2$ Hz, 1H), 7.78 (s, 1H), 7.40 (s, 1H), 2.67 (s, 3H), 2.56 (s, 3H) ppm. ^{13}C NMR (D_3CCOCD_3): $\delta=163.3$ (d, $J=6$ Hz), 155.6 (d, $J=265$ Hz), 145.0 (s), 140.6 (s), 138.6 (d, $J=14$ Hz), 135.1 (d, $J=5$ Hz), 132.9 (s), 129.1 (d, $J=5$ Hz), 127.1 (s), 119.7 (d, $J=18$ Hz) ppm. MS: m/z (%)=219 (10) [M^+], 218 (100), 175 (80), 160 (70). Anal. Calcd for $C_{12}H_{10}FNO_2$ (219.21): C, 65.75; H, 4.60. Found: C, 65.46; H, 4.33.

4.1.18. 2-Bromo-3-fluoroquinoline-4-carboxylic acid (6a). Diisopropylamine (7.0 mL, 5.1 g, 50 mmol) and 2-bromo-3-fluoroquinoline (**3a**; 11 g, 50 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (30 mL) and tetrahydrofuran (0.21 L) cooled in a methanol/dry ice bath. After 2 h at −75 °C, the mixture was poured onto an excess of freshly crushed solid carbon dioxide. The solvents were removed under reduced pressure. The residue was taken up in water (0.15 L) and washed with diethyl ether (3×25 mL). The aqueous layer was acidified with 2.0 M hydrochloric acid (25 mL) to pH 1. The precipitate formed was collected and washed with water (2×20 mL); colorless needles (from acetone); mp 196–197 °C (decomp.); yield: 12.7 g (94%). ^{1}H NMR*: $\delta=8.13$ (d, $J=7.6$ Hz, 1H), 8.08 (dd, $J=8.2$, 1.2 Hz, 1H), 7.92 (td, $J=7.6$, 1.2 Hz, 1H), 7.85 (td, $J=7.6$, 1.2 Hz, 1H) ppm. ^{13}C NMR*: $\delta=164.3$ (s), 148.6 (d, $J=261$ Hz), 145.6 (d, $J=$ 2 Hz), 132.5 (d, $J=27$ Hz), 131.5 (s), 130.3 (s), 129.5 (s), 126.6 (d, $J=16$ Hz), 126.1 (d, $J=5$ Hz), 124.8 (s) ppm. ^{19}F NMR*: $\delta=-114.3$ (s) ppm. MS: m/z (%)=270 [$M^+ +1$] (100), 269 (56) [M^+], 252 (2), 207 (4). Anal. Calcd for $C_{10}H_5BrFNO_2$ (270.06): C, 44.48; H, 1.87. Found: C, 44.40; H, 1.91.

4.1.19. 2-Bromo-6-chloro-3-fluoroquinoline-4-carboxylic acid (6b). Prepared analogously from 2-bromo-6-chloro-3-fluoroquinoline (**3b**; 6.5 g, 25 mmol); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 207–209 °C (decomp.); yield: 6.62 g (87%). ^{1}H NMR*: $\delta=8.1$ (m, 2H), 7.89 (dd, $J=9.1$, 2.2 Hz, 1H) ppm. ^{13}C NMR*: $\delta=162.9$ (s), 148.9 (d, $J=264$ Hz), 143.0 (d, $J=3$ Hz), 134.0 (s), 132.4 (d, $J=27$ Hz), 130.8 (s), 130.5 (s), 124.9 (s), 124.2 (d, $J=16$ Hz), 123.9 (s) ppm. MS: m/z (%)=304 (47) [$M^+ +$ 1], 303 (100) [M^+], 259 (6), 224 (15), 179 (16). Anal. Calcd for $C_{10}H_4BrClFNO_2$ (304.50): C, 39.44; H, 1.32. Found: C, 39.55; H, 1.16.

4.1.20. 2-Bromo-3,7-difluoroquinoline-4-carboxylic acid (6c). Prepared analogously from 2-bromo-3,7-difluoroquinoline (**3c**; 6.1 g, 25 mmol); colorless needles (from methanol); mp 200–202 °C (decomp.); yield: 4.90 g (68%). ^{1}H NMR (D_3CCOCD_3): $\delta=8.27$ (dd, $J=9.5$, 6.5 Hz, 1H), 7.79 (dd, $J=9.5$, 2.4 Hz, 1H), 7.70 (tdd, $J=9.3$, 2.4, 1.0 Hz, 1H) ppm. ^{13}C NMR*: $\delta=163.6$ (s), 162.9 (dm, $J=244$ Hz), 148.2 (d, $J=259$ Hz), 146.0 (symm. m), 133.7 (d, $J=$ 27 Hz), 128.5 (dm, $J=166$ Hz), 126.3 (dd, $J=16$, 3 Hz), 121.8 (symm. m), 120.2 (ddd, $J=167$, 25, 4 Hz), 113.3 (dd, $J=168$, 22 Hz) ppm. ^{19}F NMR: $\delta=-115.0$ (d, $J=7.6$ Hz), −109.0 (quint, $J=7.6$ Hz) ppm. MS: m/z (%)=288 (55) [$M^+ +1$], 287 (100) [M^+], 243 (4), 208 (16), 163 (18). Anal. Calcd for $C_{10}H_4BrF_2NO_2$ (288.05): C, 41.70; H, 1.40. Found: C, 41.75; H, 1.42.

4.1.21. 2-Bromo-3-fluoro-7-methoxyquinoline-4-carboxylic acid (6d). Prepared analogously from 2-bromo-3-fluoro-7-methoxyquinoline (**3d**; 6.4 g, 25 mmol); colorless needles (from aqueous *N*,*N*-dimethylformamide); mp 210–212 °C (decomp.); yield: 6.23 g (83%). ^{1}H NMR*: $\delta=7.94$ (d, $J=$ 9.3 Hz, 1H), 7.50 (d, $J=2.5$ Hz, 1H), 7.46 (dd, $J=9.3$, 2.5 Hz, 1H), 3.93 (s, 3H) ppm. ^{13}C NMR*: $\delta=163.5$ (s), 160.6 (s), 146.5 (d, $J=258$ Hz), 146.4 (s), 131.2 (d, $J=$ 27 Hz), 126.0 (d, $J=4$ Hz), 125.8 (d, $J=16$ Hz), 121.9 (s), 118.5 (s), 107.2 (s), 55.8 (t, $J=27$ Hz) ppm. MS: m/z (%)=

300 (100) [$M^+ + 1$], 299 (36) [M^+], 256 (4), 222 (16). Anal. Calcd for $C_{11}H_7BrFNO_3$ (300.08): C, 44.03; H, 2.35. Found: C, 44.26; H, 2.38.

4.1.22. 2,8-Dibromo-3-fluoroquinoline-4-carboxylic acid (6e). Prepared analogously from 2,8-dibromo-3-fluoroquinoline (**3e**; 24 g, 79 mmol); colorless needles (from acetonitrile); mp 175–176 °C (decomp.); yield: 25.4 g (92%). ^{1}H NMR*: $\delta=8.26$ (d, $J=7.6$ Hz, 1H), 8.05 (d, $J=7.9$ Hz, 1H), 7.70 (t, $J=7.9$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=163.0$ (s), 148.5 (d, $J=263$ Hz), 141.4 (s), 134.0 (s), 132.8 (d, $J=27$ Hz), 129.0 (s), 126.1 (d, $J=17$ Hz), 125.4 (s), 125.2 (d, $J=4$ Hz), 123.0 (s) ppm. MS: *m/z* (%)=348 (75) [$M^+ + 1$], 347 (100) [M^+], 346 (8), 268 (12), 145 (15). Anal. Calcd for $C_{10}H_4Br_2FNO_2$ (348.95): C, 34.42; H, 1.16. Found: C, 34.59; H, 1.27.

4.1.23. 2-Bromo-3-fluoro-5,7-dimethylquinoline-4-carboxylic acid (6f). Prepared analogously from 2-bromo-3-fluoro-5,7-dimethylquinoline (**13**; 43 g, 0.17 mol); colorless needles (from aqueous acetone); mp 192–194 °C (decomp.); yield: 41.6 g (82%). ^{1}H NMR (D_3CCOCD_3): $\delta=7.70$ (s, 1H), 7.43 (s, 1H), 2.70 (s, 3H), 2.50 (s, 3H) ppm. ^{13}C NMR*: $\delta=165.7$ (s), 148.5 (s), 146.0 (s), 140.1 (s), 133.6 (d, $J=5$ Hz), 133.2 (s), 129.9 (d, $J=26$ Hz), 126.8 (d, $J=19$ Hz), 126.2 (s), 20.8 (s), 19.5 (s) ppm. MS: *m/z* (%)= 298 (100) [$M^+ + 1$], 297 (36) [M^+], 281 (10), 254 (18), 253 (17), 172 (26). Anal. Calcd for $C_{12}H_9BrFNO_2$ (298.11): C, 48.35; H, 3.04. Found: C, 48.76; H, 3.10.

4.1.24. 3-Fluoroquinoline-4-carboxylic acid.[1] (7a) Palladium (10% on charcoal, 0.13 g) was added to a solution of 2-bromo-3-fluoroquinoline-4-carboxylic acid (**6a**; 6.8 g, 25 mmol) and triethylamine (7.0 mL, 5.1 g, 50 mmol) in methanol (50 mL), which was stirred under an atmosphere of hydrogen (1 atm) at 25 °C. After 4 h, the required amount of hydrogen had been taken up. The reaction mixture was filtered and concentrated. Upon acidification with a 1.0 M aqueous solution of hydrochloric acid (30 mL) to pH 1, a precipitate settled out which was collected by filtration; colorless needles (from acetone); mp 242–243 °C (decomp.); yield: 4.06 g (85%). ^{1}H NMR*: $\delta=9.07$ (d, $J=1.0$ Hz, 1H), 8.14 (dd, $J=8.2$, 1.0 Hz, 1H), 8.06 (dd, $J=$ 8.2, 1.0 Hz, 1H), 7.84 (td), $J=7.0$, 1.0 Hz, 1H), 7.78 (t, $J=$ 7.0 Hz) ppm. ^{13}C NMR*: $\delta=164.3$ (s), 151.6 (d, $J=259$ Hz), 144.9 (s), 141.9 (d, $J=28$ Hz), 129.5 (s), 129.2 (s), 128.9 (s), 124.9 (d, $J=5$ Hz), 123.9 (s), 123.7 (d, $J=13$ Hz) ppm. MS: *m/z* (%)=192 (32) [$M^+ + 1$], 191 (100) [M^+], 174 (16), 173 (9), 147 (4), 135 (11).

4.1.25. 6-Chloro-3-fluoroquinoline-4-carboxylic acid (7b). 2-Bromo-6-chloro-3-fluoroquinoline-4-carboxylic acid (**6b**; 7.6 g, 25 mmol) and tin(II) chloride (4.8 g, 25 mmol) were added to a 5.0 M solution (0.10 mL) of hydrogen chloride in anhydrous ethanol and heated under reflux for 4 h. After evaporation of the solvent, the residue was treated with water (50 mL). The precipitate was collected and washed with water (2×20 mL); colorless needles (from acetone); mp 251–254 °C (decomp.); yield: 4.85 g (86%). ^{1}H NMR*: $\delta=9.11$ (s, 1H), 8.2 (m, 2H), 7.85 (dd, $J=11.5$, 2.3 Hz, 1H) ppm. ^{13}C NMR*: $\delta=$ 163.8 (s), 152.6 (d, $J=263$ Hz), 143.4 (s), 142.7 (d, $J=27$ Hz), 133.7 (s), 131.6 (s), 129.7 (s), 125.0 (s), 123.7 (s), 122.3 (d, $J=$ 13 Hz) ppm. MS: *m/z* (%)=226 (100) [$M^+ + 1$], 225 (72) [M^+], 190 (3), 208 (11), 181 (5). Anal. Calcd for $C_{10}H_5ClFNO_2$ (225.60): C, 53.24; H, 2.23. Found: C, 53.18; H, 1.96.

4.1.26. 3,7-Difluoroquinoline-4-carboxylic acid (7c). Prepared as described above for the acid **7a**, from 2-bromo-3,7-difluoroquinoline-4-carboxylic acid (**6c**; 7.2 g, 25 mmol); colorless tiny needles (from aqueous *N*,*N*-dimethylformamide); mp 250–251 °C (decomp.); yield: 4.90 g (70%). ^{1}H NMR (D_3CCOCD_3): $\delta=9.13$ (s, 1H), 8.17 (dd, $J=9.6$, 5.6 Hz, 1H), 7.93 (dd, $J=9.6$, 2.8 Hz, 1H), 7.73 (td, $J=8.6$, 2.8 Hz, 1H) ppm. ^{13}C NMR*: $\delta=163.8$ (s), 161.6 (d, $J=$ 245 Hz), 151.3 (d, $J=258$ Hz), 146 (symm. m), 143.1 (dd, $J=186$, 28 Hz), 127.5 (dm, $J=166$ Hz), 123.7 (d, $J=$ 14 Hz), 121.0 (s), 119.4 (dd, $J=25$, 4 Hz), 113.4 (dd, $J=26$, 4 Hz) ppm. MS: *m/z* (%)=210 (29) [$M^+ + 1$], 209 (100) [M^+], 208 (17), 192 (14), 15 (8). Anal. Calcd for $C_{10}H_5F_2NO_2$ (209.15): C, 57.43; H, 2.41. Found: C, 57.15; H, 2.44.

4.1.27. 3-Fluoro-7-methoxyquinoline-4-carboxylic acid (7d). Prepared analogously from 2-bromo-3-fluoro-7-methoxyquinoline-4-carboxylic acid (**6d**; 7.5 g, 25 mmol); golden yellow platelets (from *N*,*N*-dimethylformamide); mp 267–270 °C (decomp.); yield: 3.81 g (69%). ^{1}H NMR*: $\delta=9.00$ (s, 1H), 7.99 (d, $J=8.9$ Hz, 1H), 7.52 (d, $J=$ 2.5 Hz, 1H), 7.44 (dd, $J=8.9$, 2.5 Hz, 1H), 3.95 (s, 3H) ppm. ^{13}C NMR*: $\delta=164.5$ (s), 159.8 (s), 150.7 (d, $J=256$ Hz), 146.7 (s), 141.7 (d, $J=27$ Hz), 125.9 (s), 123.8 (d, $J=14$ Hz), 121.6 (s), 118.6 (s), 107.9 (s), 56 (m) ppm. MS: *m/z* (%)=223 (5) [$M^+ + 2$], 222 (37) [$M^+ + 1$], 221 (100) [M^+], 191 (4), 178 (11). Anal. Calcd for $C_{11}H_8FNO_3$ (221.18): C, 59.73; H, 3.65. Found: C, 59.92; H, 3.60.

4.1.28. 8-Bromo-3-fluoro-4-quinolinecarboxylic acid (7e). Prepared as described above for the acid **7b** 2,8-dibromo-3-fluoroquinoline-4-carboxylic acid (**6e**; 10 g, 30 mmol) was treated with tin(II) chloride (5.7 g, 30 mmol) to afford colorless tiny needles (from aqueous *N*,*N*-dimethylformamide); mp 224–225 °C (decomp.); yield: 6.89 g (85%). ^{1}H NMR*: $\delta=9.19$ (s, 1H), 8.23 (d, $J=7.3$ Hz, 1H), 8.07 (d, $J=8.6$ Hz, 1H), 7.67 (t, $J=8.0$ Hz, 1H) ppm. ^{13}C NMR*: $\delta=164.0$ (s), 152.2 (d, $J=262$ Hz), 142.9 (d, $J=28$ Hz), 141.5 (s), 133.0 (s), 129.5 (s), 125.6 (d, $J=3$ Hz), 125.2 (s), 124.7 (s), 124.5 (d, $J=14$ Hz) ppm. MS: *m/z* (%)=270 (56) [$M^+ + 1$], 269 (100) [M^+], 251 (6), 225 (26), 190 (8), 146 (24). Anal. Calcd for $C_{10}H_5BrFNO_2$ (270.06): C, 44.48; H, 1.87. Found: C, 44.66; H, 1.82.

4.1.29. 3-Fluoro-5,7-dimethylquinoline-4-carboxylic acid (7f). Prepared as described for the acid **7a** from 2-bromo-3-fluoro-5,7-dimethylquinoline-4-carboxylic acid (**6f**; 7.5 g, 25 mmol); colorless prisms (from ethanol); mp 196–197 °C (decomp.); yield: 4.38 g (80%). ^{1}H NMR (D_3CCOCD_3): $\delta=8.99$ (s, 1H), 7.78 (s, 1H), 7.42 (s, 1H), 2.65 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C NMR*: $\delta=167.0$ (s), 151.6 (d, $J=253$ Hz), 146.2 (s), 140.4 (d, $J=27$ Hz), 133.4 (d, $J=5$ Hz), 132.8 (s), 127.3 (s), 125.1 (d, $J=17$ Hz), 120.6 (s), 20.8 (s), 19.7 (s) ppm. MS: *m/z* (%)=221 (9) [$M^+ + 2$], 220 (57) [$M^+ + 1$], 219 (100) [M^+], 201 (33), 175 (35), 172 (56). Anal. Calcd for $C_{12}H_9BrFNO_2$ (219.21): C, 65.75; H, 4.60. Found: C, 65.64; H, 4.51.

4.1.30. 3-Fluoro-5,7-dimethyl-2-[(thiocarbamoyl)hydrazonomethyl]quinoline-4-carboxylic acid (8b). Butylmagnesium chloride (25 mmol) in tetrahydrofuran (12 mL) and 2-bromo-3-fluoro-5,7-dimethylquinoline-4-carboxylic acid (**6f**, 7.5 g, 25 mmol) were added consecutively to a solution of butyllithium (50 mmol) in hexanes (35 mL) and tetrahydrofuran (80 mL) kept in an ice bath. After 2 h at 0 °C, the mixture was treated with *N*,*N*-dimethylformamide (2.1 mL, 2.0 g, 25 mmol). At 25 °C, it was poured into a 2.0 M aqueous solution of citric acid (50 mL) and extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (2×25 mL). The bright yellow powder obtained after the evaporation of the volatiles was dissolved in 70% aqueous ethanol (50 mL). Thiosemicarbazide (2.3 g, 25 mmol) was added and the mixture was heated under reflux for 1 h. The golden yellow tiny needles were collected by filtration and washed with 70% aqueous ethanol (2×10 mL); 195–196 °C (decomp.); 6.24 g (78%). ^{1}H NMR*: δ=11.93 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 7.77 (s, 1H), 7.57 (s, 1H), 7.42 (s, 1H), 2.64 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C NMR*: δ=178.7 (s), 166.6 (s), 150.0 (d, J=263 Hz), 145.5 (s, broad), 142.0 (d, J=12 Hz), 139.2 (s), 138.6 (s, broad), 133.3 (s, broad), 133.1 (d, J=5 Hz), 126.9 (s), 126.5 (s), 120.6 (s), 20.8 (s), 19.4 (s) ppm. MS: *m*/*z* (%)=276 (31), 221 (96), 189 (100), 172 (61), 146 (30). Anal. Calcd for $C_{14}H_{13}FN_4O_2S$ (320.34): C, 52.49; H, 4.09. Found: C, 52.75; H, 4.17.

4.1.31. 2-Bromo-3-fluoroquinoline-4-carbaldehyde (9a). Diisopropylamine (10 mL, 7.1 g, 70 mmol) and 2-bromo-3-fluoroquinoline (**3a**; 16 g, 70 mmol) were added consecutively to a solution of butyllithium (70 mmol) in hexanes (45 mL) and tetrahydrofuran (0.30 L) cooled in a dry ice/methanol bath at -75 °C. After 2 h the mixture was treated with *N*,*N*-dimethylformamide (5.9 mL, 5.6 g, 70 mmol). Again 2 h later, it was poured into a 2.0 M aqueous solution of citric acid (0.15 L) and extracted with diethyl ether (3×70 mL). The combined organic layers were washed with brine (0.10 L) and evaporated; pale yellow needles (from heptanes); mp 76–78 °C (reprod.); yield: 17.4 g (98%). ^{1}H NMR: δ=10.81 (s, 1H), 9.0 (m, 1H), 8.1 (m, 1H), 7.77 (symm. m, 2H) ppm. ^{13}C NMR: δ=188.7 (symm. m), 155.5 (d, J=274 Hz), 145.8 (d, J=3 Hz), 132.5 (d, J=27 Hz), 130.7 (s), 130.1 (s), 129.1 (s), 125.2 (d, J=6 Hz), 123.3 (s), 122.0 (d, J=4 Hz) ppm. MS: *m*/*z* (%)=254 (23) [M^++1], 253 (55) [M^+], 225 (24), 146 (100), 126 (40). Anal. Calcd for $C_{10}H_5BrFNO$ (254.06): C, 47.28; H, 1.98. Found: C, 47.50; H, 1.90.

4.1.32. 2-Bromo-4-(1,3-dioxolan-2-yl)-3-fluoroquinoline (9b). At 0 °C, the boron trifluoride diethyl ether complex (25 mL, 28 g, 80 mmol) was added to a solution of 2-bromo-3-fluoro-quinoline-4-carbaldehyde (**9a**; 10 g, 40 mmol) and ethylene glycol (3.4 mL, 3.7 g, 60 mmol) in anhydrous dichloromethane (0.44 L). After 24 h at 25 °C, the mixture was poured into a 1.0 M aqueous solution of sodium hydrogen carbonate (0.30 L). The aqueous layer was extracted with dichloromethane (3×40 mL). The combined organic layers were washed with water (2×40 mL) and dried. Evaporation of the solvent afforded the product as colorless needles (from a mixture of hexanes and diethyl ether); mp 121–123 °C (reprod.); yield: 11.5 g (97%). ^{1}H NMR: δ=8.25 (d, J=8.6 Hz, 1H), 8.06 (d, J=8.6 Hz, 1H), 7.70 (t, J=8.3 Hz, 1H), 7.61 (t, J=8.3 Hz, 1H), 6.49 (s), 4.4 (symm. m, 2H), 4.2 (symm. m, 2H) ppm. ^{13}C NMR: δ=150.7 (d, J=264 Hz), 145.5 (d, J=3 Hz), 132.2 (d, J=28 Hz), 129.3 (s), 128.0 (s), 126 (m), 124.8 (d, J=5 Hz), 98.1 (d, J=4 Hz), 665.7 (s) ppm. MS: *m*/*z* (%)=298 (98) [M^++1], 297 (22) [M^+], 254 (5), 218 (9), 145 (25). Anal. Calcd for $C_{12}H_9BrFNO_2$ (298.11): C, 48.35; H, 3.04. Found: C, 48.40; H, 2.80.

4.1.33. 4-(1,3-Dioxolan-2-yl)-3-fluoroquinoline-2-carboxylic acid (10a). A solution containing 2-bromo-4-(1,3-dioxolan-2-yl)-3-fluoroquinoline (**9b**; 10 g, 35 mmol) and butyllithium (35 mmol) in tetrahydrofuran (50 mL), diethyl ether (0.10 L) and hexanes (25 mL) was stored 6 h at −100 °C before being poured onto an excess of freshly crushed dry ice. After addition of water (0.15 L) the reaction mixture was washed with diethyl ether (3×35 mL). When the aqueous layer was acidified to pH 1, the product precipitated. It was collected and washed with water (2×20 mL); colorless prisms (from acetone); mp 117–118 °C (decomp.); yield: 8.66 g (94%). ^{1}H NMR (D_3CCOCD_3): δ=8.49 (d, J=8.6 Hz, 1H), 8.17 (d, J=8.6 Hz, 1H), 7.85 (dd, J=8.3, 7.0 Hz, 1H), 7.76 (dd, J=8.0, 6.7 Hz, 1H), 6.56 (s, 1H), 4.4 (m, 2H), 4.2 (m, 2H) ppm. ^{13}C NMR*: δ=164.4 (d, J=5 Hz), 152.2 (d, J=267 Hz), 143.9 (d, J=3 Hz), 141.9 (d, J=19 Hz), 130.1 (s broad), 129.6 (s), 129.3 (s), 126.4 (d, J=6 Hz), 125.0 (d, J=5 Hz), 96.9 (d, J=7 Hz), 65.4 (s) ppm. MS: *m*/*z* (%)=263 (2) [M^+], 219 (46), 200 (8), 147 (64), 73 (100). Anal. Calcd for $C_{13}H_{10}FNO_4$ (263.22): C, 59.32; H, 3.83. Found: C, 59.05; H, 3.70.

4.1.34. 3-Fluoro-4-formylquinoline-2-carboxylic acid (10b). 4-(1,3-Dioxolan-2-yl)-3-fluoro-quinoline-2-carboxylic acid (**10a**; 6.6 g, 25 mmol) in tetrahydrofuran (60 mL) and 2.0 M hydrobromic acid (0.19 L) was stored 24 h at 25 °C before being extracted with diethyl ether (3×25 mL). The combined organic layers were washed with brine (2×25 mL) and dried with anhydrous sodium sulfate. After evaporation of the volatiles a light yellow solid was left behind, which crystallized from aqueous acetone and was isolated as colorless tiny needles; mp 114–115 °C (decomp.); 8.65 g (79%). ^{1}H NMR*: δ=10.75 (s, 1H), 8.90 (symm. m, 1H), 8.2 (symm. m, 1H), 7.9 (symm. m, 2H) ppm. ^{13}C NMR*: δ=189.4 (symm. m), 163.8 (d, J=4 Hz), 156.1 (d J=277 Hz), 143.8 (d J=3 Hz), 142.2 (d, J=18 Hz), 131.6 (s)129.9 (s), 124.6 (s), 124.4 (d, J=4 Hz), 122.7 (d, J=4 Hz) ppm. MS: *m*/*z* (%)=219 (4) [M^+], 218 (10), 200 (8), 175 (94), 147 (100), 127 (20), 120 (20). Anal. Calcd for $C_{11}H_6FNO_3$ (219.17): C, 60.28; H, 2.76. Found: C, 60.22; H, 2.75.

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Synthetic studies related to diketopyrrolopyrrole (DPP) pigments. Part 2: The use of esters in place of nitriles in standard DPP syntheses: Claisen-type acylations and furopyrrole intermediates☆

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Abstract—Ethyl 2-aryl-4,5-dihydro-5-oxopyrrole-3-carboxylates react with esters or acyl halides in the presence of a strong base to give 4-acyl derivatives, which exist predominantly as either *E*- or *Z*-enols. These are cyclised, either in solution at temperatures >200 °C or by microwave irradiation, to 3,6-disubstituted 1*H*-furo[3,4-*c*]pyrrolediones which, after *N*-protection, are convertible by reaction with primary amines into novel *N*,*N*′-disubstituted DPP derivatives.

The synthesis of 3,6-diaryl derivatives of the 2*H*,5*H*-pyrrolo[3,4-*c*]pyrrole-1,4-dione (diketopyrrolopyrrole or DPP) ring system, e.g. **1** (R = Ar), is routinely accomplished by reaction of ethyl 4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate **2** with aromatic nitriles in the presence of a strong base such as sodium *t*-amyloxide,[1,2] and non-aromatic nitriles react similarly with compound **2a** to give analogues of **1** where R = alkyl or cycloalkyl.[3] In Part 1 of this series[1] we have described attempts to use α,β-unsaturated nitriles in these processes: however, the propensity of such nitriles to undergo conjugate rather than 'normal' addition leads initially to the anions **3** and thence to the novel cyclopenta[*c*]pyrrole derivatives **4** (Scheme 1). These products, although highly coloured, appear to be of limited value as pigments, since when incorporated into a PVC film, they show a tendency to migrate out of the latter when it is placed in contact with a second surface.

1. Results and discussion

The corresponding reactions of the pyrrolinecarboxylate ester **2a** with α,β-unsaturated esters were considered worthy of investigation, in the expectation that the analogous products **5** containing an ester group might have potential as pigments. Reaction of the pyrrolinecarboxylate ester **2a** with ethyl cinnamate and sodium *t*-amyloxide under reflux gave a bright orange product, the ^{1}H NMR and infra-red spectra of which confirmed the presence of both ethyl ester and amide functionality. However, the mass spectrum indicated a molecular mass of 361, which was not consistent with the expected product **5** (molecular mass 359), and the ^{1}H NMR spectrum indicated that the alkenic double bond of the cinnamate had been retained in the product. An identical product resulted from reaction of the pyrrolinecarboxylate ester **2a** with *methyl* cinnamate, indicating that the ester group in the product originated in compound **2a** rather than the cinnamate. Structure **6** was therefore proposed for this product, and the overall reaction was recognised as a Claisen-type acylation (Scheme 2). Direct confirmation of the structure **6** was sought using X-ray crystallography, but suitable crystals could not be obtained; it is of course conceivable that this solid consisted of a mixture of crystalline tautomers: not only the keto isomer **6** but also, for example, **6*E*** and **6*Z***. However, in situ methylation of the crude reaction product prior to the final acidification (the

☆ Part 1, see Ref. 1.

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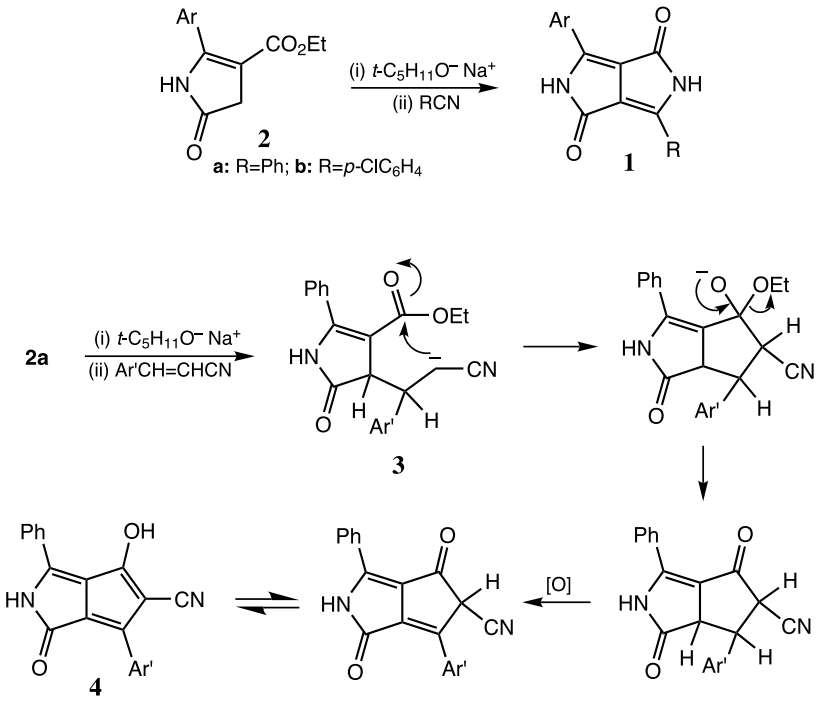


Scheme 1.

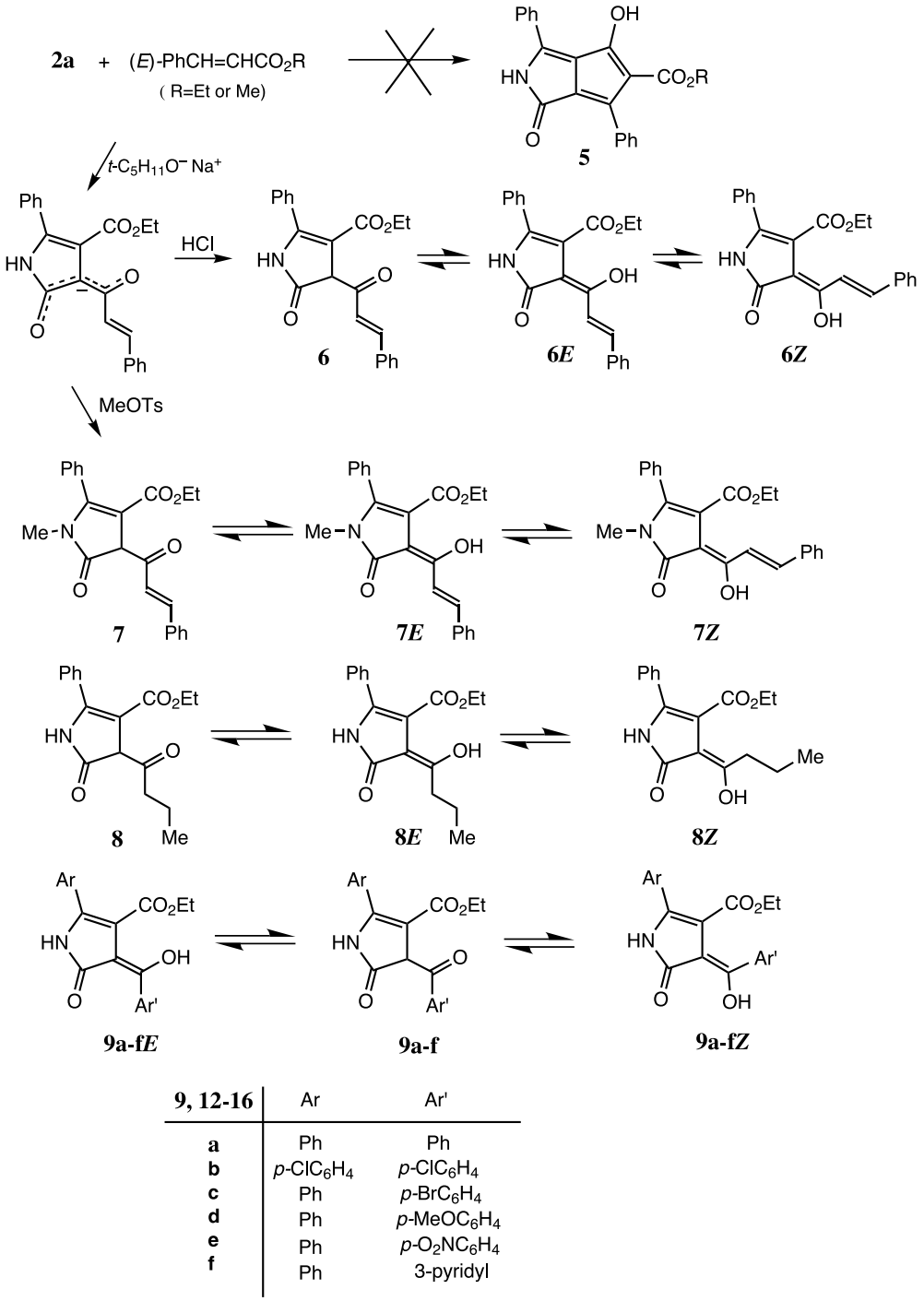
method already described[1] for the methylation of compounds of type **4**) gave an orange *N*-methyl derivative, the structure of which was confirmed as the *E*-enol of **7** by X-ray crystallography (Fig. 1). The coplanarity of the enol and ester functions, and the relatively short distance (2.51 Å) between the enolic and ester carbonyl oxygens is consistent with intramolecular hydrogen bonding between these two functional groups.

Other alkyl and aryl esters react similarly with the pyrrolinecarboxylate ester **2a**. The reaction using ethyl butanoate yielded an almost colourless solid, which was sufficiently crystalline to be identified by X-ray crystallography as the analogous *E*-enol **8*E*** (Fig. 2); and the corresponding reactions of the esters **2a** with ethyl benzoate and sodium *t*-amyloxide gave a beige-coloured enol, the isolated crystal of which was, interestingly, the *Z*-enol **9a*Z*** (Fig. 3); in this molecule hydrogen bonding is apparent (O⋯O distance 2.57 Å) between the enolic hydrogen and the oxygen of the pyrrolinone carbonyl group. Acylations of the esters **2a** and **2b** using various acyl chlorides, with sodium hydride as the base, give broadly similar results: although this process is more convenient in practice, the yields of the acylated products **9a–f** are generally lower. The results are tabulated below (Table 1); the zero yield in several attempted preparations of the *p*-methoxybenzoyl analogue **9d** was unexpected.

The disparity in configuration between the various isolated enols is not immediately explicable. It may be that the keto-isomer and both *E*- and *Z*-enols are all present in solution, and the compound which is isolated in each case is either the most stable, or the least sterically hindered, or merely the one which happens to be the least soluble under these particular conditions. In the case of the benzoyl compound **9a**, the ^{1}H NMR spectrum (in $CDCl_3$) shows the presence of *four* ethoxy-groups, with an approximate integral ratio 70:14:5:11. The main product shows, unusually, the quartet due to the ester methylene group at δ 3.56, with the three other methylene resonances at δ 4.10, 3.75 and 3.45, respectively. In most other cases, the ^{1}H NMR spectrum contains one major and one minor methylene resonance, one with $\delta<4$ and the other with $\delta>4$. Since compounds **6**, **7**, **8** and **9a** are all sharp-melting solids, both by visual observation and (in some cases) by differential scanning calorimetry (DSC), it seems a reasonable supposition that in each case the crystalline isomer isolated is likely to be the principal isomer in solution; and that those with $\delta(CH_2)<4$ are *Z*-enols whereas those with $\delta(CH_2)>4$ have the *E*-configuration.

The fact that some of these Claisen reaction products are obtained in relatively low yield does not necessarily mean a low conversion, but difficulty of isolation: for example the 'one-pot' preparation of the *N*-methyl compound **7** from **2a** by acylation followed by in situ methylation gives a higher overall yield than the two-step sequence in which the intermediate **6** is isolated and purified.

Conversion of these enols into derivatives of DPP requires three further steps. Rubin,[3] Langhals[4] and their co-workers have previously shown that heating of dialkyl 2,3-dibenzoylsuccinates to ca. 300 °C gives diketofurofurans **10**, and that these fused dilactones are converted into *N*,*N*′-diarylated DPPs, **11**, by reaction with a primary aromatic amine in the presence of *N*,*N*′-dicyclohexylcarbodiimide and a catalytic amount of trifluoroacetic acid (Scheme 3(a)). It is now shown that the aroylated pyrrolinone esters **9a–f** may be similarly cyclised to 3,6-diaryl-1*H*-furo[3,4-*c*]-pyrrole-1,4(5*H*)-diones **12a–f** (Scheme 3(b)), a process



9, 12-16	Ar	Ar'
a	Ph	Ph
b	*p*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$
c	Ph	*p*-BrC$_6$H$_4$
d	Ph	*p*-MeOC$_6$H$_4$
e	Ph	*p*-O$_2$NC$_6$H$_4$
f	Ph	3-pyridyl

Scheme 2.

which presumably involves $Z \rightarrow E$ isomerisation as the first step. Heating to 240 °C in Dowtherm® A for prolonged periods gives moderate yields of the cyclised products, but the yields may be significantly improved and the reaction times greatly reduced when the cyclisations are carried out in the cavity of a microwave reactor. The results are tabulated below (Table 2). Unexpectedly the cinnamoyl and butanoyl compounds **7** and **8**, the principal isomer of which already has the *E*-configuration and might have been expected to undergo cyclisation more readily, underwent only extensive decomposition under similar conditions, and no furopyrrole was isolated. This behaviour is also observable by DSC, where a broad exotherm occurs immediately above the melting temperatures of both compounds.

Conversion of the furopyrroles **12a–f** into DPP derivatives by adaptation of the above literature procedures[3,4] appears to require prior protection of the amido-nitrogen: methylation and benzylation are straightforwardly achieved by standard procedures, and these derivatives (**14** and **13**, respectively) then undergo the ring-opening and

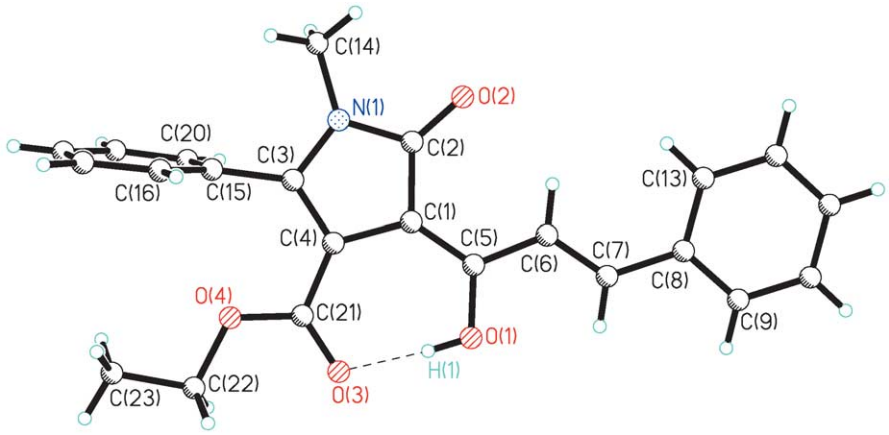


Figure 1. X-ray structure of compound **7**. Selected bond lengths (Å): C(1)–C(5), 1.383(4); C(3)–C(4), 1.370(4); C(5)–C(6), 1.448(5); C(6)–C(7), 1.331(5); C(2)–O(2), 1.235(4); C(5)–O(1), 1.330(4). Selected interbond angles (°): C(4)–C(1)–C(5), 130.2(3); C(1)–C(2)–N, 105.9(3); C(4)–C(3)–N, 109.9(3); C(1)–C(4)–C(21), 128.3(5); C(4)–C(21)–O(3), 124.7(3). Selected torsion angles (°): O(1)–C(5)–C(1)–C(4), 0.6(6); C(1)–C(4)–C(21)–O(3), −2.2(6); C(2)–C(1)–C(5)–O(1), 178.8(3); C(6)–C(7)–C(8)–C(9), −172.8(4); C(4)–(C3)–C(15)– are cts (Å): O(1)···O(3), 2.51; O(3)···H(1), 1.70 (estimated).

ring-closure sequence, leading to the N^5-protected 2,3,6-triaryl-DPP derivatives **16** and **15**.

Langhals et al. had previously shown[4] that the conversion of the furofurans **10** into DPPs **11** required the presence of *N*,*N*′-dicyclohexylcarbodiimide and a catalytic amount of trifluoroacetic acid; in the absence of such reagents the ring-closure step did not apparently occur, and the isolated product[3] from the reaction of **10** with aniline alone was provisionally assigned the structure **17a** or **17b**, although definitive proof of structure was lacking. In our series, however, reaction of the *N*-methylated furopyrrole **14a** with aniline alone led to the enamine **18a**, the structure of which was established by X-ray crystallography (Fig. 4), and the product from the corresponding reaction of **14c** is the analogue **18c**. This suggests that ring-opening of the furopyrroles **14** may involve nucleophilic attack by the amine at C-3 (Scheme 4) rather than at C-1 as implied by the intermediacy of amides such as **17**.

2. X-ray crystallography

In the crystals selected for analysis, the enolic nature of each of compounds **7**, **8** and **9a** is evident from the observed bond lengths (see the data accompanying Figs. 1–3). In each case the length of the carbon–carbon bond joining the acyl group to the pyrroline ring is less than 1.4 Å, indicative of substantial double-bond character, whereas the acyl carbon–oxygen bond lengths (>1.3 Å) are considerably longer than expected for a normal C=O double bond, such as are found in the pyrrolinone carbonyl groups (1.23–1.26 Å). In compounds **7** and **8** the coplanar alignment of the enolic hydroxyl and ester groups, together with the relatively short distance between the enolic and carbonyl oxygen atoms (ca. 2.5 Å; well within the accepted range[5]) is taken as indicative of intramolecular hydrogen bonding between these two functionalities. By similar criteria, the crystal of compound **9a** reveals a structure in which intramolecular hydrogen bonding occurs between the enolic hydrogen and the

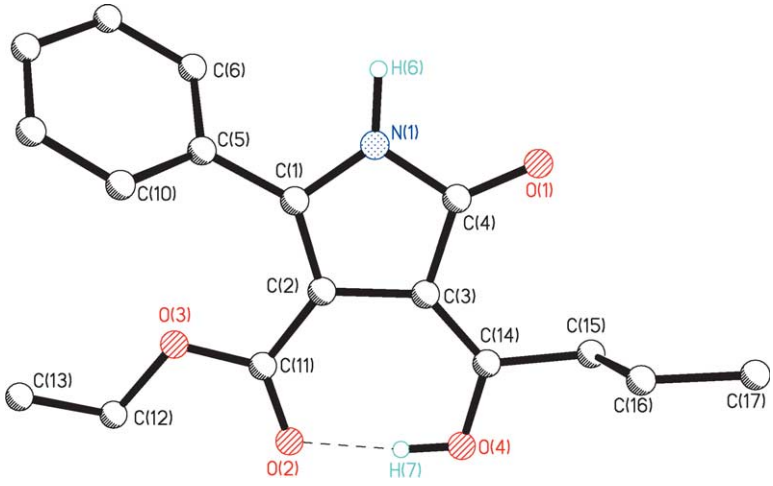


Figure 2. X-ray structure of compound **8**. Selected bond lengths (Å): C(3)–C(14), 1.368(4); C(4)–O(1), 1.243(3); C(14)–O(4), 1.322(3); C(3)–C(4), 1.455(4); C(2)–C(3), 1.477(4); C(1)–C(2), 1.368(4). Selected interbond angles (°): C(2)–C(3)–C(14), 132.2(3); C(3)–C(4)–N, 106.1(2); C(2)–C(1)–N, 109.3(3); C(3)–C(2)–C(11), 125.4(3); C(2)–C(11)–O(2), 125.1(3). Selected torsion angles (°): O(4)–C(14)–C(3)–C(2), 0.0(5); O(2)–C(11)–C(2)–C(3), 4.9(5); C(4)–C(3)–C(14)–O(4), 177.8(3); C(2)–C(1)–C(5)–C(6), −133.7(4). Non-bonded contacts (Å): O(2)···O(4), 2.52; O(2)···H(7), 1.64 (estimated).

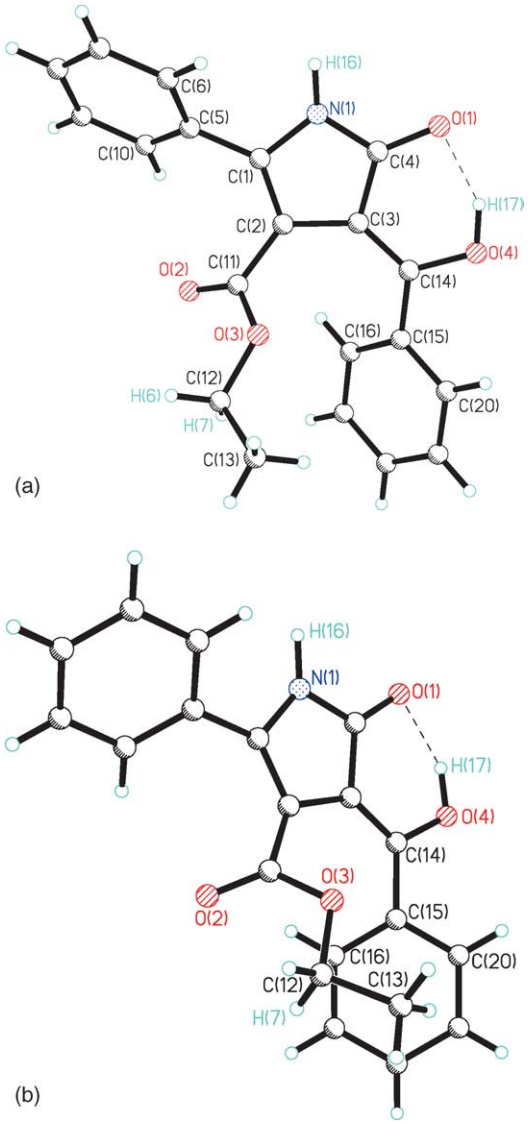


Figure 3. X-ray structure of compound **9a**. [View **3b** shows the close proximity of the ester methylene protons (*ca*. 2.8 Å) to the mean plane of the phenyl ring.] Selected bond lengths (Å): C(3)–C(14), 1.372(4); C(4)–O(1), 1.260(3); C(14)–O(4), 1.342(4); C(3)–C(4), 1.447(4); C(2)–C(3), 1.460(4); C(1)–C(2), 1.357(4). Selected interbond angles (°): C(3)–C(4)–O(1), 127.8(3); C(4)–C(3)–C(14), 119.4(3); C(3)–C(14)–O(4), 118.9(3). Selected torsion angles (°): C(1)–C(2)–C(11)–O(3), 123.4(3); C(3)–C(2)–C(11)–O(2), 141.7(4); C(3)–C(14)–C(15)–C(16), 32.8(5); C(2)–C(1)–C(5)–C(6), 132.5(4); C(4)–C(3)–C(14)–O(4), 6.3(5). Non-bonded contacts (Å): O(1)···O(4), 2.57; O(1)···H(17), 1.70 (estimated).

pyrrolinone oxygen atom; interestingly both the phenyl moiety of the benzoyl substituent and the ester group lie significantly out of the plane of the heterocyclic ring. In the enamine **18a**, there is evidently intramolecular hydrogen bonding between the anilino-NH and the pyrrolinone oxygen.

3. Conclusion

Whereas reaction of the pyrrolinecarboxylate ester **2a** with nitriles leads directly to 3,6-disubstituted DPP derivatives,[1] the corresponding reaction of **2a** with esters proceeds in four distinct stages; (a) *C*-acylation; (b) thermal cyclisation of the acyl compounds, with or without the aid of microwaves, to give furo[3,4-*c*]pyrroles; (c) *N*-protection and (d) ring-opening of the furopyrroles, followed by ring-closure. This sequence constitutes the first reliable general route to N^5-protected 2,3,6-triarylated DPPs.

4. Experimental

4.1. General

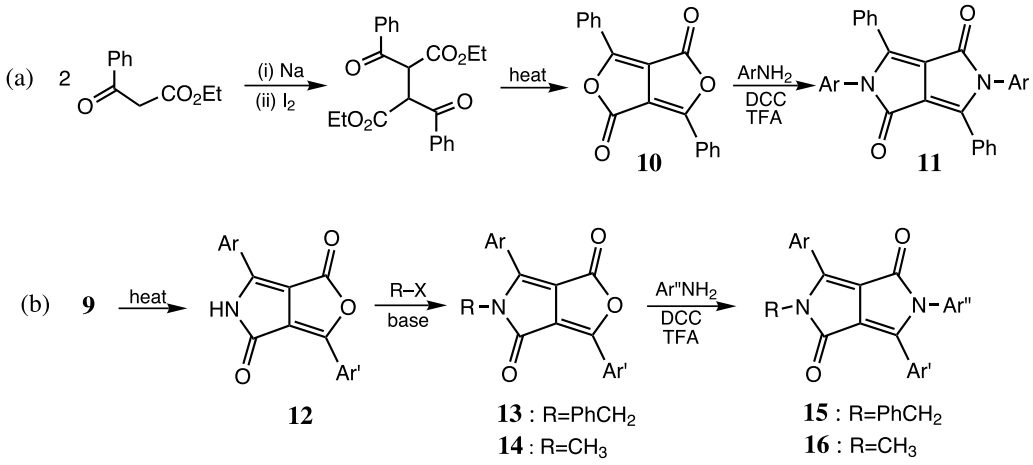
FT-IR spectra were recorded for Nujol mulls; frequencies are expressed in cm^{-1}. Unless otherwise indicated, UV–vis spectra were recorded (wavelengths expressed in nm) for solutions in dimethyl sulfoxide (DMSO), and ^1H and ^{13}C NMR spectra were obtained at 300 and 75.4 MHz, respectively, for solutions in DMSO-d_6 (or, where indicated, $CDCl_3$). Chemical shifts (δ) are expressed relative to $SiMe_4$ ($\delta_H=\delta_C=0$) and coupling constants (J) in Hz. Mass spectra and accurate mass measurements were obtained using electron impact (EI) ionisation at 70 eV, chemical ionisation (CI) using a VG Autospec instrument, or electrospray ionisation (ESI) with a Micromass LCT instrument. The microwave reactor was a CEM Discover™ model, with a circular single mode cavity design and a maximum operating power of 300 W; the samples were contained in sealed glass tubes, whereby the pressure was allowed to increase to a maximum of 2.07 MPa (300 psi).

2-Methylbutan-2-ol (*t*-amyl alcohol) was dried by heating under reflux with sodium metal for several hours followed by distillation on to 4 Å molecular sieves. Sodium *t*-amyloxide solution was obtained by dissolving the appropriate quantity of sodium, cut into small pieces, in boiling *t*-amyl alcohol under nitrogen: this process normally

Table 1. Acylated derivatives of ethyl 2-aryl-4,5-dihydro-5-oxopyrrole-3-carboxylates **2**

Compound	Yield (%), acylating agent		δ_H (OCH_2CH_3)		Isomer ratio (*Z*/*E*)
	RCO_2Et	RCOCl	Major	Minor	
6	59, 40	17	4.00	3.57	<1:10
7			3.97		
8	67	33			
9a	33	10	3.56	4.10	5:1
9b	78	14	3.62	4.19	ca. 2.5:1
9c	—	44	3.63	4.27	2:1
9d	0	0			
9e	—	60	3.62	—	
9f	89	—	3.50	—	

The empty cells in the table indicates that the reaction was not attempted or that the minor isomer was not detected.



Scheme 3.

Table 2. 3,6-Diaryl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-diones **12** and their derivatives

Compound	Yield (%)		Visible absorption, λ_{max}/nm (log ε in brackets)	
	Conventional heating	Microwave heating	Parent compound **12** (in DMSO)	*N*-Me deriv. **14** (in CH_2Cl_2)
12a	40	86, 70	455, 487 (4.41, 4.45)	453 (4.34)
12b	68	—	463, 495 (4.47, 4.52)	
12c	—	94	461, 493 (4.45, 4.49)	454 (4.20)
12e	—	87	487, 511 (4.38, 4.38)	482 (4.24)
12f	—	19	457, 487 (4.02, 4.03)	

The — in the 'yield' column indicates that the reaction was not attempted.

required several hours but could be accelerated by the addition of a catalytic amount of anhydrous iron(III) chloride.

'Ether' refers to diethyl ether and 'petrol' to the fraction of bp 40–60 °C. Ethyl 4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate **2a** was prepared according to the patented procedure.[6] The *p*-chlorophenyl analogue **2b** was supplied by Ciba Specialty Chemicals Inc. as an off-white solid of mp 198 °C, and was used without further purification. Solutions were dried over anhydrous sodium sulfate or magnesium sulfate.

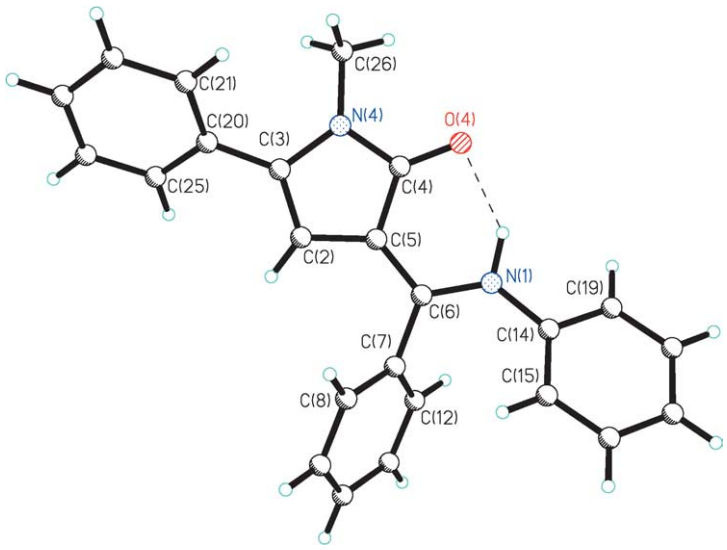
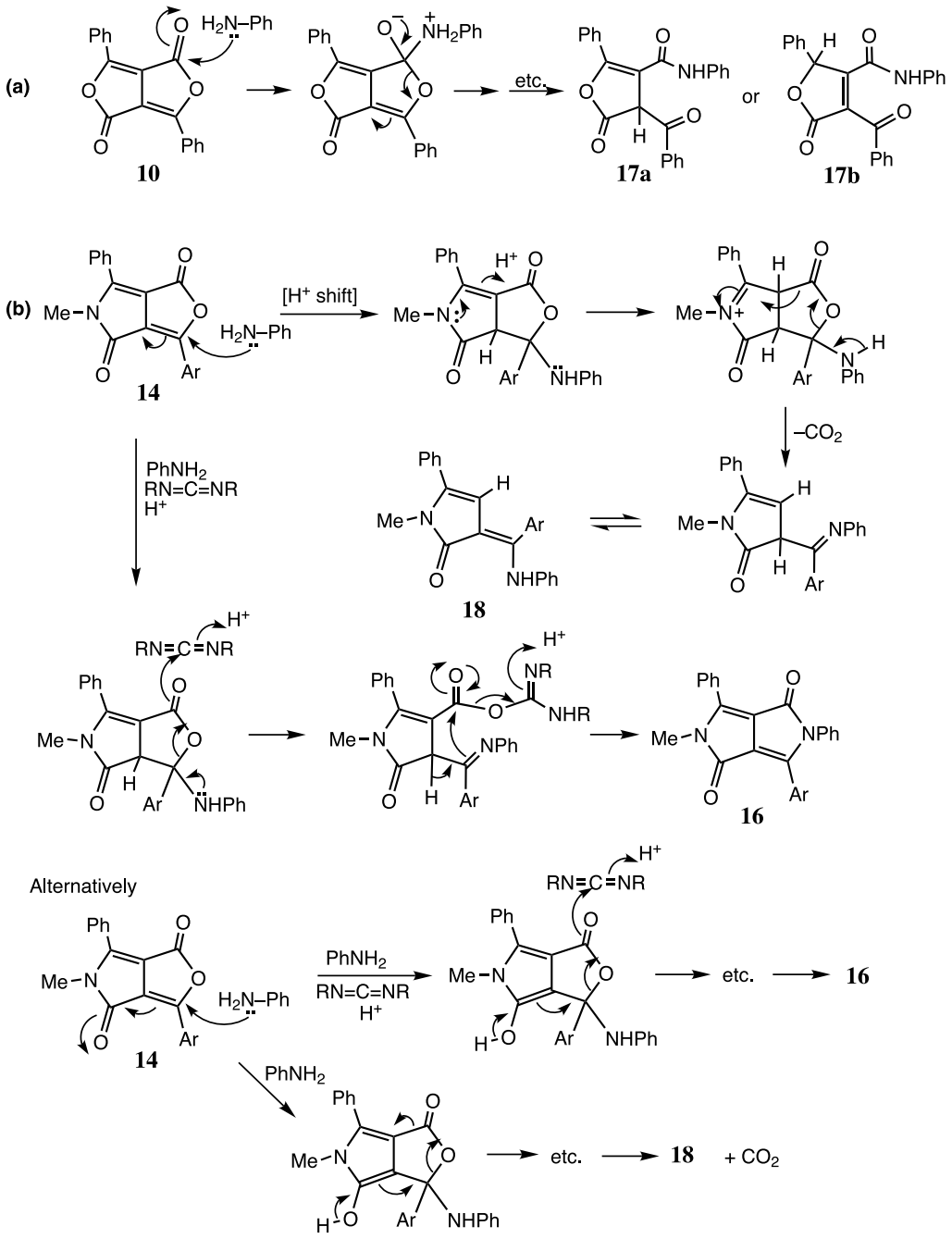


Figure 4. X-ray structure of compound **18a**. Selected bond lengths (Å): C(2)–C(3), 1.356(2); C(4)–C(5), 1.456(2); C(5)–C(6), 1.382(2); C(4)–O, 1.2504(17), C(6)–C(7), 1.481(2); C(6)–N, 1.3573(18); N–C(14), 1.4116(18); C(3)–C(20), 1.4632(19). Selected interbond angles (°): C(2)–C(5)–C(4), 106.39(12); C(4)–C(5)–C(6), 123.25(13); C(3)–C(2)–C(5), 108.46(12); C(5)–C(6)–N, 118.89(13); C(5)–C(4)–O, 128.84(13). Selected torsion angles (°): C(4)–C(5)–C(6)–N, −1.4(2); C(6)–C(5)–C(4)–O, −6.1(2); C(2)–C(3)–C(20)–C(21), 139.92(16); C(5)–C(6)–C(7)–C(8), −56.79(19); C(6)–N–C(14)–C(15), −23.4(2); N–C(6)–C(7)–C(8), 127.70(14); C(5)–C(2)–C(3)–N, 1.14(15). Non-bonded contacts (Å): N···O, 2.7421(16).



14a, 16a, 18a: Ar=Ph; **14c, 16c, 18c**: Ar=*p*-BrC_6H_4

Scheme 4.

4.1.1. Ethyl 4-cinnamoyl-4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate 6. (a) Sodium (1.21 g, 52.6 mmol) was added, with stirring and under nitrogen, to dried *t*-amyl alcohol (70 cm^3) and the mixture heated to reflux (105–110 °C) until all the sodium dissolved. The solution was cooled to 25 °C, then the pyrrolinecarboxylate ester **2a** (2.00 g, 8.6 mmol) and ethyl cinnamate (2.55 g, 14.5 mmol) were added. The mixture was then heated to reflux for 2 h, during which time an intense orange colour developed. The cooled mixture was then added to an ice-cooled mixture of methanol (20 cm^3) and concentrated hydrochloric acid (5 cm^3) and the bright orange precipitate was filtered off, washed with methanol and dried in vacuo at 40 °C. Yield 3.05 g (59%).

(b) The above method was repeated, using the pyrrolinecarboxylate ester **2a** (2.00 g, 8.6 mmol), sodium *t*-amyloxide [from sodium, (0.60 g, 26.1 mmol)] in dried *t*-amyl alcohol (25 cm^3) and methyl cinnamate (1.40 g, 8.6 mmol); the mixture was heated to reflux for 2.5 h, then cooled and added to an ice-cold mixture of methanol (10 cm^3) and water (20 cm^3), and acidified dropwise with concentrated

hydrochloric acid (3 cm^3). The orange precipitate was filtered off, washed with methanol and water then dried in vacuo. Yield 1.25 g (40%).

Compound **6** had mp 238–240 °C. (Found: C, 72.8; H, 5.3; N, 3.8. $C_{22}H_{19}NO_4$ requires C, 73.1; H, 5.3; N, 3.9%). *m/z* 361 ($M^{+\cdot}$, 100%), 315 (77), 238 (72). δ_H 0.88 (3H, t, J=6.6 Hz, OCH_2CH_3), 4.00 (2H, q, J=6.6 Hz, OCH_2CH_3), 7.43–7.47 (8H, m, Ar-H), 7.59 (1H, d, J=15.7 Hz, CH=CHPh), 7.64–7.67 (2H, m, Ar-H), 8.62 (1H, d, J=15.7 Hz, CH=CHPh), 11.11 (1H, s, NH). A minor signal occurred at δ 3.57 (q, OCH_2).

(c) The pyrrolinone ester **2a** (2.00 g, 8.66 mmol) was added to sodium hydride (1.73 g, 43.25 mmol) THF (200 cm^3), and the mixture was stirred for 30 min. Cinnamoyl chloride (1.44 g, 8.66 mmol) was then added and the mixture stirred at room temperature overnight, acidified (HCl), and extracted with ethyl acetate. The dried extract on concentration gave the enol **6** as an orange solid (523 mg, 17%), mp 247–250 °C, spectroscopically identical with the products from (a) and (b).

4.1.2. Ethyl 4-cinnamoyl-4,5-dihydro-1-methyl-5-oxo-2-phenylpyrrole-3-carboxylate 7. The dianion of the cinnamoyl-pyrrolinecarboxylate ester **6** was prepared as above, from the pyrrolinecarboxylate ester (5.00 g, 21.6 mmol), ethyl cinnamate (3.88 g, 22.0 mmol) and sodium *t*-amyloxide (from sodium, 1.51 g, 65.7 mmol) in *t*-amyl alcohol (25 cm^3). The orange solution was cooled to 25 °C, methyl *p*-toluenesulfonate (15.88 g, 85.3 mmol) was added and the mixture heated under reflux for 1 h, cooled, added to water (30 cm^3), extracted with ethyl acetate, and the extract dried and concentrated. Recrystallisation (propan-2-ol–tetrahydrofuran) gave an orange solid (6.27 g, 77%), mp 190–192 °C. (Found: C, 73.4; H, 5.6; N, 3.7. $C_{23}H_{21}NO_4$ requires C, 73.6; H, 5.6; N, 3.7%). *m/z* 375 ($M^{+\cdot}$, 100%), 329 (98). δ_H ($CDCl_3$) 0.75 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.97 (3H, s, NCH_3), 3.97 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.24–7.48 (8H, m, Ar-H), 7.67–7.76 (3H, m, Ar-H and CH=CHPh), 8.76–8.84 (1H, d, J=15.5 Hz, CH=CHPh).

4.1.3. Ethyl 4-butanoyl-4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate 8. (a) The pyrrolinecarboxylate ester **2a** (2.00 g, 8.6 mmol) and ethyl butanoate (1.00 g, 8.6 mmol) were added successively, under nitrogen, at 80–90 °C to a stirred solution of sodium *t*-amyloxide, prepared as above from sodium (0.61 g, 26.5 mmol) in *t*-amyl alcohol (25 cm^3). The mixture was heated to reflux for 5 h, then cooled and added to an ice-cold mixture of water (100 cm^3) and methanol (10 cm^3). Dropwise acidificaton (conc. HCl) gave a purple precipitate which was filtered off, washed with methanol then water and decolourised in hot propan-2-ol with charcoal, to yield almost colourless crystals (1.74 g, 67%).

(b) The pyrrolinone ester **2a** (1.00 g, 4.33 mmol) was added to sodium hexamethyldisilazide (1 M solution in THF, 13.4 cm^3), and the mixture was stirred for 30 min. Butanoyl chloride (0.46 g, 0.45 cm^3, 4.33 mmol) was then added and the mixture stirred at room temperature overnight, then acidified (HCl), extracted with ethyl acetate, and the extract dried and concentrated under reduced pressure. Yield 0.43 g (33%).

Compound **8** had mp 173–174 °C. (from ethanol or 1,4-dioxan). (Found: C, 68.1; H, 6.6; N, 4.7. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%). δ_H ($CDCl_3$) 0.96 (3H, t, J=7.4 Hz, $CH_2CH_2CH_3$), 1.03 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.65–1.78 (2H, m, $CH_2CH_2CH_3$), 3.04 (2H, br t, J=7.0 Hz, $CH_2CH_2CH_3$), 4.10 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.39–7.42 (5H, m, Ar-H), 8.85 (1H, br s, NH). A minor signal occurred at δ 3.73 (q, OCH_2).

4.1.4. Ethyl 4-benzoyl-4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate 9a. (a) The pyrrolinecarboxylate ester **2a** (5.03 g, 21.8 mmol) and ethyl benzoate (3.27 g, 21.8 mmol) were added successively at 25 °C to a solution of sodium *t*-amyloxide, prepared as above from sodium (1.50 g, 65.2 mmol) and *t*-amyl alcohol (40 cm^3), and the mixture was then heated to reflux for 5.5 h. The resulting orange solution was cooled and added to an ice-cooled mixture of methanol (10 cm^3) and water (50 cm^3), then acidified dropwise with concentrated hydrochloric acid (3 cm^3) and extracted with tetrahydrofuran/diethyl ether; the extract was dried and concentrated, to give amber-coloured crystals (2.38 g, 33%), mp 156–157 °C. (from ethanol–water).

(b) The pyrrolinone ester **2a** (1.50 g, 6.5 mmol) and benzoyl chloride (0.91 g, 0.75 cm^3, 6.5 mmol) were added successively to sodium hydride (0.55 g, 27.75 mmol) in THF (100 cm^3), and the mixture stirred at room temperature overnight, then added to water, acidified (HCl) and the organic component extracted with ethyl acetate and dried. Recrystallisation from ethanol gave the benzoylpyrrolinone ester (100 mg, 9.5%), mp 157–158 °C, identical to the product of method (a).

Found: C, 71.5; H, 5.2; N, 4.2. $C_{20}H_{17}NO_4$ requires C, 71.6; H, 5.1; N, 4.2%. ν_{max} 3170 (NH), 2720 (H-bonded OH), 1720 (ester C=O), 1630 (lactam C=O), 1610 and 1600 (C=C). δ_H 0.60 (3H, t, J=7.2 Hz, OCH_2CH_3—major), 0.95 (3H, t, J=7.2 Hz, CH_2CH_3—minor), 3.56 (2H, q, J=7.2 Hz, CH_2CH_3—major), 4.10 (2H, q, J=7.2 Hz, CH_2CH_3—minor) 7.42–7.62 (6H, m, *m*/*p*-Ar-H), 7.62–7.80 (4H, m, *o*-Ar-H), 9.52 (1H, br. s, NH). Other minor signals (each OCH_2, q) occur at δ 3.75 and 3.45. δ_C 175.4 (lactam C=O), 170.7 (ester C=O), 165.0 (C=C(OH)Ph), 135.7 (Ph-C=C–CO_2Et), 131.8 (Ar), 130.6 (quat. Ar), 130.2 (quat. Ar), 129.9 (Ar), 129.4 (Ar), 128.9 (2×C, Ar), 128.8 (2×C, Ar), 128.7 (Ar), 128.3 (Ar), 128.0 (Ar), 108.0 (Ph-C=C–CO_2Et), 105.1 (C=C–C=C(OH)Ph), 61.0 (CH_2), and 13.6 (CH_3). *m/z* 335 ($M^{+\cdot}$, 54%), 289 (100), 261 (7), 105 (56).

4.1.5. Ethyl 4-(*p*-chlorobenzoyl)-4,5-dihydro-5-oxo-2-(*p*-chlorophenyl)-pyrrole-3-carboxylate 9b. This compound was prepared similarly to **9a**, from the pyrrolinone ester **2b** (26.29 g, 99 mmol), ethyl *p*-chlorobenzoate (18.27 g, 99 mmol) and sodium *t*-amyloxide [from sodium, 6.82 g (297 mmol) in *t*-amyl alcohol (230 cm^3)], with the reactants being added at 70 °C and the mixture being heated under reflux for 22 h. The product was recrystallised from a mixture of ethanol, propan-2-ol, and water; yield, 31.36 g

(78%). The alternative route, using *p*-chlorobenzoyl chloride and sodium hydride as base, gave **9b** in a yield of only 14%.

Compound **9b** had mp 170–172 °C. (Found: C, 59.4; H, 4.1; N, 3.7; Cl, 17.4. $C_{20}H_{15}Cl_2NO_4$ requires C, 59.4; H, 3.7; N, 3.5; Cl, 17.5%). δ_H ($CDCl_3$) 0.74 (3H, t, $J=7.2$ Hz, CH_2CH_3), 3.62 (2H, q, $J=7.2$ Hz, CH_2CH_3), 7.40, 7.44, 7.55 and 7.59 (each 2H, 2×AA′BB′) and 8.63 (NH). [A minor isomer showed resonances at δ 1.05 (CH_2CH_3) and 4.19 (OCH_2)].

4.1.6. Ethyl 4-(*p*-bromobenzoyl)-4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate 9c. The pyrrolinone ester **2a** (0.85 g, 3.69 mmol) was added to sodium hydride (0.59 g, 14.75 mmol) in THF (40 cm^3). After stirring for 30 min at room temperature, a solution of freshly prepared *p*-bromobenzoyl chloride (0.81 g, 3.69 mmol) in THF (10 cm^3), and a catalytic amount (a few crystals) of DMAP were added, and the mixture was stirred at room temperature overnight, then acidified (dil. HCl) and extracted with ether. Concentration of the dried extract in vacuo gave the enol as a yellow crystalline solid (0.67 g, 44%), mp 189 °C (from ethanol). (Found: C, 58.4; H, 3.5; N, 3.3. $C_{20}H_{16}BrNO_4$ requires C, 58.0; H, 3.9; N, 3.4%). δ_H 0.76 (3H, t, $J=7.2$ Hz, CH_2CH_3), 3.63 (2H, q, $J=7.2$ Hz, CH_2CH_3), 7.43–7.52 (3H, m, ArH), 7.59–7.66 (4H, m, ArH), 7.74–7.80 (2H, m, ArH) and 11.90 (1H, s, NH). *m/z* (CI) 414/416 [96/100%, $(M+1)^+$] A minor product showed ethoxy-group resonances at δ_H 1.27 (t, CH_2CH_3) and 4.27 (q, OCH_2); the ratio of the two products was ca. 2:1.

4.1.7. Compound 9d. Repeated attempts to prepare ethyl 4-(*p*-methoxybenzoyl)-4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate **9d** by either of the above acylation methods were unsuccessful; in every case the only product isolated was *p*-methoxybenzoic acid.

4.1.8. Ethyl 4-(*p*-nitrobenzoyl)-4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate 9e. The pyrrolinone ester **2a** (6.35 g, 27.5 mmol) was added to a mixture of sodium hydride (2.00 g, 82.5 mmol) and THF (1 dm^3), and this was stirred at room temperature for 15 min. *p*-Nitrobenzoyl chloride (5.50 g, 29.5 mmol) was then added, and the mixture was stirred overnight. Methanol and then water were added, and the mixture acidified (HCl). The organic component was extracted with ether, the extract was dried, the solvent evaporated, and the residue washed with methanol to give the nitro compound as a yellow solid (6.31 g, 60%), mp 254 °C (by DSC). (Found: C, 63.1; H, 4.15; N, 7.3. $C_{20}H_{16}N_2O_6$ requires C, 63.2; H, 4.2; N, 7.4%). δ_H 0.75 (3H, t, $J=6.6$ Hz, OCH_2CH_3), 3.62 (2H, q, $J=6.6$ Hz, OCH_2CH_3), 7.35–7.45 (3H, m, *m*/*p*-Ph-H), 7.50–7.56 (2H, m, *o*-Ph-H), 7.84 and 8.30 (each 2H, AA′BB′, Ar-H), and 11.95 (1H, s, NH); *m/z* (ESI−ve) 380 (22%, $M^{+\cdot}$), 379 [100, $(M-1)]^+$.

4.1.9. Ethyl 4-nicotinyl-4,5-dihydro-5-oxo-2-phenylpyrrole-3-carboxylate 9f. The pyrrolinone ester **2a** (8.43 g, 36.5 mmol) and methyl nicotinate (5.00 g, 36.5 mmol) were added successively to sodium *t*-amyloxide [from sodium, 2.52 g (0.11 mol) in *t*-amyl alcohol (100 cm^3)], and the mixture heated to reflux overnight. After cooling to room temperature, water was added, and the mixture acidified (HCl). The organic component was extracted with ether, and a precipitate formed in the aqueous layer. This precipitate was filtered off, the remaining aqueous layer was evaporated to dryness and the organic component was extracted with methanol. Evaporation of the methanol gave the nicotinyl compound **9f** as a yellow solid (10.90 g, 89%), mp 194–197 °C (from ethanol). (Found: C, 67.6; H, 4.5; N, 8.2. $C_{19}H_{16}N_2O_4$ requires C, 67.85; H, 4.8; N, 8.3%). δ_H 0.70 (3H, t, $J=6.5$ Hz, OCH_2CH_3), 3.50 (2H, q, $J=6.5$ Hz, OCH_2CH_3), 7.31–7.41 (3H, m, 2× Ar-H+ Py-5-H), 7.43–7.53 (3H, m, Ar-H), 7.93 (1H, br dt, $J=7.9$, 1.5 Hz, Py-4-H), 8.65 (1H, br d, $J=4.8$ Hz, Py-6-H), 8.70 (1H, d, $J=1.5$ Hz, Py-2-H) and 11.89 (1H, s, NH). *m/z* (ESI −ve) 336 (22%, $M^{+\cdot}$), 335 [100, $(M-1)]^+$.

4.1.10. 3,6-Diphenyl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 12a. (a) A mixture of compound **9a** (10.00 g, 29.9 mmol) and Dowtherm® A (200 cm^3) was heated to 230–240 °C under nitrogen for 64 h. The solution was then cooled to room temperature and added dropwise to petrol (300 cm^3); the fluorescent orange precipitate was filtered off, washed with hexane and dried in vacuo. Yield 3.48 g (40%).

(b) The benzoylpyrrolinone ester **9a** was subjected to flash vacuum pyrolysis (500 °C/8×10^{-3} Torr), on a very small scale (50 mg) for ca. 45 min. The product from this heating gave the desired furopyrrole **12a** as a orange solid.

(c) The benzoylpyrrolinone ester **9a** (100 mg, 0.30 mmol) was irradiated in a microwave reactor, without solvent, heating to 250 °C for 10 min. The crude product was then allowed to cool, methanol was added, and the solid filtered off and washed with further methanol. This gave the furopyrrole **12a** (73 mg, 86%). On a larger scale, irradiation of compound **9a** (643 mg), heating to 180 °C. for 10 min, gave the furopyrrole **12a** (387 mg, 70%).

The benzoylpyrrolinone ester **9a** (100 mg, 0.30 mmol) and toluene (2 cm^3) were irradiated in a microwave reactor, heating up to 250 °C over 40 min. The solution was cooled, and the precipitate filtered off and washed with methanol to give the furopyrrole **12a** as an orange solid (22 mg, 26%), the remainder being unchanged starting material. Extension of the reaction time to 1 h gave **12a** in 48% yield.

Compound **12a** had mp >300 °C (dec.) (broad DSC endotherm at ca. 320 °C). (Found: C, 74.9; H, 4.2; N, 4.8. $C_{18}H_{11}NO_3$ requires C, 74.7; H, 3.8; N, 4.8%). ν_{max} 1760 (ester C=O), 1670 (lactam C=O), 1625 (C=C). δ_H 7.48–7.54 (6H, m, Ar-H), 8.12–8.17 (2H, m, Ar-H), 8.17–8.23 (2H, m, Ar-H) and 11.87 (1H, s, NH); δ_C 161.4 and 159.3 (2×C=O), 152.2 and 148.1 (2×quat.), 132.8, 132.6, 129.1 (2C), 128.0, 127.0 (all Ar-C–H), 126.8, 126.4, 115.8 and 102.8 (4×quat). *m/z* 289 ($M^{+\cdot}$, 100%), 204 (20), 105 (35), 77 (35).

4.1.11. 3,6-Bis-(*p*-chlorophenyl)-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 12b. (a) A mixture of compound **9b** (15.00 g, 37 mmol) and Dowtherm® A (300 cm^3) was heated to 205–210 °C during 48 h, then cooled and added

dropwise to petrol (1 l). The fluorescent purple solid was filtered off, washed with further petrol and dried in vacuo. Yield 8.95 g (68%), mp 387 °C (by DSC). (Found: C, 60.3; H, 2.8; N, 3.9. $C_{18}H_9Cl_2NO_3$ requires C, 60.4; H, 2.5; N, 3.9%). δ_H 7.67, 7.73, 8.25, 8.34 (each 2H, 2×AA′BB′) and 12.25 (1H, br s, NH). *m/z* (EI) 357/359/361 ($M^{+\cdot}$, 95/63/8%), 139/141 (100/35, ClC_6H_4CO), 111/113 (85/26, ClC_6H_4), 75 (35).

(b) The *p*-chlorobenzoylpyrrolinone ester **9b** (58 mg, 0.14 mmol) was irradiated in a microwave reactor, without solvent, heating to 200 °C over 10 min. The crude product was then allowed to cool, methanol was added, and the solid filtered off and washed with further methanol. This gave the furopyrrole as a red solid (42 mg, 82%).

4.1.12. 3-(*p*-Bromophenyl)-6-phenyl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 12c. The *p*-bromobenzoylpyrrolinone ester **9c** (154 mg, 0.37 mmol) was irradiated with microwave radiation without solvent, heating to 250 °C for 10 min. The crude product was then allowed to cool, methanol was added and the solid filtered off and washed with methanol. This gave the furopyrrole as a red solid (129 mg, 94%), mp 295 °C (subl., dec.) (Found: C, 58.9; H, 2.6; N, 3.7. $C_{18}H_{10}BrNO_3$ requires C, 58.7; H 2.7; N, 3.8%). δ_H 7.43–7.47 (3H, m, Ar-H), 7.66 and 7.98 (each 2H, AA′BB′, *p*-BrC_6H_4), 8.13–8.17 (2H, m, Ar-H) and 11.88 (1H, s, NH). *m/z* (CI) 368/370 [100/94%, $(M+1)^+$].

4.1.13. 3-(*p*-Nitrophenyl)-6-phenyl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 12e. The *p*-nitrobenzoylpyrrolinone ester **9e** (300 mg, 0.90 mmol) was irradiated with microwave radiation without solvent, heating to 270 °C for 15 min. The crude product was then allowed to cool, methanol was added and the solid filtered off and washed with methanol. This gave the furopyrrole as a red solid (230 mg, 87%), mp 340 °C (by DSC). (Found: C, 64.4; H, 2.9; N, 8.4. $C_{18}H_{10}N_2O_5$ requires C, 64.7; H, 3.0; N, 8.4%). δ_H 7.58–7.69 (3H, m, *m*/*p*-Ph), 8.28–8.34 (2H, m, *o*-Ph), 8.38 (4H, s, *p*-$O_2NC_6H_4$) and 12.15 (1H, s, NH). *m/z* (ESI −ve) 334 (21%, $M^{+\cdot}$), 333 [100%, $(M-1)]^+$.

4.1.14. 6-Phenyl-3-(3-pyridyl)-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 12f. The nicotinylpyrrolinone ester **9f** (100 mg, 0.30 mmol) was irradiated with microwave radiation without solvent, heating to 230 °C for 10 min. The crude product was then allowed to cool, methanol was added and the solid filtered off and washed with methanol. This gave the furopyrrole **12f** as a red solid (16 mg, 19%), the remainder being an intractable black tar. Compound **12f**, mp 333 °C (by DSC), could not be obtained in analytical purity (Found: C, 69.25; H, 3.5; N, 9.8. $C_{17}H_{10}N_2O_3$ requires C, 70.3; H, 3.5; N, 9.65%) but showed the correct ^{1}H NMR and accurate mass: δ_H 7.63–7.74 (5H, m, Ph-H), 8.33–8.39 (1H, m, Py-5-H), 8.56 (1H, dt, J=8.2, 1.9 Hz, Py-4-H), 8.79 (1H, dd, J=1.5, 4.8 Hz, Py-6-H), 9.41 (1H, d, J=1.9 Hz, Py-2-H) and 12.09 (1H, s, NH). *m/z* (ESI −ve) 290 (20%, $M^{+\cdot}$), 289.0618 [100%, $(M-1)^+$; $C_{17}H_9N_2O_3$ requires 289.0613].

4.1.15. 5-Benzyl-3,6-diphenyl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 13a. Compound **12a** (1.00 g, 3.4 mmol) was added under nitrogen at 25 °C to a suspension of sodium hydride (55–65% dispersion in mineral oil; 0.20 g) in tetrahydrofuran (100 cm^3), and the mixture heated briefly to reflux during 5 min. The solution was cooled to room temperature, benzyl bromide (0.70 g, 4.1 mmol) was added, and the mixture heated under reflux for 19 h, then cooled. Water (50 cm^3) was added and the mixture extracted with a mixture of tetrahydrofuran and ethyl acetate (1:1). The extract was dried and concentrated, and the residue mixed with petrol and immersed in an ultrasonic bath for 20 min. The product **13a** (0.97 g, 74%) was filtered off and dried in vacuo: it had mp (DSC) ca. 213 °C (slow decomp. >150 °C). (Found: C, 78.8; H, 4.9; N, 3.6. $C_{25}H_{17}NO_3$ requires C, 79.1; H, 4.5; N, 3.7%). δ_H 5.09 (2H, s, CH_2), 7.10–7.14 (2H, m, Ar-H), 7.19–7.50 (4H, m, Ar-H), 7.52–7.64 (3H, m, Ar-H), 7.65–7.80 (4H, m, Ar-H) and 8.31–8.40 (2H, m, Ar-H). *m/z* (EI) 379 ($M^{+\cdot}$, 33%), 105 (50), 91 (100).

4.1.16. 2-Benzyl-3,5,6-triphenyl-DPP 15a. A mixture of compound **13a** (10.0 g, 26.4 mmol), *N*,*N*′-dicyclohexylcarbodiimide (13.5 g, 65.5 mmol), and aniline (5.0 g, 53.8 mmol) in dichloromethane (300 cm^3) containing trifluoroacetic acid (3 drops) was stirred under nitrogen at 40 °C for 16 h. Further portions of aniline (15.0 g) and *N*,*N*′-dicyclohexylcarbodiimide (10.0 g) were then added, heating was continued for a further 24 h and finally the solvent was distilled off. The residue was recrystallised from 1,4-dioxan and the fluorescent orange product **15a** washed sequentially with hot propan-2-ol, methanol and water. Yield 1.87 g (16%), mp 270–272 °C. (Found: C, 81.9; H, 4.8; N, 6.2. $C_{31}H_{22}N_2O_2$ requires C, 81.9; H, 4.9; N, 6.2%). δ_H ($CDCl_3$) 5.05 (2H, s, PhCH_2N), 7.16–7.24 (4H, m, Ar-H), 7.27–7.50 (12H, m, Ar-H), 7.66–7.70 (2H, m, Ar-H) and 7.74–7.79 (2H, m, Ar-H). *m/z* (EI) 454 ($M^{+\cdot}$, 100%), 363 (10), 335 (16), 292 (14), 180 (31), 91 (41). λ_{max} (CH_2Cl_2) 468 (log ε 4.26).

4.1.17. 5-Methyl-3,6-diphenyl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 14a. (a) Sodium hydride (55–65% dispersion in mineral oil: 0.16 g) was added under nitrogen to a stirred mixture of the furopyrrole **12a** (0.99 g, 3.4 mmol) in dry tetrahydrofuran (200 cm^3) and the mixture heated to boiling for ca. 5 min (until hydrogen evolution ceased), then cooled to 25 °C. Iodomethane (1.46 g, 10.3 mmol) was added and the mixture stirred at 25 °C for 16 h. Water (100 cm^3) was added and the mixture extracted several times with a mixture of tetrahydrofuran and ethyl acetate (2:1). The combined extracts were dried and concentrated, the residue was redissolved in DMSO (20 cm^3) and reprecipitated by dropwise addition to water (200 cm^3). The fluorescent orange product was filtered off, washed with water and dried in vacuo.

(b) A mixture of the furopyrrole **12a** (1.19 g, 4.12 mmol), methyl *p*-toluenesulfonate (1.15 g, 6.18 mmol), potassium carbonate (1.14 g, 8.24 mmol) and DMF (40 cm^3) was stirred at room temperature overnight. Water was then added, and the organic component extracted with dichloromethane. The extract was dried and the solvent was removed; washing of the residue with water then methanol

gave the methylated compound **14a** as a red solid (0.85 g, 68%), mp 198–200 °C.

(Found: C, 75.2; H, 4.5; N, 4.6. $C_{19}H_{13}NO_3$ requires C, 75.3; H, 4.3; N, 4.6%). ν_{max} 1755 (ester C=O), 1700 (lactam C=O) and 1625 (C=C). δ_H ($CDCl_3$) 3.46 (3H, s, NCH_3), 7.52–7.62 (6H, m, 2×*m*/*p*-Ph-H), 7.81–7.85 (2H, m, *o*-Ph-H) and 8.39–8.43 (2H, m, *o*-Ph-H).

4.1.18. 3-(*p*-Bromophenyl)-5-methyl-6-phenyl-1*H*-furo[3,4-*c*]pyrrole-1,4(5*H*)-dione 14c. A mixture of the furopyrrole **12c** (1.50 g, 4.08 mmol), methyl *p*-toluenesulfonate (1.14 g, 6.12 mmol), potassium carbonate (1.13 g, 8.16 mmol) and DMF (60 cm^3) was stirred at room temperature overnight. Water was then added, and the organic component extracted with dichloromethane. The extract was dried, the solvent was removed and the residue washed with water then methanol, to give the methylated compound as a red solid (0.83 g, 53%), mp 215–216 °C. (Found: C, 59.6; H, 2.9; N, 3.6. $C_{19}H_{12}BrNO_3$ requires C, 59.7; H, 3.2; N, 3.7%). δ_H ($CDCl_3$) 3.38 (3H, s, NCH_3), 7.50–7.54 (3H, m, *m*/*p*-Ph), 7.61 and 8.19 (each 2H, AA′BB′, *p*-C_6H_4Br), 7.73–7.78 (2H, m, *o*-Ph). *m*/*z* (ESI) 404/406 $(M+Na)^+$.

4.1.19. 5-Methyl-3-(*p*-nitrophenyl)-6-phenyl-1*H*-furo-[3,4-*c*]pyrrole-1,4(5*H*)-dione 14e. A mixture of furopyrrole **12e** (0.90 g, 2.7 mmol), methyl *p*-toluenesulfonate (0.75 g, 4.04 mmol), potassium carbonate (1.00 g, 7.2 mmol) and DMF (40 cm^3) was stirred at room temperature overnight. Water was then added and the organic component extracted with dichloromethane. The extract was dried, solvent was removed and the residue washed with water then methanol, to give the red methylated compound **14e** (0.65 g, 70%), mp 253–255 °C. (Found: C, 65.4; H, 3.3; N, 7.8. $C_{19}H_{12}N_2O_5$ requires C, 65.5; H, 3.5; N, 8.0%). δ_H ($CDCl_3$) 3.49 (3H, s, NCH_3), 7.60–7.65 (3H, m, *m*/*p*-Ph-H), 7.84–7.88 (2H, m, *o*-Ph-H), 8.38 and 8.55 (each 2H, AA′BB′, *p*-$O_2NC_6H_4$). *m*/*z* (ESI) 349 (100%, $[M+1]^+$).

4.1.20. 5-Methyl-2,3,6-triphenyl-DPP 16a. A solution of the furopyrrole **14a** (0.50 g, 1.65 mmol), aniline (1.54 g, 16.5 mmol), *N*,*N*′-di-*i*-propylcarbodiimide (1.04 g, 1.29 cm^3, 8.25 mmol) and trifluoroacetic acid (3 drops) in dichloromethane (100 cm^3) was stirred at room temperature for 8 days. The solvent was distilled off and the residue washed with methanol, to give the orange DPP (0.16 g, 25%), mp 267–269 °C. (Found: C, 79.4; H, 5.0; N, 7.3. $C_{25}H_{18}N_2O_2$ requires C, 79.35; H, 4.8; N, 7.4%). ν_{max} 1675 (C=O). δ_H 3.42 (3H, s, CH_3), 7.15–7.20 (2H, m, Ar-H *o*-Ph-H), 7.28–7.41 (6H, m, Ar-H), 7.51–7.56 (3H, *m*/*p*-Ph-H), 7.62–7.68 (2H, m, Ar) and 7.91–7.95 (2H, m, Ar-H). *m*/*z* (ESI-+ve) 402 $(M+Na+1)^+$, 401 $(M+Na)^+$. λ_{max} (CH_2Cl_2) 468 (log ε 4.11).

4.1.21. 6-(*p*-Bromophenyl)-2-methyl-3,5-diphenyl-DPP 16c. A mixture of furopyrrole **12c** (300 mg, 0.79 mmol), aniline (146 mg, 1.57 mmol), DCC (323 mg, 1.57 mmol), trifluoroacetic acid (2–3 drops) and dichloromethane (100 cm^3) was stirred at room temperature for 6 days. The solvent was removed and washing of the residue with methanol gave the DPP as a red solid (173 mg, 55%), mp 255–256 °C. (Found: C, 65.4; H, 3.7; N, 6.2. $C_{25}H_{17}BrN_2O_2$ requires C, 65.7; H, 3.8; N, 6.1%). δ_H ($CDCl_3$) 3.35 (3H, s, NCH_3), 7.07–7.12 (2H, m, Ar-H), 7.26–7.40 (5H, m, Ar-H), 7.43–7.49 (5H, m, Ar-H) and 7.83–7.88 (2H, m, Ar-H). λ_{max} (CH_2Cl_2) 479 (log ε 4.20).

4.1.22. 2-Methyl-6-(*p*-nitrophenyl)-3,5-diphenyl-DPP 16e. A mixture of furopyrrole **12e** (100 mg, 0.29 mmol), aniline (53 mg, 0.57 mmol), DCC (118 mg, 0.57 mmol), trifluoroacetic acid (2–3 drops) and dichloromethane (25 cm^3) was stirred at room temperature for 72 h. The solvent was removed, and washing of the residue with methanol gave the pyrrolopyrrole as a red solid (63 mg, 52%), mp 233–235 °C. (Found: C, 71.0; H, 3.7; N, 9.7. $C_{25}H_{17}N_3O_4$ requires C, 70.9; H, 4.05; N, 9.9%). δ_H ($CDCl_3$) 3.45 (3H, s, NCH_3), 7.15–7.20 (2H, m, *o*-Ph), 7.36–7.44 (3H, m, *m*/*p*-Ph), 7.55–7.60 (3H, m, *m*/*p*-Ph), 7.81 and 8.16 (each 2H, AA′BB′, *p*-$C_6H_4NO_2$), and 7.93–7.98 (2H, m, *o*-Ph). *m*/*z* (ESI) 447 (28%, $[M+Na+1]^+$), 446 (100%, $[M+Na]^+$). λ_{max} (CH_2Cl_2) 493 (log ε 4.15).

4.1.23. *Z*-1-Methyl-5-phenyl-3-[1-phenyl-1-(phenylamino)methylidene]-2,3-dihydro-pyrrol-2-one 18a. A solution of furopyrrole **14a** (135 mg, 0.38 mmol) and aniline (85 μl, 0.77 mmol) in toluene (3 cm^3) was irradiated at 150 °C for 10 min. The solution was cooled, and the solvent removed under reduced pressure. Recrystallisation from ethanol gave the pyrrolinone as an orange solid (106 mg, 68%), mp 194.5–197.5 °C. (Found: C, 81.6; H, 5.4; N, 7.8. $C_{24}H_{20}N_2O$ requires C, 81.8; H, 5.7; N, 8.0%). δ_H ($CDCl_3$) 3.34 (3H, s, NCH_3), 5.71 (1H, s, CH), 6.72–6.77 (2H, m, *o*-PhN), 6.93–7.00 (1H, m, *p*-PhN), 7.07–7.15 (2H, m, *m*-PhN), 7.28–7.34 (1H, m, Ar-H), 7.34–7.42 (9H, m, Ar-H) and 11.82 (1H, s, NH). *m*/*z* (ESI+ve): 352 (100%, $M^{+\cdot}$), 353 (44%, $[M+1]^+$), 375 (92%, $[M+Na]^+$), 376 (23%, $[M+Na+1]^+$).

4.1.24. *Z*-3-[1-(*p*-Bromophenyl)-1-(phenylamino)methylidene]-1-methyl-5-phenyl-2,3-dihydropyrrol-2-one 18c. This was similarly prepared from furopyrrole **14c** (250 mg, 0.65 mmol) and aniline (119 μl, 1.31 mmol) in toluene (5 cm^3). The orange pyrrolinone (105 mg, 38%) had mp 179.5–181.5 °C. (from ethanol). (Found: C, 67.15; H, 4.2; N, 6.4. $C_{24}H_{19}BrN_2O$ requires C, 66.8; H, 4.4; N, 6.5%). δ_H ($CDCl_3$) 3.36 (3H, s, NCH_3), 5.68 (1H, s, CH), 6.76–6.81 (2H, m, *o*-PhN), 6.97–7.05 (1H, m, *p*-PhN), 7.12–7.18 (2H, m, *m*-PhN), 7.28 and 7.52 (each 2H, AA′BB′, *p*-BrC_6H_4), 7.30–7.45 (5H, m, Ar-H) and 11.80 (1H, s, NH).

4.2. X-ray crystallography

The intensity data for compounds **7**, **8** and **9a** were recorded at 293(1) K with a Rigaku AFC7S diffractometer using graphite-monochromated Mo-Kα radiation (λ=0.7107 Å), and the structures of **8** and **9a** (Figs. 2 and 3) were solved by direct methods using SIR92[7] and refined by full-matrix least squares on *F*, using the TeXsan system 1.[8] In the case of compound **7**, the structure refined with two independent molecules in the asymmetric unit which are chemically identical, and was solved using SHELXS-86.[9] The intensity data for compound **18a** were recorded using a Siemens/Bruker SMART diffractometer, with data being integrated

using the SAINT[10] and SADABS[11] programs, the structure solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL[12]).

The systematic absences allowed unique assignment of all the space groups. All hydrogen atoms were located from difference maps, and were included in the refinements as riding atoms in idealised positions with isotropic displacement parameters; all non-hydrogen atoms were refined anisotropically. All data were corrected for Lorentz, polarisation and long-term intensity fluctuations. Absorption effects were corrected on the basis of multiple equivalent reflections or by semi-empirical methods. All hydrogen atoms were assigned isotropic displacement parameters and were constrained to idealised geometries. Crystallographic data (excluding structure factors) for compounds **7**, **8**, **9a** and **18a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 243378, 243379, 243380 and 243381, respectively. Copies of the data may be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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