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Contents

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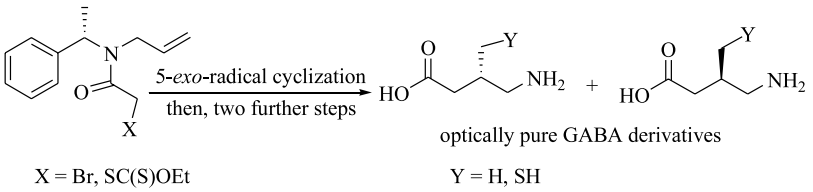
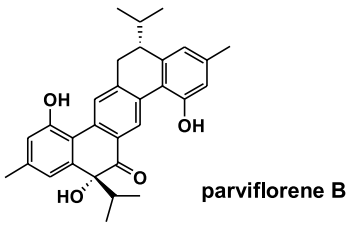
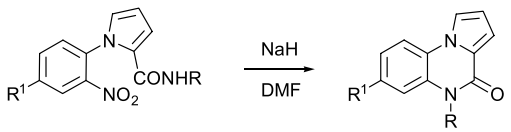
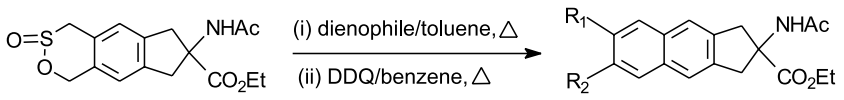


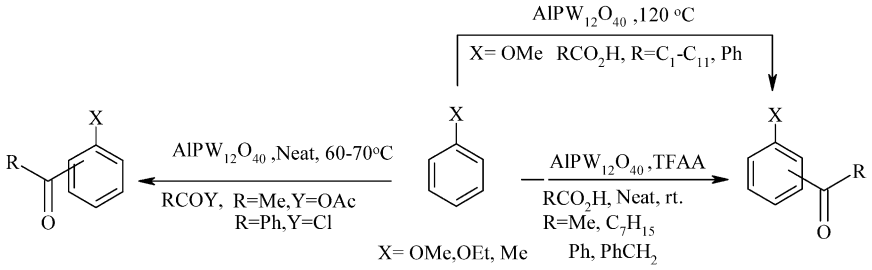


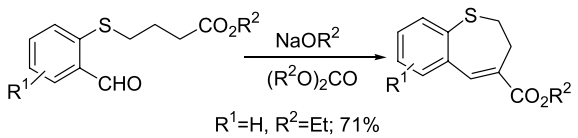


R^1 = H or Me, R = Et, C_6H_{11}, Ph, 2-$HO_2CC_6H_4$, 2-$MeO_2CC_6H_4$, 4-ClC_6H_4 or 4-$MeOC_6H_4$



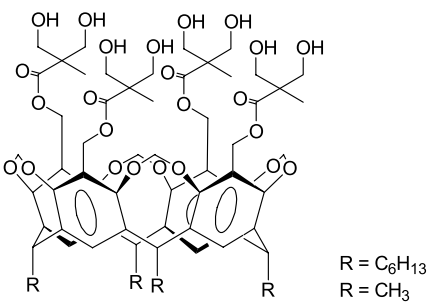
Synthesis of various benzo-annulated indane-based α-amino acid (AAA) derivatives are reported via a [4+2] and [2+2+2] cycloaddition reactions as key steps. Here, *o*-xylylene based AAA moiety has been used as a reactive intermediate and by adopting this strategy various indane-based constrained AAA dervatives are prepared.

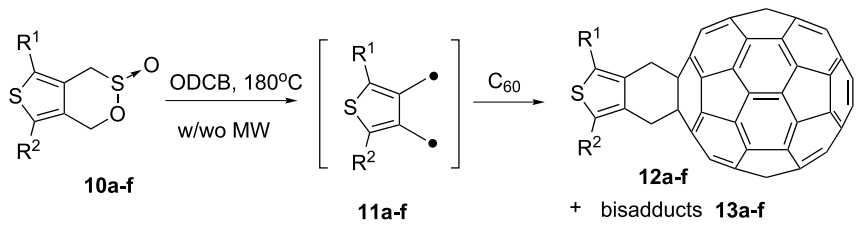


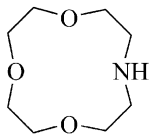


R^1=H, R^2=Et; 71%

The synthesis of novel cavitands containing eight hydroxyl groups was accomplished in eight steps beginning from commercially available resorcinol and the corresponding aldehydes. The synthesis combines two classical approaches to cavitand chemistry and yields the target octol cavitand molecules in gram quantities with no chromatographic separations. A variety of octaester derivatives were then prepared from the parent octols and their spectral properties are reported.







12-crown-O_3N **1**

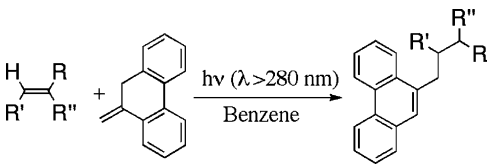
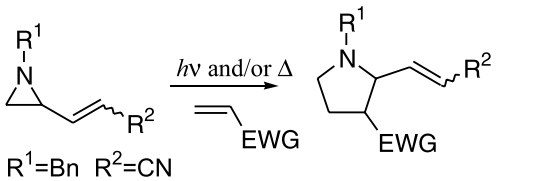
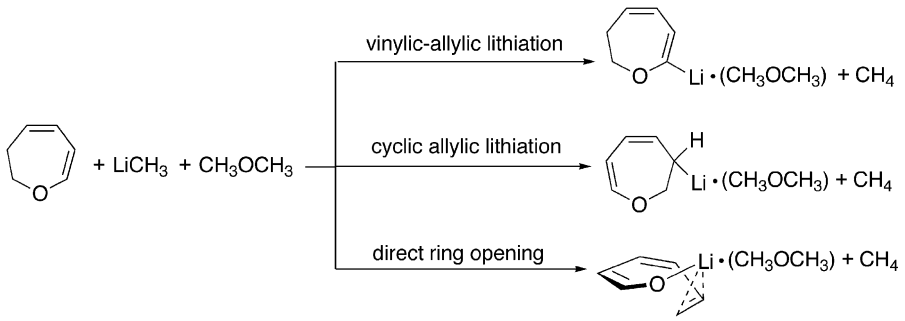


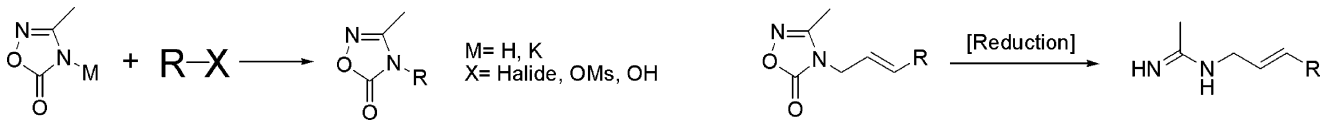
Photo-irradiation of 9-methylene-9,10-dihydrophenanthrene in the presence of styrene derivatives gave ene-adducts. In the absence of conjugated alkenes, 9-[2-(phenanthryl)ehtyl]-9,10-dihydrophenanthrene and 9-methyl phenanthrene were isolated.

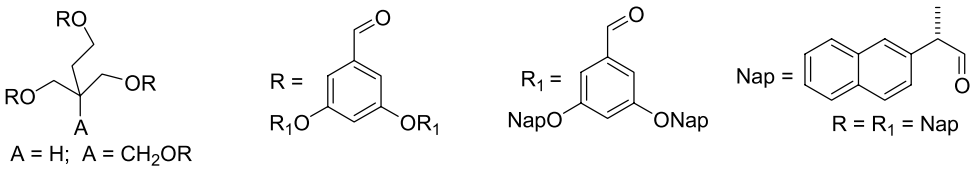


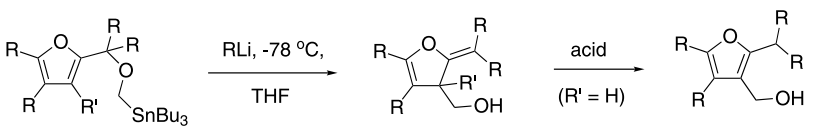
R^1=Bn R^2=CN
R^1=Bn R^2=CO_2Et
R^1=Ph R^2=CO_2Et
R^1=Tr R^2=CO_2Et

head-to-head adducts

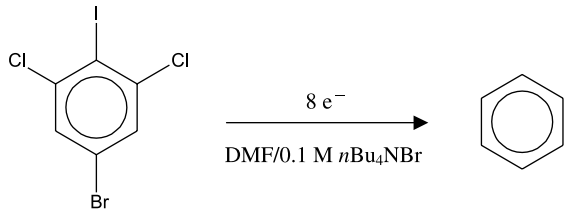


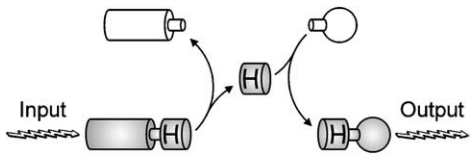


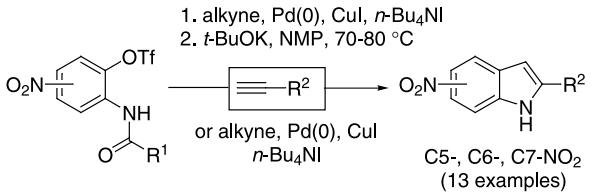


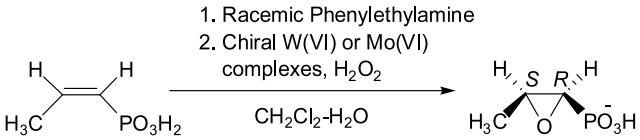


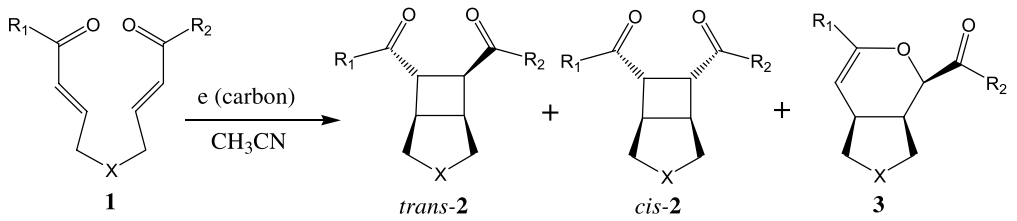
Furans and benzofurans of type **1** were dearomatized via the [2,3]-Still–Wittig rearrangement. Enol ethers **2** could be isolated or isomerized to the corresponding furans **3**. The substitution pattern at the homofuranylic position had a strong influence on reaction behavior. Benzofurans rearranged with the greatest efficiency, and employment of a 3-substituted benzofuran (**1**; $R' = CH_3$) allowed the creation of a quaternary carbon center.

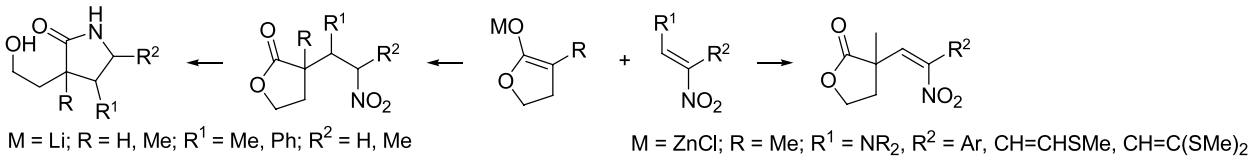


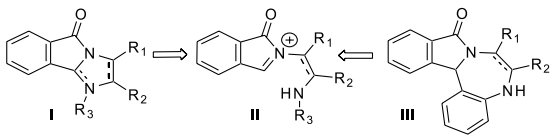












Fused imidazoisoindolinones and diazepinoisoindolinones were synthesized efficiently using *N*-acyliminum ion chemistry.

OTHER CONTENTS

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ⓘ+ Supplementary data available via ScienceDirect

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The 5-*exo-trig* radical cyclization reaction under reductive and oxidative conditions in the synthesis of optically pure GABA derivatives

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Abstract—Free radical precursors **4a** and **4b** were synthesized and treated under reductive or oxidative conditions to obtain the corresponding optically pure pyrrolidinones **5–8**, which were subsequently transformed into corresponding optically pure GABA derivatives **9–11**. When reductive radical conditions (**4a**→**7** and **8**) were used, a Ph_{1-5} migration product **14** was obtained; presumably depending upon the specific conformation of the rotamer precursor and also **14** was found to be a kinetic product.

1. Introduction

γ-Aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the mammalian central nervous system.[1] The GABA derivatives have been subject to further biological studies and they have showed an extensive spectrum of biological activity.[2] Some of the most important GABA derivatives are Gabapentin (**1**),[3] Vigabatrin (**2**),[4] and Baclofen (**3**)[5] which not only have been introduced as anticonvulsant agents but recently have shown to be a potential treatment for neurogenic pain[6] (see Fig. 1).

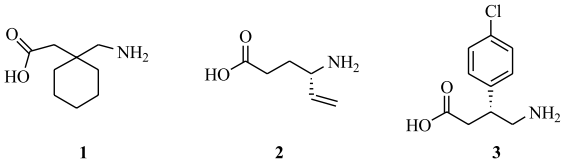
Additionally some derivatives of Gabapentin **1** (with alkyl groups or sulfur atom into the cyclohexane ring framework) have been synthesized and tested, and same biological activity compared to Gabepentin itself has been observed.[7] Thus, developing of novel synthetic routes for the synthesis of the compounds above represents an active synthetic challenge.

In this regard, this work describes a novel and accessible route for the synthesis of optically pure GABA derivatives β-substituted. The key of this work is the use of the (*S*)-α-methylbenzylamine as chiral auxiliary,[8] and the well-studied 5-*exo-trig* radical cyclization[9] as strategy for the construction of the corresponding 4-substituted pyrrolidinones (**5–8**). Then, by removing of the chiral auxiliary followed by an aqueous hydrolysis, the corresponding optically pure GABA derivatives β-substituted will be obtained (**9–12**, Scheme 1).

2. Results and discussion

The synthesis of radical precursors **4a** and **4b** commences with an allylation reaction of (*S*)-α-methylbenzylamine followed by N-acylation reaction with bromoacetylbromide to afford **4a**. The exposure of **4a** to potassium ethylxanthate leads the formation of the radical precursor **4b** (Scheme 2).

The 5-*exo* radical cyclization was achieved by dropwise addition of tributyltin hydride and catalytic amounts of AIBN to **4a** in benzene at reflux when the separable pyrrolidinones **7** (43%), **8** (38%) were obtained, and a $Ph_{1,5}$-migration product **14** (11%) was also obtained, and very small amount of the reduction product (~3%, not showed) was detected (see Scheme 3).



1 2 3

Figure 1. Some GABA derivatives with pharmacological activity.

Keywords: 5-*exo* Radical cyclization; Reductive and oxidative conditions; GABA derivatives; Ar1,5-migracion.

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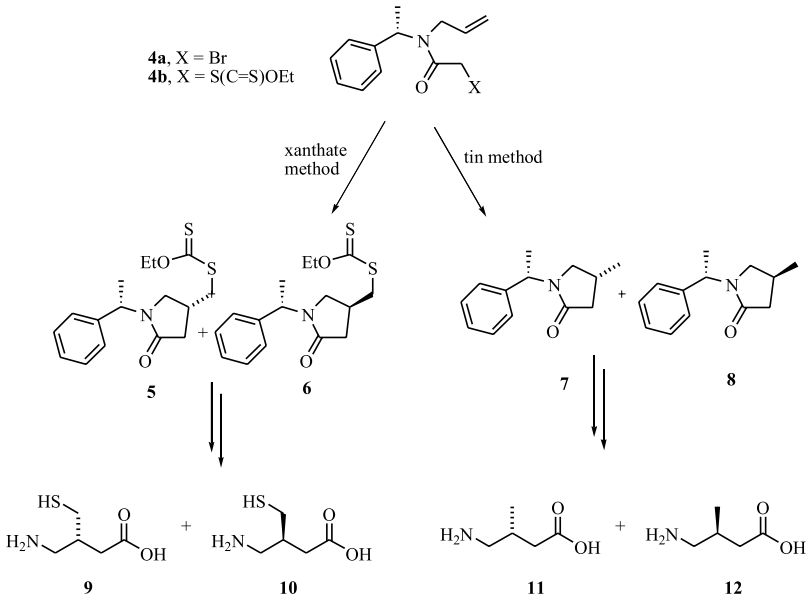
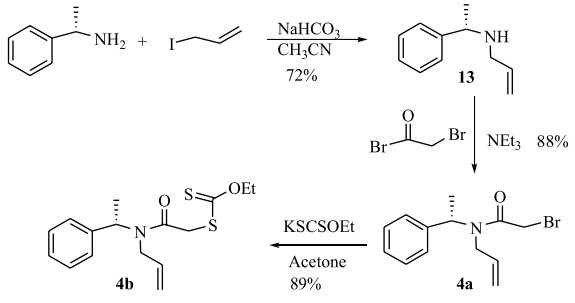


Scheme 1. Synthetic strategy for the synthesis of optically pure GABA derivatives.

Although the Ar_{1-5}-migration is a well recorded free radical process (neophyl rearrangement),[10] we believe that in this particular case the slow rotation of the amide bond may contribute to the rearrangement. By a simple inspection of the ^1H NMR spectra of **4a** at room temperature, a pair of set sharp peaks were observed, indicating the existence of a mixture of *E*/*Z* rotamers in a ratio of 3:1, favoring to *Z* rotamer[11–13] (see Scheme 4).

Geometrically speaking, the formation of pyrrolidinones **7** and **8** is achieved when the *Z*-**4a** rotamer is present and the Ph_{1-5}-migration product **14** when the *E*-**4a** rotamer is highly populated or the rotation of the amide bond is quite slow. In order to support this hypothesis, we synthesized the radical precursor **15**, expecting with the increment of the molecular polarity (NH bond) a rapid rotation of the amide bond and reducing the half-time of the *E* rotamer which presumably is the responsible for the formation of the Ph_{1-5} migration product **16** (see Scheme 5).

The ^1H NMR spectra of the compound **15** at room temperature did show a single set of sharp peaks, indicating a single rotamer or a very rapid interconversion between both rotamers *E*-**15** and *Z*-**15**. Thus, treating to the radical precursor **15** under the same conditions as **4a**, the reduction product **15** was only observed, and no even traces of the Ph_{1-5} migration product **16** were detected.

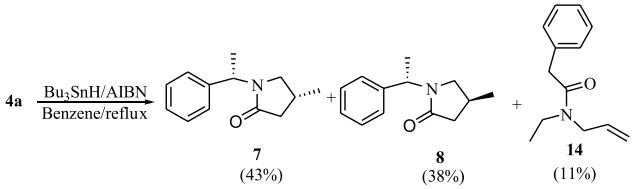


Scheme 2. Synthesis of the radical precursors **4a** and **4b**.

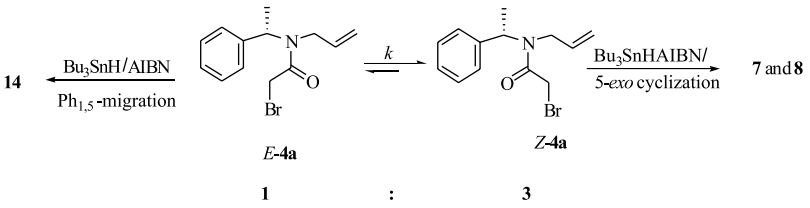
In this sense, we found interesting to study the dynamic nature of the Ph_{1-5}-migration product. Thus, it was observed by adding catalytic amounts of selenol (0.2 equiv as diphenyl diselenide)[14] that the yield of the Ph_{1-5} migration product **14** was increased (from 11% with Bu_3SnH to 18% with PhSeH). On the other hand, by using a much poorer hydrogen donor like tris(trimethyl)silyl silane (TTMSS), the formation of **14** was inhibited. These results suggest a thermodynamic and kinetic process in the **C**↔**D**↔**E** equilibriums, in which **14** seems to be a kinetic product: only a very fast hydrogen donor like selenol can be capable to capture the radical **E**.[15] On the other hand, in the presence of the slow hydrogen donor there is not chance to capture the short half-life time radical **E**, and the reaction course goes back to the formation of the pyrrolidinones **7** and **8** (see Scheme 6).[16] It is important to mention that the ratio of the pyrrolidinones was not changed by using different hydrogen donor.

On the other hand, the 5-*exo*-radical cyclization for xanthate **4b** under pseudo-catalytic oxidizing conditions afforded the pyrrolidinones **5** and **6**, (Scheme 7). This very well-known chain radical process[17] allows forming a carbon–sulfur bond that eventually will afford to optically pure 3-mercapto-methyl-γ-aminoacids **9** and **10**. As it was mentioned before, the incorporation of the sulfur atom in the structure of the GABA derivatives increase significantly the pharmacological activity.[7]

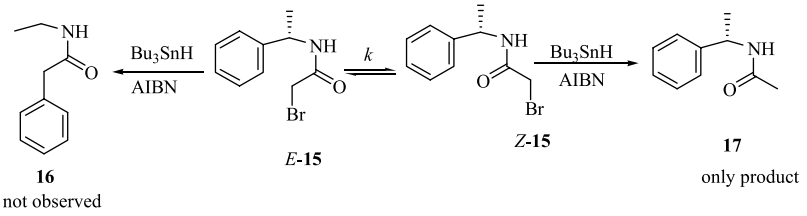
Although **4b** showed the same conformational behavior as **4a**, no evidence for the formation of the Ph_{1-5}-migration



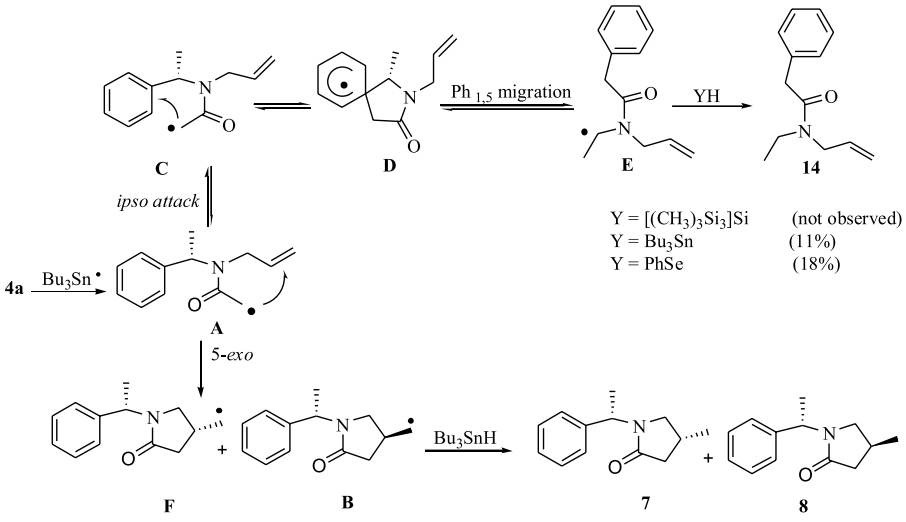
Scheme 3. Synthesis of pyrrolidinones **7** and **8** by 5-*exo trig* radical cyclization of **4a** under reductive conditions.



Scheme 4. Dependence of the free radical reaction course upon the conformation of the rotamers.



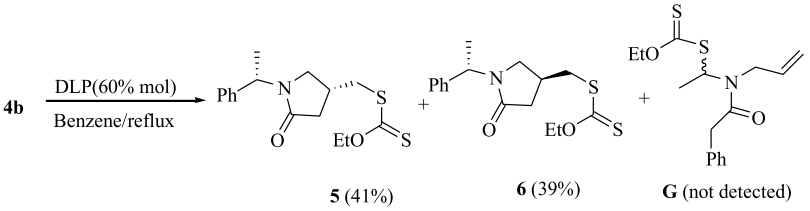
Scheme 5. Rapid equilibrium between *E*-**15** and *Z*-**15** rotamers.



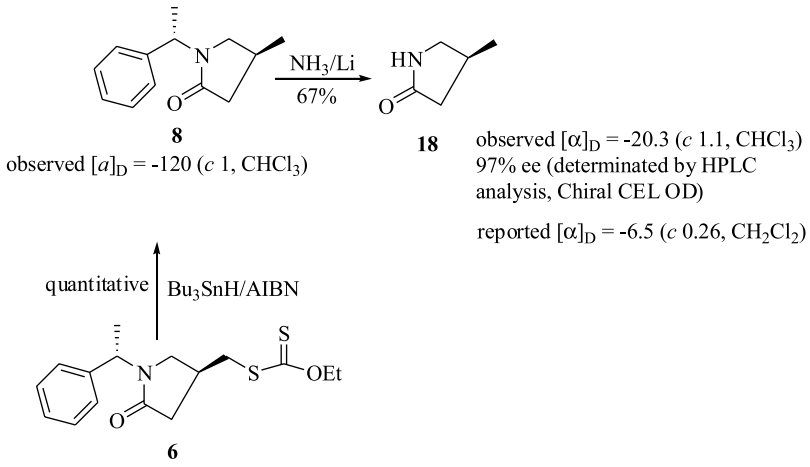
Scheme 6. Dynamic nature of the $Ph_{1,5}$-migration product.

product **G** was found. The reasons for the failure might be due to the direct oxidation of the radical **E** by DLP into cationic specie,[18] which is transformed into byproducts like enamines or its corresponding hydrolysis products; but unfortunately none of them were observed or isolated. It might be also due to the slow addition of the radical **E** to the thiocarbonyl of the starting material **4b** (propagation step), so the radical **E** can not be trapped by xanthate group leading the equilibriums toward the formation of the pyrrolidinones **5** and **6** only, this supports the theory of only a very fast hydrogen donor like selenol can be capable to capture the radical **E**.

Having the optically pure pyrrolidinones (**5**–**8**) in our hands, the assignment of the absolute configuration at C4 was carried out by simple chemical correlation. Birch debenzylation of pyrrolidinone **8** afforded pyrrolidinone **18**, which was identical with the sample reported by Meyers and Snyder,[19] except the magnitude of the $[\alpha]_D$ (observed $[\alpha]_D = -20.3$ (*c* 1, $CHCl_3$), reported by Meyers and Snyder $[\alpha]_D = -6.5$ (*c* 0.26, CH_2Cl_2), see Scheme 8). The optical purity of **18** was determined by HPLC analysis in a chiral stationary phase of Chiralcel OD, hexane/2-propanol (93:7) as eluent.



Scheme 7. Synthesis of pyrrolidinones **5** and **6** by 5-*exo* radical cyclization oxidative of **4a** under oxidative conditions.



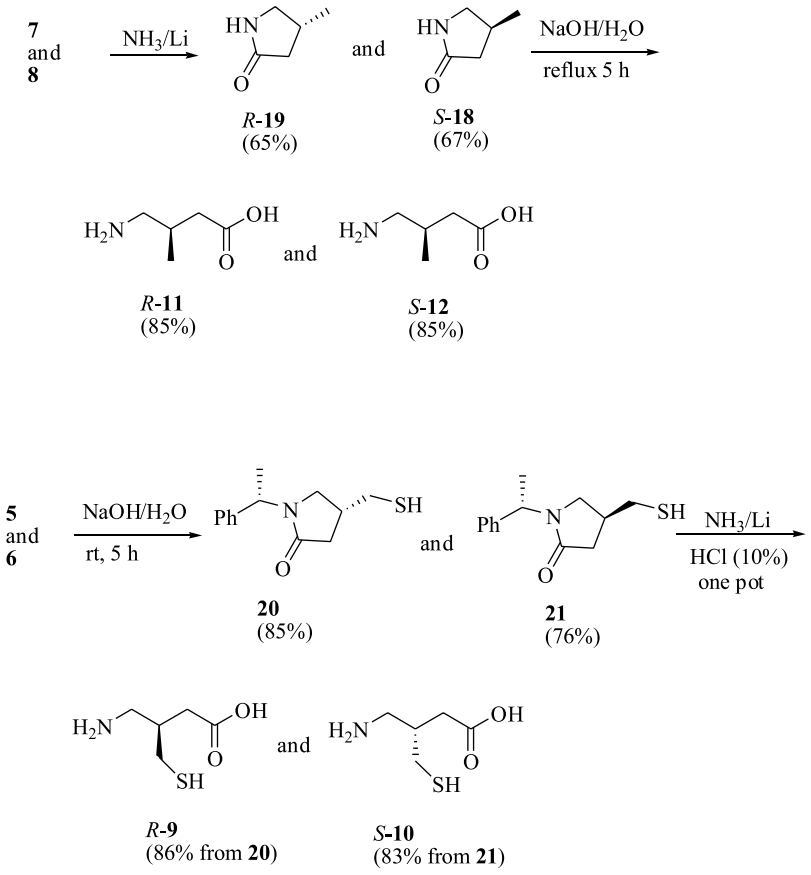
Scheme 8. Determination of the absolute stereochemistry at C4 for **8** and **6** by chemical correlation.

Confirmation of the absolute stereochemistry for xanthates **5** and **6** was achieved by reductive removal of the xanthate group from **6** with tributyltin hydride and AIBN, (see Scheme 6).

Finally, pyrrolidinones **7** and **8** were separately debenzylated followed by an alkaline hydrolysis with NaOH yielding the corresponding (*R*) and (*S*)-3-methyl-4-aminobutyric acids *R*-**11** and *S*-**12**.[20] On the other hand, pyrrolidinones **5** and **6** were separately hydrolyzed under controlled conditions by adding aqueous NaOH to obtain the corresponding (*R*) and (*S*)-4-(mercaptomethyl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-ones **20** and **21**. Then, a Birch debenzylation-acid hydrolysis in one pot produced to the optically pure (*R*) and (*S*)-4-amino-3-(mercaptomethyl) butanoic acids *R*-**9** and *S*-**10**, (see Scheme 9).

3. Conclusion

A practical procedure for the synthesis of optically pure GABA derivatives is reported. As the result of the use of reductive free radical conditions in the 5-*exo-trig* cyclization reaction for the construction of the pyrrolidinones



Scheme 9. Synthesis of optically pure GABA derivatives.

framework, a Ph_{1-5}-migration product was observed, which presumably depends upon the conformation of the amide rotamer precursor, and it also showed to be a kinetic product. Besides, another use of the beneficial catalytic effect of the selenol in the free radical reactions is reported, in this case in the Ph_{1-5}-migration reaction.

4. Experimental

4.1. General

Instrumental NMR studies were carried out with Varian mercury 400 and 300 instruments. Internal reference (TMS) for ^1H and ^{13}C. Chemical shifts are stated in parts per million. COSY, HSQC, and NOESY experiments have been carried out in order to assign the ^1H and ^{13}C spectra completely. High resolution Mass spectra (FAB^+ ion mode) were realized on a Jeol JMS-SX102A 10 KV and Elemental Analysis at Service de Microanalyse I.C.S.N.-C.N.R.S.-France. IR were carried out with a SHIMADZU FTIR-8400 instrument.

4.1.1. (*S*)-*N*-(1-Phenylethyl)prop-2-en-1-amine 13. To a solution of (*S*)-(−)-α-methylbenzylamine (3 g, 24.7 mmol) and sodium carbonate (3.14 g, 29.7 mmol) in 40 mL of dry acetonitrile at 0 °C was allowed to react for 15 min before to add allyl iodine (4.9 g, 29.7 mmol) dissolved in 5 mL of acetonitrile. The reaction mixture was stirred for 4 h at room temperature before add 30 mL of water, extracted with ethyl acetate, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (2:1, hexane/ethyl acetate) to give 2.85 g of **13** (72%) as a white solid. Mp=103–104 °C; $[\alpha]_D=-62.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38 (d, 3H, $J=6.4$ Hz), 1.75 (b, 1H), 3.12 (m, 2H), 3.82 (q, 1H, $J=6.4$ Hz), 5.09 (d, 1H, $J=10$ Hz), 5.15 (d, 1H, $J=17.2$ Hz), 5.91 (m, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.1, 49.9, 57.2, 115.2, 126.1, 126.4, 127.9, 136.5, 144.9. EI-MS *m/z* 161 (M+).

4.1.2. (*S*)-*N*-Allyl-2-bromo-*N*-(phenylethyl)acetamide 4a. To a solution of **13** (1 g, 6.2 mmol) and DMAP (1.13 g, 9.24 mmol) in 30 mL of dry THF at 0 °C was allowed to react for 15 min before to add bromoacetyl bromide (1.5 g, 7.44 mmol) dissolved in 5 mL of dry THF. The reaction mixture was warmed up to room temperature and allowed to stir for 2 h before to add 20 mL of water, extracted with ethyl acetate, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography through silica gel (5:1, hexane/ethyl acetate) to give 1.53 g (88%) of **13** as colorless oil; $[\alpha]_D=-157.5$ (*c* 1.7, $CHCl_3$); NMR data is given separately for each rotamer: *Z*-**4a** ^1H NMR (400 MHz, $CDCl_3$) δ: 1.50 (d, 3H, $J=7.2$ Hz), 3.64 (dd, 1H, $J=18.0$, 4.8 Hz), 3.82 (dd, 1H, $J=18.0$, 4.8 Hz), 3.84 (d, 1H, $J=10.8$ Hz), 3.89 (d, 1H, $J=10.8$ Hz), 5.01 (m, 2H), 5.60 (m, 1H), 6.00 (q, 1H, $J=7.2$ Hz), 7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.3, 27.2, 46.2, 51.6, 116.4, 127.2, 127.6, 128.3, 134.6, 139.8, 167.2; *E*-**4a** ^1H NMR (400 MHz, $CDCl_3$) δ: 1.67 (d, 3H, $J=6.8$ Hz), 3.44 (dd, 1H, $J=16.0$, 6.4 Hz), 3.89 (d, 1H, $J=10.0$ Hz), 3.99 (d, 1H, $J=10.0$ Hz), 4.05 (dd, 1H, $J=16.0$, 5.2 Hz), 5.00 (m, 2H), 5.17 (q, 1H, $J=6.8$ Hz), 5.71 (m, 1H), 7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.6, 26.6, 45.5, 56.5, 116.2, 126.4, 127.6, 128.5, 133.5, 139.7, 166.8; IR (CCl_4) 3029 ($CH=CH_2$), 1646 (C=O) cm^{-1}; Anal. Calcd for $C_{13}H_{16}BrNO$: C, 55.33; H, 5.72. Found: C, 55.12; H, 5.81.

4.1.3. (*S*)-*N*-Allyl-2-ethylxanthate-*N*-(phenylethyl)acetamide 4b. Radical precursor **4a** (1.11 g, 3.93 mmol) was treated with potassium ethylxanthate (0.95 g, 5.9 mmol) in 30 mL of acetone at 0 °C for 2 h. Evaporated under reduced pressure, and the residue was purified by column chromatography through silica gel (5:1, hexane/ethyl acetate) to give 1.2 g (89%) of **4b** as colorless oil; $[\alpha]_D=-165.3$ (*c* 1, $CHCl_3$); NMR data is reported as a mixture of *E*/*Z* rotamers: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.39 (t, 6H, $J=7.2$ Hz), 1.51 (d, 3H, $J=7.2$ Hz), 1.67 (d, 3H, $J=6.8$ Hz), 3.49 (dd, 1H, $J=15.2$, 6.0 Hz), 3.71 (dd, 1H, $J=18.0$, 5.2 Hz), 3.87 (dd, 1H, $J=18.0$, 5.2 Hz), 4.02 (d, 1H, $J=16.0$ Hz), 4.10 (dd, 1H, $J=15.2$, 6.0 Hz), 4.12 (d, 1H, $J=16.0$ Hz), 4.23 (q, 1H, $J=15.6$ Hz), 4.62 (q, 4H, $J=7.2$ Hz), 4.98 (dd, 2H, $J=11.2$, 4.0 Hz), 5.13 (dd, 2H, $J=14.0$, 2.4 Hz), 5.25 (q, 1H, $J=7.2$ Hz), 5.60 (m, 1H), 5.72 (m, 1H), 6.06 (q, 1H, $J=7.2$ Hz), 7.18–7.32 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 16.5, 18.2, 40.0, 40.2, 46.0, 46.3, 51.9, 56.1, 70.3, 70.4, 116.3, 117.0, 126.5, 127.3, 127.3, 127.6, 128.2, 128.5, 134.0, 134.3, 139.9, 167.0, 213.7; IR (CCl_4) 1667 (C=O), 1235 (C=S) cm^{-1}; Anal. Calcd for $C_{16}H_{21}NO_2S_2$: C, 59.41; H, 6.54. Found: C, 59.53; H, 6.72.

4.2. The 5-*exo*-radical cyclization under reductive condition (Tin method)

(*R*) and (*S*)-4-Methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-ones **7** and **8**, and *N*-allyl-*N*-ethyl-2-phenylacetamide **14**. To a solution of **4a** (0.2 g, 0.7 mmol) in 30 mL of benzene at 80 °C was added dropwise (in a period of 1 h) Bu_3SnH (0.21 g, 0.71 mmol) and AIBN (20 mg) dissolved in 30 mL of benzene. The reaction mixture was allowed to stir for 2 h before evaporating under reduced pressure. The residue was purified by column chromatography through silica gel (only hexanes until tin residues come out, then a system of 4:1, hexane ethyl acetate is used) to give 60 mg of **7** (43%), 53 mg of **8** (38%), and 16 mg of **14** (12%) all as colorless oils.

4.2.1. (*R*)-4-Methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one 7. $[\alpha]_D=-93.3$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.96 (d, 3H, $J=7.2$ Hz), 1.51 (d, 3H, $J=7.2$ Hz), 2.02 (dd, 1H, $J=16.4$, 6.4 Hz), 2.37 (m, 1H), 2.50 (dd, 1H, $J=9.6$, 5.6 Hz), 2.59 (dd, 1H, $J=16.8$, 8.4 Hz), 3.41 (dd, 1H, $J=9.6$, 7.6 Hz), 5.50 (q, 1H, $J=7.2$ Hz), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 19.6, 26.3, 39.7, 48.6, 49.3, 126.8, 127.1, 128.2, 139.8, 173.6; IR (CCl_4) 1677 (C=O) cm^{-1}; FABS *m/z* 204.1381 $(M+H)^+$ (Calcd for $C_{13}H_{17}NO_2O_4$: 204.1389).

4.2.2. (*S*)-4-Methyl-1-((*S*)-1-phenylethyl)pyrrolidin-2-one 8. $[\alpha]_D=-120$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.08 (d, 3H. $J=6.8$ Hz), 1.50 (d, 3H, $J=7.6$ Hz), 2.10 (dd, 1H, $J=16.4$, 7.2 Hz), 2.30 (m, 1H), 2.57 (dd, 1H, $J=16.8$, 8.8 Hz), 2.87 (dd, 1H, $J=9.2$, 6.0 Hz), 3.01 (t, 1H, $J=8.2$ Hz), 5.48 (q, 1H, $J=7.2$ Hz), 7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 19.5, 26.5, 39.7, 48.6,

49.5, 126.7, 127.1, 128.2, 139.9, 173.6; IR (CCl_4) 1681 (C=O) cm^{-1}; FABS *m/z* 204.1383 $(M+H)^+$ (Calcd for $C_{13}H_{17}NO$: 204.1389).

4.2.3. *N*-Allyl-*N*-ethyl-2-phenylacetamide 14. NMR data is reported as a mixture of *E*/*Z* rotamers: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.08 (t, 3H, $J=7.2$ Hz), 1.12 (t, 3H, $J=7.2$ Hz), 3.31 (q, 2H, $J=7.2$ Hz), 3.40 (q, 2H, $J=7.2$ Hz), 3.67 (s, 3H), 3.73 (s, 3H), 3.86 (dt, 2H, $J=4.8$, 2.0 Hz), (d, 2H, $J=6.0$ Hz), 5.06–5.22 (m, 4H), 5.72 (m, 2H), 7.27 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.6, 13.8, 40.7, 40.8, 42.0, 47.4, 50.0, 116.6, 116.8, 126.6, 126.7, 128.2, 128.6, 128.7, 133.2, 133.5, 135.2, 170.3, 170.7; Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 82.12; H, 9.24.

4.3. The 5-*exo*-radical cyclization under oxidative conditions (Xanthate method)

(*R*) and (*S*)-4-(Methyl-ethoxythiocarbonil)1-((*S*)-1-phenylethyl)pyrrolidin-2-ones **5** and **6**. A solution of **4b** (0.2 g, 0.61 mmol) and DLP (0.08 g, 0.2 mmol) in 50 mL of benzene was refluxed for 30 min, then, the reaction mixture was evaporated under reduced pressure and the residue was purified by preparative TLC on silica gel (4:1, hexane/ethyl acetate) yielding 0.82 mg of **5** (41%), and 78 mg of **6** (39%).

4.3.1. (*R*)-4-(methyl-ethoxythiocarbonil)1-((*S*)-1-phenylethyl)pyrrolidin-2-one 5. $[\alpha]_D=-72.6$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.39 (t, 3H, $J=6.8$ Hz), 1.51 (d, 3H, $J=7.2$ Hz), 2.22 (dd, 1H, $J=16.4$, 5.2 Hz), 2.70 (m, 3H), 2.99 (dd, 1H, $J=13.6$, 6.8 Hz), 3.14 (dd, 1H, $J=13.8$, 6.4 Hz), 3.46 (dd, 1H, $J=12.0$, 9.6 Hz), 4.62 (q, 2H, $J=6.8$ Hz), 5.49 (q, 1H, $J=7.2$ Hz), 7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 16.0, 30.8, 37.4, 39.6, 47.1, 48.9, 70.2, 127.0, 127.6, 128.6, 139.8, 172.7, 213.8; IR (CCl_4) 1687, 1680 (C=O), 1217 (C=S), 1050 (C–S) cm^{-1}; FABS *m/z* 324.1082 $(M+H)^+$ (Calcd for $C_{16}H_{21}NO_2S_2$: 324.1089).

4.3.2. (*S*)-4-(Methyl-ethoxythiocarbonil)1-((*S*)-1-phenylethyl)pyrrolidin-2-one 6. $[\alpha]_D=-85.1$ (*c* 1.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.40 (t, 3H, $J=7.2$ Hz), 1.51 (d, 3H, $J=6.8$ Hz), 2.27 (dd, 1H, $J=19.6$, 9.6 Hz), 2.61 (m, 2H), 3.0–3.35 (m, 4H), 4.62 (q, 2H, $J=7.2$ Hz), 5.48 (q, 1H, $J=6.8$ Hz), 7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 16.1, 30.7, 37.3, 39.7, 47.0, 48.8, 70.1, 126.7, 127.2, 128.2, 139.5, 172.2, 213.2; IR (CCl_4) 1683 (C=O), 1216 (C=S), 1050 (C–S) cm^{-1}; FABS *m/z* 324.1082 $(M+H)^+$ (Calcd for $C_{16}H_{21}NO_2S_2$: 324.1089).

4.3.3. (*S*) and (*R*)-4-Methylpyrrolidin-2-ones 18 and 19.[19] Birch debenzylation: A solution of **7** (0.140 g, 0.68 mmol) in 15 mL of dry THF was added to a deep blue solution of Li (0.032 g, 4.5 mmol) in condensed NH_3 (ca. 20 mL) at −70 °C within 10 min. The reaction mixture was allowed to stir for 1 h at −70 °C before to add NH_4Cl (ca. 40 mg), then neutralized with a diluted solution of HCl, extracted with ethyl acetate, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography through silica gel (hexane/ethyl acetate, 1:1) afforded the *S*-**18** (45 mg, 67%). (*S*)-4-Methylpyrrolidin-2-one **18**; $[\alpha]_D=-20.3$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.13 (d, 3H, $J=6.4$ Hz), 1.95 (dd, 1H, $J=16.8$, 7.2 Hz), 2.45 (dd, 1H, $J=16.4$, 8.8 Hz), 2.53 (m, 1H), 2.96 (dd, 1H, $J=9.6$, 6.0 Hz), 3.51 (ddd, 1H, $J=8.4$, 8.0, 1.2 Hz), 4.25 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 29.4, 38.5, 49.6, 178.5. (*R*)-4-Methylpyrrolidin-2-one **19** was obtained analogously to **18** (65%); $[\alpha]_D=+18.1$ (*c* 1 $CHCl_3$).

4.3.4. (*R*) and (*S*)-4-(Mercaptomethyl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-ones 20 and 21. Controlled alkaline hydrolysis: pyrrolidinone **5** (200 mg) were dissolved in 1 mL of ethanol and added 5 mL of an aqueous solution of NaOH (8 N). The reaction mixture was allowed to stir for 4 h at room temperature, extracted with ethyl acetate, dried with Na_2SO_4 and evaporated under reduced pressure; the residue was purified by column chromatography through silica gel (2:1, hexane/ethyl acetate) to give **20** (123 mg, 85%). (*R*)-4-(Mercaptomethyl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-one **20**; $[\alpha]_D=-97.8$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.48 (d, 3H, $J=7.2$ Hz), 2.17 (dd, 1H, $J=16.8$, 6.0 Hz), 2.28–2.53 (m, 3H), 2.59 (dd, 1H, $J=17.2$, 8.4 Hz), 2.68 (dd, 1H, $J=10.4$, 5.2 Hz), 3.43 (dd, 1H, $J=10.0$, 7.6 Hz), 5.45 (q, 1H, $J=7.2$ Hz), 7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 28.4, 34.7, 37.0, 46.5, 48.7, 126.7, 127.2, 128.2, 139.4, 172.6; Anal. Calcd for $C_{13}H_{17}NOS$: C, 60.34; H, 7.28. Found: C, 60.30; H, 7.30. (*S*)-4-(Mercaptomethyl)-1-((*S*)-1-phenylethyl)pyrrolidin-2-one **21** was obtained analogously to **20** (109 mg, 76%); $[\alpha]_D=-172$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.52 (dd, 3H, $J=7.2$ Hz), 2.25 (dd, 1H, $J=16.4$, 7.2 Hz), 2.39 (m, 1H), 2.60 (m, 3H), 3.12 (m, 2H), 5.51 (c, 1H, $J=7.2$ Hz), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.2, 28.8, 34.7, 37.2, 46.9, 48.9, 126.8, 127.3, 128.4, 173.0; Anal. Calcd for $C_{13}H_{17}NOS$: C, 60.34; H, 7.28. Found: C, 59.98; H, 7.45.

4.3.5. (*R*) and (*S*)-4-Amino-3-(mercaptomethyl)butanoic acids *R*-9 and *S*-10. Birch debenzylation–aqueous hydrolysis in one pot, general protocol: Pyrrolidinone **20** (0.230 g, 0.98 mmol) was debenzylated by using the classic Birch method followed by acidic quenching with 10 mL of an aqueous solution at10%, and allowed to stir for 30 min at room temperature, reaction mixture is evaporated under reduced pressure; residue is crystallized in ethanol to afford (*R*)-4-Amino-3-(mercaptomethyl)butanoic acids *R*-**9** as a with powder (0.125 mg, 86%). Mp=142 °C; $[\alpha]_D=+32.9$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ: 2.22 (dd, 1H, $J=16.8$, 5.2 Hz), 2.51 (dd, 1H, $J=17.2$, 7.6 Hz), 2.85 (m, 3H), 3.18 (dd, 1H, $J=10.0$, 4.4 Hz), 3.55 (dd, 1H, $J=10.0$ 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.2, 36.0, 42.2, 47.2, 178.5; IR (KBr) 3226 (OH), 2810 (SH), 1679 (C=O) cm^{-1}; Anal. Calcd for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43. Found: C, 39.98; H, 7.56. (*S*)-4-Amino-3-(mercaptomethyl)butanoic acid *S*-**10** was obtained analogously to *R*-**9** (82%). Mp=142 °C; $[\alpha]_D=-33.4$ (*c* 1.02, CH_3OH); IR (KBr) 3220 (OH), 2778 (SH), 1673 (C=O) cm^{-1}.

4.3.6. (*S*) and (*R*)-3-Methyl-4-aminobutyric acids 11 and 12.[20] Alkaline hydrolysis: pyrrolidinone *S*-**18** (80 mg, 0.8 mmol) is dissolved in 1 mL of methanol and added 5 mL of an aqueous solution of KOH (8 N). The reaction mixture is refluxed for 5 h before to add an aqueous solution of HCl (until get a pH 7), and evaporated under reduced

pressure, the residue was purified by preparative TLC on silica gel (ethyl acetate/MeOH 4:1) yielding *S*-**11** (79 mg, 85%); $[\alpha]_D = +8.1$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ: 1.04 (d, 3H, $J=6.8$ Hz), 2.18 (m, 1H), 2.30 (d, 2H, $J=7.0$ Hz), 2.88 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ: 17.7, 29.6, 43.3, 45.5, 178.6; IR (KBr) 3431 (OH), 2840 (NH_3^+), 1557 (COO^-) cm^{-1}. (*R*)-3-Methyl-4-aminobutyric acid **12** was obtained analogously to *S*-**11** (83%); $[\alpha]_D = -8.3$ (*c* 1, CH_3OH).

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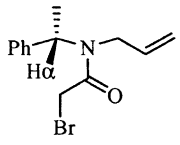
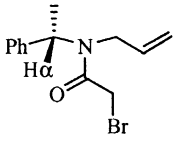
11. The geometry of the *E*/*Z* isomers for **4a** was easily determined by applying a computational calculation (Geometry optimizations for both rotamers were performed with the HF/6-31G(d,p)12 method using GAUSSIAN 98. The frequencies were calculated at the same level of theory to confirm that each stationary point corresponds to a minimum. The optimized structures at ab initio were used for obtaining energies at a higher level of theory using the B3LYP/6-311G(d,p)13 method). Above calculation are in agreement with the ^1H NMR spectra, indicating an important intramolecular hydrogen bonding between the carbonyl group and Hα (this internal hydrogen bonding is confirmed by theoretic calculation) between Hα and carbonyl group in the Z conformation, causing a downfield shift of almost 1 ppm in compare to the *E* rotamer.



E-**4a**

Hα, δ: 5.17 ppm

Relative energie = 0.76 Kcal/mol



Z-**4a**

Hα, δ: 6.0 ppm

Relative energie = 0.0 Kcal/mol

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Parviflorenes B–F, novel cytotoxic unsymmetrical sesquiterpene-dimers with three backbone skeletons from *Curcuma parviflora*

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Abstract—Five novel natural products classified as dimeric sesquiterpenes, named parviflorenes B–F (**2**–**6**), possessing three types of novel backbone frameworks, have been isolated from *Curcuma parviflora* (Zingiberaceae). The structures of **2**–**6** were elucidated by means of spectroscopic studies, and the structure of **2** was further unambiguously established by X-ray crystallographic analysis. Compounds **2**, **4**, and **6** have an unsymmetrical bis-cadinane skeleton, while compound **3** is a dimer of cadinane and iso-cadinane, and compound **5** possesses another novel carbon framework consisting of two cadinanes with different bond-connection. These new compounds with novel carbon skeletons showed cytotoxicity against tumor cell lines.

1. Introduction

Curcuma parviflora Wall. (Zingiberaceae) is widely distributed over a forest area of the northern part of Thailand,[1] and is used as an ornamental plant, and is edible, and also it has been said to be used for detoxification of scorpion bites in certain areas. During our search for bioactive natural products from tropical plants,[2] we investigated the chemical constituents of *C. parviflora* collected in Thailand, and recently isolated the cytotoxic sesquiterpene-dimer, parviflorene A (**1**) from this plant.[3] We further investigated this plant and here we describe the isolation and structure elucidation of five new sesquiterpene-dimers, parviflorenes B–F (**2**–**6**) from the underground part of *C. parviflora*. These sesquiterpene-dimers may be classified into three groups with different carbon frameworks: (i) biscadinanes (compounds **1**, **2**, **4**, and **6**); (ii) a cadinane–isocadinane adduct (compound **3**), and (iii) a biscadinane with an alternate bond connection (compound **5**). These new compounds showed cytotoxicity against KB (human adenocarcinoma) and other tumor cell lines. As described previously,[3] this plant also contained cadinane sesquiterpenes, cadalenequinone (**7**)[4] and 8-hydroxycadalene (**8**),[5] corresponding to monomers for dimers such as **1**.

2. Results and discussion

It was revealed by TLC examination that parviflorene A (**1**) and its related compounds were contained in the underground part of *C. parviflora*. The EtOAc-soluble fraction of the MeOH extracts, combined with previously obtained EtOAc and *n*-BuOH-soluble fractions of this plant, were subjected to repeated chromatography on silica gel and Sephadex LH-20, followed by purification with HPLC on ODS to give five new compounds, parviflorenes B–F (**2**–**6**), in addition to parviflorene A (**1**).

Parviflorene B (**2**) was obtained as yellow prisms, $[\alpha]_D^{24} = -16$ (*c* 1.4, MeOH), and the molecular formula was established to be $C_{30}H_{32}O_4$ by its HRFABMS data (*m/z* 456.2260, M^+, Δ −4.1 mmu). The ^{1}H NMR spectrum of **2** (Table 1) showed signals due to two singlet methyls and

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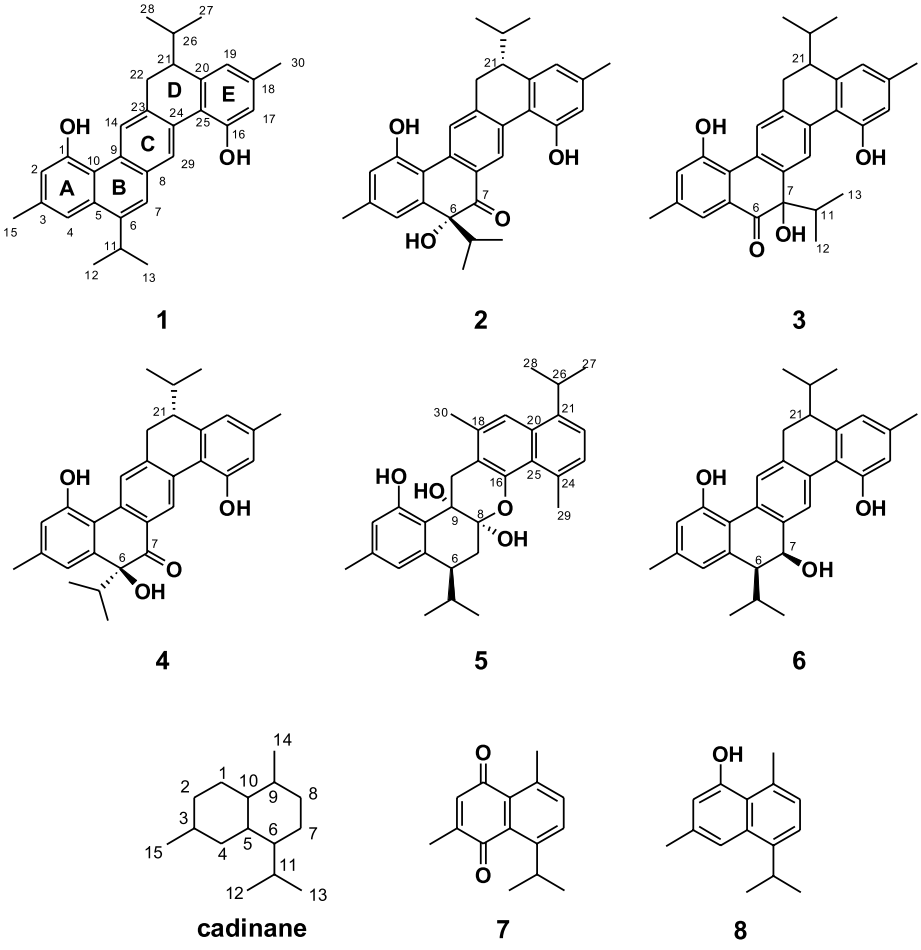


four doublet methyls; the chemical shifts of the singlet methyls [δ_H 2.25 (3H, s) and 2.23 (3H, s)] implied that these two methyl groups were attached on sp^2 carbons. The ^{13}C NMR spectrum of **2** (Table 2) showed 18 aromatic carbons, one carbonyl, 11 sp^3 carbons, one of which bore oxygen. Although the ^1H and ^{13}C NMR data of **2** were similar to those of **1**, one *O*-bearing sp^3 carbon (δ_C 81.8), and one carbonyl carbon (δ_C 204.7) were not possessed by compound **1**, and compound **2** had two fewer aromatic carbons than **1**. Since 10 out of 15 unsaturation degrees were thus accounted for, **2** was deduced to have five rings. The ^1H NMR spectrum of **2** showed six aromatic ring protons [δ_H 6.65 (1H, s), 6.64 (1H, s), 6.70 (1H, s), 6.94 (1H, s), 8.46 (1H, s), and 8.68 (1H, s)]. The ^1H–^1H COSY spectrum suggested the presence of two isopropyl groups (H_3-12/H-11/H_3-13 and H_3-27/H-26/H_3-28). The HMBC spectrum of **2** afforded long-range ^1H–^{13}C correlations as shown in Figure 1, which suggested that **2** consisted of three aromatic benzene rings (rings A, C, and E), one cyclohexadienone ring (ring B), and one cyclohexadiene (ring D). The positions of two methyls, two phenols, one carbonyl, one tertiary hydroxyl, and two isopropyl groups were clearly assignable by the HMBC correlations (Fig. 1). In particular, the HMBC correlations for H-4/C-6, H-29/C-7, H-14/C-22, and H-19/C-21 provided evidence for the connections of the A/B, B/C, C/D, and D/E rings, respectively. The methine proton on C-21 was deduced to be equatorially oriented from the two small coupling constants with the vicinal methylene protons on C-22 ($J_{21,22\alpha}$=3.5 Hz and $J_{21,22\beta}$=4.5 Hz).

Compound **2** was crystallized from methanol solution to give yellow prisms, and its structure was unambiguously established by X-ray crystallographic analysis (Fig. 2). On the basis of X-ray analysis data, two isopropyl groups on C-6 and C-21 were shown to be axial with opposite orientations on the plane of the molecule. The pentacyclic skeleton of **2** corresponded to an unsymmetric dimer of two cadinane sesquiterpenes with C–C bonds constructed between C-8 and C-14 of the two monomers. This carbon framework was the same as that proposed for parviflorene A (**1**),[3] and the basic skeleton of **1** elucidated from its spectral data[3] was, therefore, reasonably corroborated here by the X-ray analysis of **2**.[6]

Parviflorene C (**3**) was obtained as a yellow amorphous solid, and was suggested to have the molecular formula $C_{30}H_{32}O_4$ by its HRFABMS data (*m/z* 456.2288, M^+, Δ −1.3 mmu), which was identical with that of **2**. The ^1H and ^{13}C NMR data of **3** closely resembled those of **2**. However, **3** had a different substitution pattern on the B ring; isopropyl and tertiary hydroxyl groups were attached to C-7 and a carbonyl group was present on C-6, as evidenced by the HMBC correlations from the aromatic proton at H-4 (δ_H 7.25) to the carbonyl carbon at C-6 (δ_C 205.8), and from the aromatic proton at H-29 (δ_H 8.38) to the quaternary

Table 1. ^{1}H NMR data of parviflorene B–F (**2**–**6**)

Position	2[a]	3[a]	4[a] (High conc.)	4[a] (Low conc.)	5[a]	6[b]
1						
2	6.56 s	6.90 s	6.56 s	6.57 s	6.63 s	6.63 s[c]
3						
4	7.12 s	7.25 s	6.99 s	7.07 s	6.73 s	6.46 s
5						
6					3.28 m	2.54 t (5.0)
7					2.11 dd (14.0, 7.6) α 1.90 ddd (14.0, 11.0, 1.5) β	4.88 t (5.0)
8						
9						
10						
11	1.99 quint. (6.7)	2.03 m	1.86 quint. (6.7)	1.90 quint. (6.7)	2.54 m	1.87 sext. (5.8)
12	0.74 d (6.7)	0.72 d (6.9)	0.65 d (6.7)	0.66 d (6.7)	0.95 d (7.0)	0.19 br s
13	0.82 d (6.7)	0.81 d (6.9)	0.78 d (6.7)	0.81 d (6.7)	0.58 d (7.0)	0.88 d (7.0)
14	8.37 s	8.27 s	8.16 s	8.22 s	3.57 d (18.5) α 3.03 d (18.5) β	7.97 s
15	2.32 s	2.34 s	2.23 s	2.27 s	2.28 s	2.22 s
16						
17	6.55 s	6.60 s	6.63 s	6.60 s		6.64 s[c]
18						
19	6.60 s	6.61 s	6.50 s	6.57 s	7.55 s	6.46 s
20						
21	2.37 m	2.35 m	2.30 m	2.37 m		2.25 m
22	3.02 dd (15.0, 3.5) α 2.98 dd (15.0, 4.5) β	2.91 dd (15.0, 3.5) 2.89 dd (15.0, 5.0)	2.96 dd (15.9, 5.0) 2.95 dd (15.9, 2.7)	3.01 d (3.5)	7.23 d (7.5)	2.82 dd (14.5, 4.3) 2.80 dd (14.5, 2.7)
23					7.13 d (7.5)	
24						
25						
26	1.50 m	1.54 m	1.29 m	1.38 m	3.61 quint. (6.7)	1.28 m
27	0.78 d (6.7)	0.82 d (6.6)	0.69 d (6.7)	0.75 d (6.7)	1.35 d (6.7)	0.68 d (6.7)
28	0.91 d (6.7)	0.93 d (6.6)	0.76 d (6.4)	0.83 d (6.7)	1.34 d (6.7)	0.74 d (6.7)
29	8.70 s	8.38 s	8.53 s	8.56 s	2.86 s	8.45 s
30	2.29 s	2.30 s	2.26 s	2.26 s	2.33 s	2.22 s
	5.13 s [1-OH] 5.12 s [16-OH] 4.04 s [6-OH]	5.50 s [1-OH] 5.34 s [16-OH] 3.95 s [7-OH]		5.51 s [1-OH] 5.65 s [16-OH] 4.06 s [6-OH]	8.43 s [1-OH] 3.83 d (1.5) [8-OH] 3.46 s [9-OH]	9.46 s [1-OH][d] 9.41 s [16-OH][d] 5.03 s [7-OH]

[a] In $CDCl_3$.
[b] In DMSO-d_6.
[c,d] Signals may be reversed.

oxygenated carbon at C-7 (δ_C 82.1). This fact was further supported by the NOE correlation observed between H-29 (δ_H 8.38) and H_3-13 (δ_H 0.81). Compound **3**, therefore, had a different carbon skeleton from that of **1** and **2**, and it was constructed from one cadinane and one isocadinane with C–C bonds between the C-8 carbon of each unit and the C-14 carbon of the other unit. An isocadinane sesquiterpene (**9**) with a similar A–B ring partial structure to **3** was isolated from *Heterotheca inuloides* (Asteraceae), which also simultaneously contained cadinane sesquiterpenes.[7]

Parviflorene D (**4**) was obtained as a yellow amorphous solid, and its molecular formula was suggested as $C_{30}H_{32}O_4$ by its HRFABMS data (*m/z* 456.2339, M^+, Δ +3.8 mmu), which was also identical with that of **2**. The UV spectrum and ^{1}H and ^{13}C NMR data of **4** closely resembled those of **2**, and interpretation of the 2D NMR data of **4** led to the conclusion that **4** had the same planar structure as that of **2**. However, the CD spectrum of **4** displayed an opposite Cotton effect [λ_{ext} 329 nm ($\Delta\varepsilon$ −21.5), 271 (31.1), and 253 (43.2)], compared with that of **2** [λ_{ext} 333 nm ($\Delta\varepsilon$ 15.2), 271 (−28.0), and 253 (5.9)], suggesting that compound **4** was epimeric with **2** at the C-6 position.[6,8]

Parviflorene E (**5**) was obtained as a yellow amorphous solid, and its HRFABMS of **5** showed a molecular ion at *m/z* 460.2595 ($[M]^+$, Δ −1.8 mmu) consistent with the molecular formula $C_{30}H_{36}O_4$. The UV spectrum of **5** showed absorption maxima at λ_{max} (MeOH) 304 and 237 nm, indicating the presence of conjugated systems, but the absorption patterns were different from those of parviflorene A (**1**) or B (**2**). The ^{1}H NMR spectrum of **5** (Table 1) showed signals due to three singlet methyls and four doublet methyls; the chemical shifts of the singlet methyls [δ_H 2.96 (3H, s), 2.33 (3H, s), and 2.28 (3H, s)] implied that these three methyl groups were attached on sp^2 carbons. The ^{13}C NMR spectrum aided by HMQC experiments revealed the presence of 16 sp^2 carbons as well as 14 sp^3 carbons. Since, eight out of 13 degrees of unsaturation were thus accounted for, **5** was deduced to have five rings. The ^{1}H NMR spectrum of **5** (Table 1) showed the signals of five aromatic hydrogens, which were assignable to two *ortho*-coupled doublets [δ_H 7.13 (d, J=7.5 Hz) and 7.23 (d, J=7.5 Hz)], two *meta*-oriented broad singlets [δ_H 6.63 (s) and 6.73 (s)], and one isolated singlet [δ_H 7.55 (s)] from the ^{1}H–^{1}H COSY spectrum. The ^{1}H–^{1}H COSY spectrum of **5** indicated the presence of two isopropyl groups (H_3-12/H-11/H_3-13 and H_3-27/H-26/H_3-28), and revealed that the sp^3 methine [H-6: δ_H 3.28 (1H, m)] was adjacent to an sp^3 methylene [H_2-7: δ_H 2.11 (1H, dd, J= 14.0, 7.6 Hz) and 1.90 (1H, ddd, J=14.0, 11.0, 1.5 Hz)]. The HMBC spectrum of **5** afforded long-range ^{1}H–^{13}C

Table 2. ^{13}C NMR data of parviflorene B–F (**2**–**6**)

Position	2[a]	3[a]	4[a]	5[a]	6[b]
1	153.2[c]	153.0[f]	153.0[g]	155.8	154.1
2	117.0	123.7	117.8	115.9	115.3
3	138.8	139.0	138.1	139.3	135.8
4	120.8	120.5	120.5	119.8	121.8
5	143.4[d]	131.2	140.8	138.8	139.8
6	82.1	205.8	82.1	41.2	52.3
7	204.0	82.1	206.1	28.6[i]	70.0
8	127.8	137.3	127.4	98.6	136.9
9	134.4	127.0	134.4	72.9	130.0
10	114.6	121.5	115.1	121.5	118.2
11	38.6	38.0	38.9	30.8	25.4
12	17.2	17.0	17.1	20.3[j]	19.7
13	16.5	16.7	16.7	15.6	23.4
14	128.2	127.4	128.0	37.0	126.8
15	21.1[e]	20.9	21.0[h]	21.3	20.8[k]
16	153.2[c]	152.3[f]	153.3[g]	150.1	154.5
17	115.8	115.8	116.2	110.8	115.6
18	138.1	137.9	138.9	134.1	136.0
19	122.8	122.9	122.8	117.3	121.2
20	142.1[d]	143.6	142.8	132.6	142.5
21	46.4	46.7	46.5	141.6	46.2
22	33.7	32.5	33.7	122.1	32.7
23	143.4	135.8	144.1	128.3	132.3
24	131.9	131.6	131.9	132.5	130.7
25	117.0	117.8	117.2	123.4	118.1
26	28.4	28.3	28.8	28.5[i]	28.1
27	21.7	20.8	21.7	23.6	21.5
28	20.5	21.9	20.8	23.5	20.3
29	125.4	124.4	124.8	23.5	122.9
30	21.3[e]	21.2	21.1[h]	20.2[j]	20.9[k]

[a] In $CDCl_3$.
[b] In DMSO-d_6.
[c–k] Signals may be reversed.

correlations as shown in Figure 3, which suggested that **5** consisted of three aromatic benzene rings (rings A, D, and E), one cyclohexene (ring B), and one dihydropyran (ring C), explained as follows.

Three singlet methyl groups on sp^2 carbons were located on C-3, C-18, and C-24 positions based on the HMBC correlations observed from H_3-15 to C-2, C-3, and C-4, from H_3-30 to C-17, C-18, and C-19, and from H_3-29 to C-23, C-24, and C-25, respectively. Five aromatic protons described above were placed on the C-2, C-4, C-19, C-22,

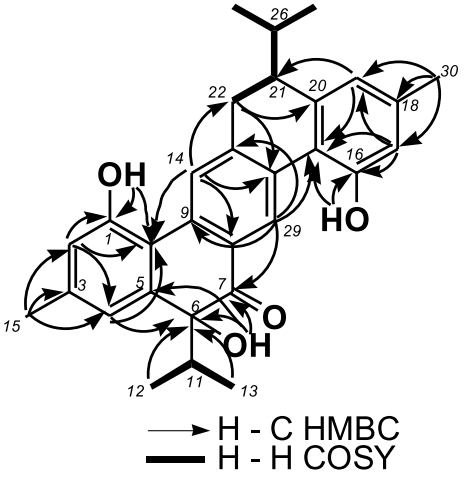


Figure 1. Key COSY and HMBC correlations for parviflorene B (**2**).

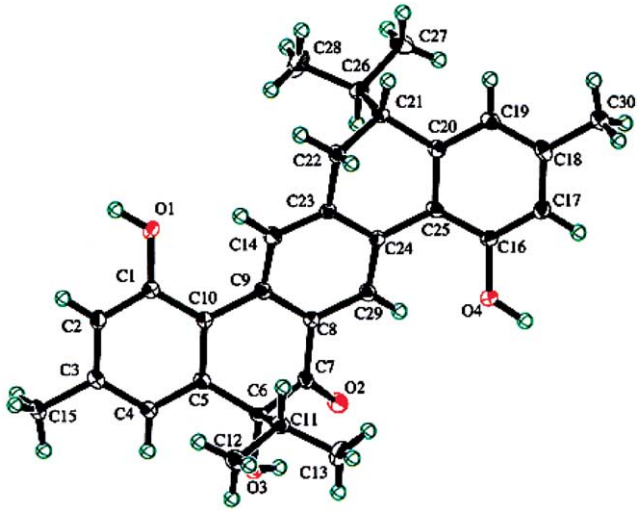


Figure 2. A computer-generated perspective drawing of parviflorene B (**2**).

and C-23 positions by the HMBC data shown in Figure 3. One isopropyl group was shown to be attached on the C-21 sp^2 carbon (HMBC correlations: H-26/C-21, H_3-27/C-21, H_3-28/C-21, and H-22/C-26), while another isopropyl group was located on the C-6 sp^3 carbon (HMBC correlations: H_3-12/C-6 and H_3-13/C-6). A phenol hydroxyl group (δ_H 8.43, s) was placed on C-1 (δ_C 155.8) on the basis of the HMBC cross-peaks from OH-1 to C-1, C-2, and C-10. The C-6 sp^3 methine carbon was attached on the C-5 aromatic carbon by the HMBC correlation from H-4 (δ_H 6.73) to C-6 (δ_C 41.2), whereas the C-7 methylene was connected to hemiacetal carbon (C-8, δ_C 98.6) from the HMBC correlation from H_2-7 to C-8 as well as the ^{1}H–^{1}H COSY correlation between H-7β (δ_H 1.90) and OH-8 (δ_H 3.83, d) presumably through long-range W-type coupling (J= 1.5 Hz). Then, C-8 was shown to be adjacent to an sp^3 quaternary carbon (C-9, δ_C 72.9) bearing a tertiary hydroxyl group (δ_H 3.46, s; OH-9) from the HMBC correlation for H_2-7/C-9, and C-9 was connected to an sp^3 methylene (C-14, δ_C 37.0; HMBC correlations: H_2-14/C-9 and H_2-14/C-8), which in turn was connected to the C-17 aromatic

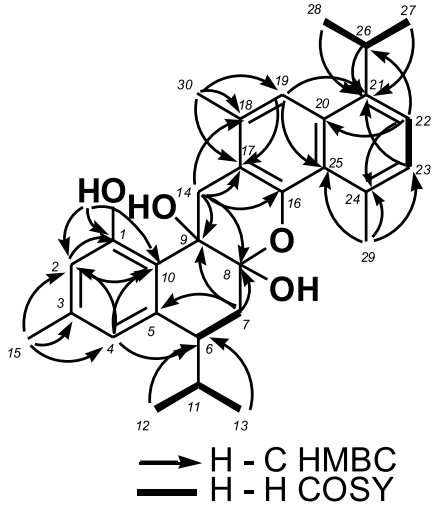


Figure 3. Key COSY and HMBC correlations for parviflorene E (**5**).

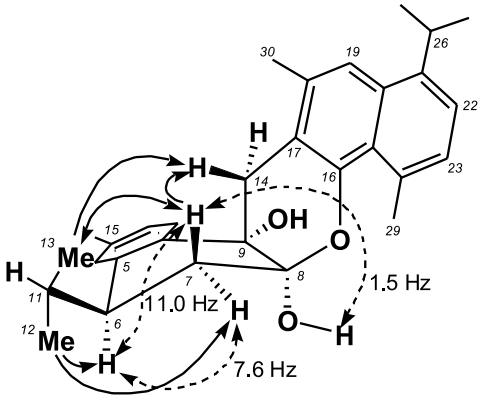
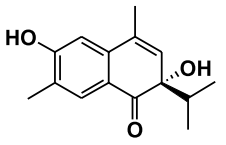


Figure 4. Selected coupling constants and NOE correlations for parviflorene E (**5**).

carbon (δ_C 110.8; HMBC correlations: H_2-14/C-16, H_2-14/C-17, and H_2-14/C-18). The ^{13}C NMR chemical shift of C-16 (δ_C 150.1) implied that this aromatic carbon was oxygenated and, therefore, was connected with the hemiacetal carbon (C-8) through an ether bond to construct a dihydropyran ring (ring C), and the remaining two quaternary carbons, C-9 and C-10, had to be connected to form a cyclohexene ring (ring B). From these results, the planar structure of **5** was constructed as shown in Figure 3. The relative stereochemistry of **5** was elucidated by NOE as well as ^1H–^1H coupling constants data as shown in Figure 4.

NOE correlations were observed for H-14β/H-7β, H-7β/H_3-13, and H_3-13/H-14β; these three hydrogen groups were suggested to be oriented β-side, while NOE were observed for H_3-12/H-6 and H_3-12/H-7α, implying that these hydrogens are located in α-side. These assignments were consistent with the coupling constants data ($J_{6,7\beta}$=11.0 Hz and $J_{6,7\alpha}$=7.6 Hz). Observation of NOE between H-14β and H-7β and the W-type coupling (J=1.5 Hz) between H-7β and the hydroxyl proton on C-8 (OH-8), aided by model considerations, strongly suggested that two hydroxyl groups on C-8 and C-9 (OH-8 and OH-9) had α-*cis* configuration. Thus, the relative configurations of C-6, C-8, and C-9 positions were revealed as shown in Figure 4.[6] The pentacyclic skeleton of compound **5** is unprecedented and corresponded to an unsymmetrical cadinane sesquiterpene dimer, which had a different manner of bond connection (type **B** in Figure 5: C-14 and C-2; C-8 and oxygen on C-1) from that of parviflorene A (**1**) or B (**2**) (type **A** in Figure 5: C-14 and C-8; C-8 and C-14). A related cadinane-dimer, named dicadalenol (**10**), has been isolated from *H. inuloides* (Asteraceae),[7] having a different bond-connection manner (type **C** in Figure 5: C-14 and C-1; C-8 and oxygen on C-2).



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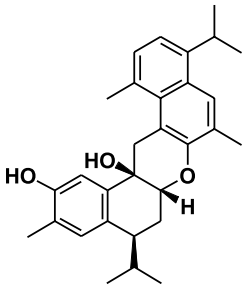


10

Parviflorene F (**6**) was obtained as an amorphous solid, and the molecular formula was established to be $C_{30}H_{34}O_3$ by its HRFABMS data (*m/z* 442.2521, M^+, Δ +1.3 mmu), possessing one less oxygen atom and two more hydrogen atoms than that of **2**. The ^1H and ^{13}C NMR spectrum of **6** (Tables 1 and 2) closely resembled those of **2**. However, the ^1H and ^{13}C NMR spectra of **6** showed no signals due to a ketone group, but showed signals due to an sp^3 oxymethine (δ_H 4.88 and δ_C 70.0; C-7), which was different from those of **2**. The ^1H–^1H COSY spectrum of **6** showed the presence of a proton connectivity network from one isopropyl group [δ_H 1.87 (1H, m; H-11), δ_H 0.19 (3H, br s; H_3-12), and δ_H 0.88 (3H, d, J=7.0 Hz; H_3-13)], to sp^3 methine [δ_H 2.54 (1H, t, J=5.0 Hz; H-6), sp^3 oxymethine [δ_H 4.88 (1H, t, J=5.0 Hz; H-7)], and a hydroxyl proton [δ_H 5.03 (1H, br s;

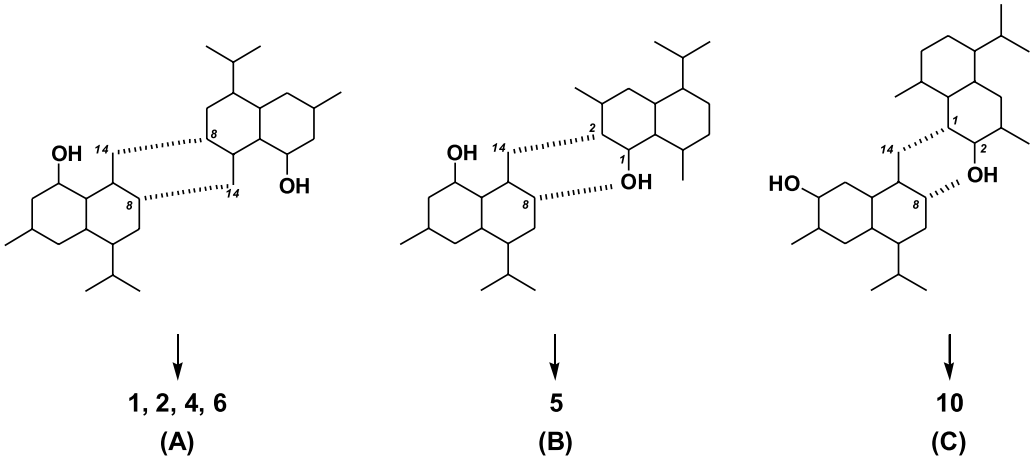
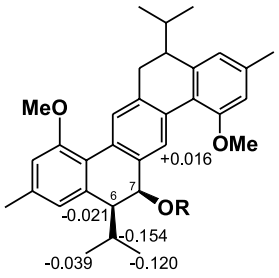


Figure 5. Three manners of dimerization of cadinane sesquiterpenes.



11a R = (*R*)-MTPA
11b R = (*S*)-MTPA

Figure 6. $\Delta\delta$ values of (*R*)- and (*S*)-MTPA esters (**11a** and **11b**).

OH-7)]. This proton-network moiety was revealed to be present at ring B from the HMBC correlation data observed for H-4/C-6, H-11/C-5, H-7/C-8, and H-29/C-7. The rest of the molecule of **6** (rings A, C, D, and E) was revealed to have the same structure as compound **2** on the basis of the ^{1}H–^{1}H COSY and HMBC correlation data as well as the comparison of ^{1}H and ^{13}C chemical shifts (Tables 1 and 2). From the NOE clearly observed between H-6 and H-7 as well as the coupling constant ($J_{6,7}=5.0$ Hz) and model considerations, these two hydrogens (H-6 and H-7) were assigned as *cis*. The isopropyl group on C-21 was deduced to be axially oriented from the two small coupling constants with the vicinal methylene protons on C-22 ($J_{21,22\alpha}=4.3$ Hz, $J_{21,22\beta}=2.7$ Hz), indicating the methine proton on C-21 is equatorially oriented.[9] The absolute configurations of C-6 and C-7 positions of **6** were elucidated as 6*S* and 7*S* on the basis of the modified Mosher's method[10] applied on the (*R*)- and (*S*)-MTPA esters (**11a** and **11b**, respectively) prepared from **6** (Fig. 6), whose phenol groups were protected by methyl ethers in advance.

The cytotoxic activity of these sesquiterpene-dimers against human adenocarcinoma cells was examined, and the IC_{50} values (μg/mL) against vincristine (VCR)-resistant KB cells are presented in Table 3. All compounds were cytotoxic to KB cell lines, and parviflorene C (**3**) showed a threefold reversal effect of VCR resistance against VCR-resistant KB cell lines.[11] Compounds **3** and **6** also exhibited cytotoxicity against LNCaP (human prostate cancer) and TNF-related apoptosis inducing ligand (TRAIL)-resistant KOB (human adult T cell leukemia) cell lines. From these results, these novel dimeric-sesquiterpene skeletons may provide a unique scaffold as new cytotoxic compounds.

Table 3. Cytotoxicity of parviflorenes A–F (**1–6**) (IC_{50} values, μg/mL)

	KB/VJ-300		LNCaP	KOB	
	VCR (+)	VCR (−)		TRAIL (+)	TRAIL (−)
1	2.6	3.1	NT	NT	NT
2	2.2	3.0	NT	NT	NT
3	1.1	3.2	3.8	4.8	6.4
4	3.1	2.8	NT	NT	NT
5	5.9	6.8	7.1	>6.3	>6.3
6	2.3	3.0	4.6	5.9	8.1

Tests toward each cell line were carried out in the absence (−) and presence (+) of 100 ng/mL of VCR and 500 ng/mL of TRAIL, respectively, which did not affect the growth of the cells. NT, not tested.

3. Experimental

3.1. Extraction and isolation

The plant *C. parviflora* was collected at Khon Kaen, Thailand. A voucher specimen is maintained at the Department of Horticulture, Faculty of Agriculture, Khon Kaen University. The air-dried underground part (280 g) was extracted with MeOH and acetone. The combined extract (12.6 g) suspended in water (200 mL) was partitioned against EtOAc (400 mL×2 and 200 mL) and *n*-BuOH (200 mL×2). The EtOAc-soluble fraction (8.0 g) and previously obtained EtOAc and *n*-BuOH-soluble fractions (2.9 g) from the whole plant were combined, and then were subjected to silica gel column chromatography (column A; 4.5×57 cm) eluted with 0–100% EtOAc in hexane. The fraction (1.5 g) eluted with 20–33% EtOAc in hexane was again subjected to silica gel column chromatography (column B; 4.0×33 cm) isocratically eluted with 20% EtOAc in hexane. A portion (277 mg) of the fraction (331 mg) mainly containing parviflorene B (**2**) was purified by gel filtration with Sephadex LH-20 (column C; 1.5×55 cm) eluted with MeOH, to give parviflorene B (**2**, 98 mg). A portion (72 mg) of another fraction (82 mg) mainly containing parviflorene D (**4**) was separated by Sephadex LH-20 (column D; 1.5×55 cm) eluted with MeOH. Finally, the fraction (5.4 mg) in the 95–105 mL elution was purified by HPLC on ODS (Develosil ODS-HG-5, 20×250 mm; eluent, 80% MeOH, flow rate, 8.0 mL/min; detection UV at 310 nm and RI) to give parviflorene C (**3**, 1.4 mg, $t_R=25$ min) and parviflorene D (**4**, 4.4 mg, $t_R=42$ min). The fraction (34 mg) in the 60–95 mL elution of column D was also purified by HPLC on ODS (Develosil ODS-HG-5, 20×250 mL; eluent, 80% MeOH, flow rate, 8.0 mL/min; detection UV at 310 nm and RI) to give parviflorene D (**4**, 25.3 mg, $t_R=42$ min). The fraction (1.57 g) of column A eluted with 10–20% EtOAc in hexane was subjected to silica gel column chromatography (column E; 5.0×20 cm) eluted with 15% EtOAc in hexane, followed by separation with Sephadex LH-20 (column F; 1.5×55 cm) eluted with MeOH. The fraction (9 mg) of column F in the 93–102 mL elution was purified by HPLC on ODS (Develosil ODS-MG-5, 10×250 mm; eluent, 95% MeOH, flow rate, 2.0 mL/min; detection UV at 300 nm and RI) to give parviflorene E (**5**, 3.0 mg, $t_R=26$ min). The fraction of column A (0.96 g) eluted with 33–50% EtOAc in hexane was partially (0.9 g) subjected to silica gel column chromatography (column G; 3.5×21 cm) eluted with 33–50% EtOAc in hexane, followed by separation with Sephadex LH-20 (column H; 1.5×63 cm) eluted with MeOH. The fraction of column H (237 mg) in the 50–95 mL elution was finally purified by MPLC on ODS (Merck LiChroprep RP-18, 25×310 mm; eluent, 85% MeOH, flow rate, 10.0 mL/min; detection UV at 280 nm and RI) to give parviflorene F (**6**, 195 mg).

3.1.1. Parviflorene B (2). Yellow crystal from MeOH; mp >300 °C; $[\alpha]_D^{26}=-16$ (*c* 1.4, MeOH); IR (KBr) ν_{max} 3420, 2950, 1690, 1620, 1460, 1300, and 1160 cm^{-1}; ^{1}H and ^{13}C NMR in $CDCl_3$ (Tables 1 and 2); UV (MeOH) λ_{max} nm (log ε) 378 (3.9), 326 (4.4), 313 (4.4), 275 (4.6), 237 (4.4), and 218 (4.5); CD (0.043 mM, MeOH, 22 °C) $\Delta\varepsilon$ (λ_{ext} nm) −6.4 (380), 0 (358), 3.0 (310), 3.5 (305), 0 (291), −28.1

(275), −1.1 (259), 5.9 (254), 0 (245), −1.8 (242), 0 (239), 16.0 (228), and 9.0 (219); EIMS *m/z* (%) 456 (M^+, 15) and 413 (M−$(CH_3)_2CH$, 100); HRFABMS calcd for $C_{30}H_{32}O_4$ (M^+) 456.2301, found *m/z* 456.2260.

3.1.2. Parviflorene C (3). Yellow amorphous; $[\alpha]_D^{24}=+44$ (*c* 0.7, MeOH); IR (KBr) ν_{max} 3380, 2960, 2925, 2866, 1698, 1682, 1610, 1298, 1161, and 1014 cm^{-1}; ^1H and ^{13}C NMR in $CDCl_3$ (Tables 1 and 2); UV (MeOH) λ_{max} nm (log ε) 387 (3.8), 323 (4.2), 308 (4.2), 285 (4.3), and 220 (4.4); CD (0.014 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) −5.7 (387), 0 (356), 7.0 (335), 0 (310), −20.5 (278), 0 (262), 24.5 (245), 5.8 (230), 14.4 (221), 0 (221), and −6.0 (207); FABMS (NBA) *m/z* 456 (M^+); HRFABMS calcd for $C_{30}H_{32}O_4$ (M^+) 456.2301, found *m/z* 456.2288.

3.1.3. Parviflorene D (4). Yellow amorphous; $[\alpha]_D^{24}=+242$ (*c* 1.15, MeOH); IR (KBr) ν_{max} 3380, 2960, 2920, 2870, 1700, 1670, 1650, 1620, 1300, and 1160 cm^{-1}; ^1H and ^{13}C NMR in $CDCl_3$ (Tables 1 and 2); UV (MeOH) λ_{max} nm (log ε) 378 (3.9), 326 (4.4), 312 (4.3), 275 (4.6), 237 (4.4), and 218 (4.5); CD (0.025 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) 0 (371), −24.2 (329), 0 (306), 6.8 (287), 380 (271), 52.5 (253), 4.5 (232), 0 (228), −25.0 (219), and −9.0 (209); FABMS (NBA) *m/z* 457 $[M+H]^+$; HRFABMS calcd for $C_{30}H_{32}O_4$, (M^+) 456.2301, found *m/z* 456.2339.

3.1.4. Parviflorene E (5). Yellow amorphous; $[\alpha]_D^{24}=-105$ (*c* 1.17 MeOH); IR (film) ν_{max} 3340, 2960, 2930, 2870, 1710, 1700, and 1630 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 304 (3.9), 237 (4.7), and 206 (4.9); CD (0.017 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) −2.1 (354), 0 (321), 1.5 (288), 0 (270), −1.2 (254), 0 (250), 28.1 (234), 0 (215), and −10.6 (205); ^1H and ^{13}C NMR in $CDCl_3$ (Tables 1 and 2); EIMS *m/z* (%) 460 (M^+, 48), 442 (M−H_2O, 26), 424 (M−$2H_2O$, 18), 381 (18), and 234 (100); FABMS *m/z* 460 (M^+); HRFABMS calcd for $C_{30}H_{34}O_4$ (M^+) 460.2614, found *m/z* 460.2595.

3.1.5. Parviflorene F (6). Yellow amorphous; $[\alpha]_D^{24}=+195$ (*c* 1.0, MeOH); IR (film) ν_{max} 3280, 2950, 2870, 1620, and 1310 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 340 (4.5), 326 (4.5), 289 (4.1), 258 (4.0), 250 (4.1), and 226 (4.6); CD (0.023 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) −21.9 (339), −19.1 (333), −23.3 (325), −2.2 (301), −16.0 (287), 0 (271), 150 (242), 0 (231), and −37.0 (224); ^1H and ^{13}C NMR in DMSO-d_6 (Tables 1 and 2); EIMS *m/z* (%) 442 (M^+, 9), 424 (M−H_2O, 100), and 381 (20); FABMS (NBA) *m/z* 442 [M^+]; HRFABMS calcd for $C_{30}H_{34}O_3$, (M^+) 442.2508, found *m/z* 442.2521.

3.1.6. Preparation of the (*R*)- and (*S*)-MTPA esters (11a and 11b). A solution of **6** (17 mg) in MeOH (1 mL) was treated with 10% TMS-CHN_2 in hexane (0.5 mL) at room temperature for 14 h. The reaction mixture was evaporated and purified over a silica gel column chromatography eluted with hexane/EtOAc to afford dimethyl ether (14 mg), which was then dissolved in dry pyridine (20 μL), and treated with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPA-Cl] (5 μL) at rt for 14 h. After addition of 3-[(dimethylamino)propyl]amine (3 μL), the reaction mixture was evaporated and purified over a silica gel column chromatography eluted with hexane/EtOAc to give the (*R*)-MTPA ester (**11a**): ^1H NMR ($CDCl_3$, at 55 °C) δ_H 6.660 (1H, s; H-2), 6.674 (1H, s; H-4), 2.862 (1H, t, *J*=5.0 Hz; H-6), 6.364 (1H, br d, *J*=4.0 Hz; H-7), 1.726 (1H, br s; H-11), 0.414 (3H, br s; H_3-12), 0.735 (3H, d, *J*=5.2 Hz; H_3-13), 8.019 (1H, s; H-14), 6.732 (1H, s; H-17), 6.629 (1H, s; H-19), 2.964 (1H, dd, *J*=14.7, 4.8 Hz; H-22), 2.913 (1H, dd, *J*=14.7, 2.8 Hz; H-22′), 0.771 (3H, d, *J*=6.7 Hz; H_3-27), 0.799 (3H, d, *J*=6.7 Hz; H_3-28), and 8.304 (1H, s; H-29); EIMS *m/z* (%) 686 (M^+, 41), 452 (100), 409 (12), 367 (42), and 352 (9). The (*S*)-MTPA ester (**11b**) was also prepared from **6** by the same procedures using (*R*)-MTPA chloride. Compound **11b**: ^1H NMR ($CDCl_3$, at 55 °C) δ_H 6.667 (1H, s; H-2), 6.694 (1H, s; H-4), 2.883 (1H, t, *J*=5.0 Hz; H-6), 6.422 (1H, br d, *J*=4.0 Hz; H-7), 1.880 (1H, br s; H-11), 0.453 (3H, br s; H_3-12), 0.855 (3H, d, *J*=5.2 Hz; H_3-13), 8.003 (1H, s; H-14), 6.723 (1H, s; H-17), 6.628 (1H, s; H-19), 2.954 (1H, dd, *J*=14.7, 4.8 Hz; H-22), 2.904 (1H, dd, *J*=14.7, 2.8 Hz; H-22′), 0.776 (3H, d, *J*=6.7 Hz; H_3-27), 0.797 (3H, d, *J*=6.7 Hz; H_3-28), and 8.234 (1H, s; H-29); EIMS *m/z* (%) 686 (M^+, 9), 452 (100), 409 (11), 367 (37), and 352 (8).

3.2. X-ray crystallographic analysis

All measurements were made on a Rigaku/MSC Mercury CCD diffractometer with graphite monochromated Mo Kα radiation (λ=0.71069 Å). The data were collected at a temperature of −173±1 °C to a maximum 2θ value of 57.0°. A total of 0 oscillation images were collected. Crystal data: triclinic, $C_{33.5}H_{46}O_{7.5}$ (M_r 568.73), space group *P*1 (#1) with *a*=11.389 (3) Å, *b*=11.715 (3) Å, *c*=12.858 (3) Å, α=83.200 (3)°, β=76.259 (3)°, γ=69.671 (3)°, *V*=1561.5 (6) $Å^3$, *Z*=2, and D_{calcd}=1.210 g/cm^3. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 5695 observed reflections ($I>1.50\sigma(I)$, $2\theta<56.98°$) and 740 variable parameters and converged with unweighted and weighted agreement factors of $R=0.053$, $R_w=0.066$.

Crystal data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CDCC deposition number 233828. The supplementary crystallographic data for this paper can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1233 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/).

3.3. Cultured cell lines for cytotoxicity tests and measurement of cell viability

VCR selected multidrug resistant variants of the human epidermoid carcinoma KB cells (KB/VJ-300)[12] were a gift from Prof. M. Kuwano (Kyushu University School of Medicine). The human prostate carcinoma LNCaP (human prostate cancer) cells were a gift from Prof. S. Egawa (Kitasato University School of Medicine). All these cells were maintained in culture flasks in MEM medium supplemented with 10% fetal calf serum (FCS) and 60 μg/mL of kanamycin. KOB cells (human adult T-cell leukemia)

were a gift from Prof. T. Yamada (Graduate School, Nagasaki University), and were maintained in RPMI-1640 medium supplemented with 10% FCS and 60 μg/mL of kanamycin.

For the in vitro drug treatment experiments, tumor cells (1.1×10^4 cells/mL for KB cells, and 2×10^4 cells/mL for LNCaP cells) were seeded in 195 μL of culture medium/well in 96-well plates (Corning Glass Works), and incubated for 24 h at 37 °C in a 5% CO_2–95% air atmosphere. The cells were treated in triplicate with 5 μL of graded concentrations of samples, and were then incubated in a CO_2 incubator at 37 °C for 72 h. Cell viability was determined by the colorimetric assay using MTT.[13] For KOB cells, 3.5×10^5 cells/mL of the cells were seeded in 95 μL of culture medium/well in 96-well plates, and were treated with 5 μL of graded concentrations of samples in the absence or presence of 0.5 μg/mL of TRAIL, and were then incubated for 42 h at 37 °C in a 5% CO_2–95% air atmosphere. Cell viability was determined by the colorimetric assay using the alamer blue.[14]

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Synthesis of 5-alkyl(or aryl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones by denitrocyclisation of *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides. Evidence of a Smiles rearrangement

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Abstract—An efficient method for the synthesis of hitherto unknown alkyl(or aryl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones **8a**–**g**, **16** and **17** has been established. The method is based on the synthesis of the corresponding *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides **3a**–**c** and **7a**–**c**,**e** which undergo denitrocyclisation with NaH in DMF in 4.5 or 2 h. When **3a** was treated with NaH in DMF for 30 min the product of a Smiles rearrangement, **9**, was isolated. Under similar conditions but for 4.5 h **9** was converted into **8a**. This confirms the involvement of a Smiles rearrangement during the denitrocyclisation process. Conversion of **3b** into isomeric pyrroloquinoxalinones **12** and **13** confirms a process involving two pathways, direct denitrocylisation of **3b** and Smiles rearrangement of **3b** followed by denitrocylisation, respectively. Furthermore, denitrocylisation of **7d** into pyrroloquinoxalinones **16** and **17** suggests that similar cyclisation pathways are followed by *N*-arylcarboxamides.

1. Introduction

Pyrrolo[1,2-*a*]quinoxalines are best known as high-affinity and selective agonists of the 5-HT_3 receptors.[1–3] More recently, several bispyrrolo[1,2-*a*]quinoxaline derivatives were found to have significant antimalarial activity[4] whereas certain pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones have shown promising antiviral[5] and antiallergic[6] properties.

5-Alkylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones may be formed by first synthesising the lactam derivatives[1–3,7] followed by alkylation.[5] Other routes include the use of benzimidazolium *N*-ylides in 1,3-dipolar cycloadditions with alkenes[6,8] and alkynes[9] or reaction with 2,2-dihydropoly(per)fluoroalkanoates,[10] and by reductive ring-opening/ring-closure of pyridazinoquinoxalinones.[11]

2. Results and discussion

Following our previous interest in the synthesis of pyrrolo[1,2-*a*]quinoxalines[12] we now wish to report our findings that lead to the synthesis of 5-alkyl(or aryl)-pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones by denitrocyclisation of *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides.

Carboxamides **3a**–**c** were prepared by reacting appropriate 2-trichloroacetylpyrroles **2a**–**b**, derived by treating 1-arylpyrroles **1a**–**b** with trichloroacetyl chloride, with diethylamine or cyclohexylamine in 1,4-dioxane for 1.5 h (Scheme 1).

In contrast, the preparation of aromatic carboxamides **7a**–**e** required first hydrolysis of trichloroacetyl derivative **2a** to the carboxylic acid **4**, conversion of the latter with thionyl chloride into acid chloride **5** and then, without isolation, treatment of **5** with aromatic amines **6a**–**e** for 2 days in a 1:1 pyridine–toluene mixture (Scheme 2). Attempts to react 4-chloro-2-nitroaniline or 2-trifluoromethylaniline with acid chloride failed. This is probably due to a combination of steric and electronic reasons which is reflected in the low yield (45%) of **7b**. Railey and Johnson have previously prepared a large number of *N*-alkyl(or aryl)-4,5-dihalo-1*H*-pyrrole-2-carboxamides, as potential antibacterial agents, in a similar manner.[13]

Upon treating carboxamides **3a**,**c** or **7a**–**c**,**e** with NaH in DMF for 4.5 or 2 h, pyrroloquinoxalinones **8a**–**f** were obtained in excellent yields (77–95%). The work-up involved adding to water and neutralising with 2 N HCl. This led to hydrolysis of the initially formed ester **8e** to the carboxylic acid **8d**. The ester **8e** was isolated when the

Keywords: Pyrroles; Pyrroloquinoxalinones; Denitrocyclisation; Defluorocyclisation; Smiles rearrangement.
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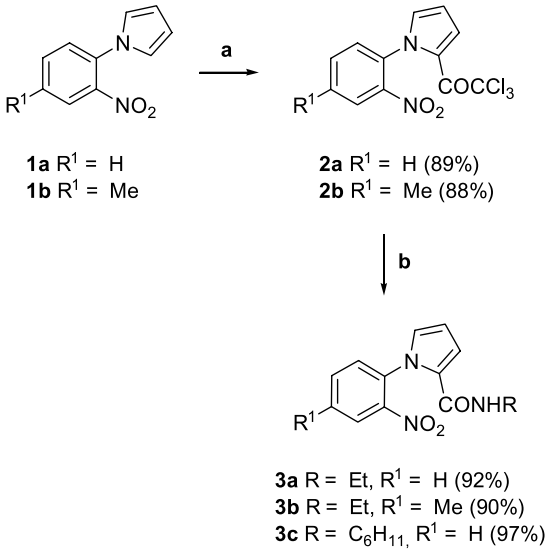
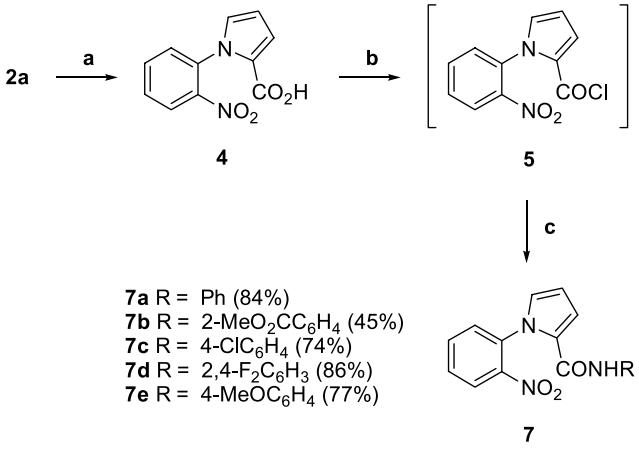


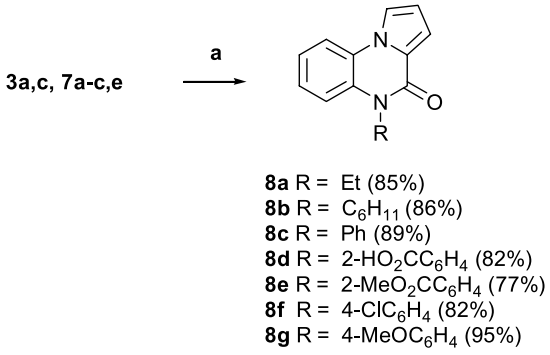
Scheme 1. Reagents (a) Cl_3CCOCl, 1,4-dioxane; (b) 70% $EtNH_2$ in H_2O, CH_2Cl_2 or cyclohexylamine, Et_3N, 1,4-dioxane, 75 °C.



Scheme 2. Reagents (a) 10% aq. NaOH, reflux; (b) $SOCl_2$, reflux; (c) **6a** $PhNH_2$, **6b** 2-$MeO_2CC_6H_4NH_2$, **6c** 4-$ClC_6H_4NH_2$, **6d** 2,4-$F_2C_6H_3NH_2$ or **6e** 4-$MeOC_6H_4NH_2$, pyridine.

reaction mixture was poured into ice-water containing sodium bicarbonate. To the best of our knowledge, this intramolecular displacement of an aromatic nitro group by *N*-substituted carboxamides, under mild conditions, to form 5-substituted pyrroloquinoxalinones, is unprecedented in the literature. The closest analogy was published by Nacci et al.[7c] who cyclised 1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide to the parent pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one, by heating in DMF containing potassium carbonate (Scheme 3).

It was interesting to note that TLC examination of reactions **3a** or **c** with NaH in DMF after 0.5 h, revealed a new spot together with spots corresponding to starting material and product. We therefore investigated further the reaction of **3a** with NaH in DMF by allowing it to proceed for 0.5 h. After work-up and column chromatography three compounds were isolated, starting material **3a**, pyrroloquinoxalinone **8a** and carboxamide **9** in 13, 27 and 21% yield, respectively (Scheme 4). This result provides conclusive evidence that a Smiles rearrangement is taking place. Furthermore, reaction



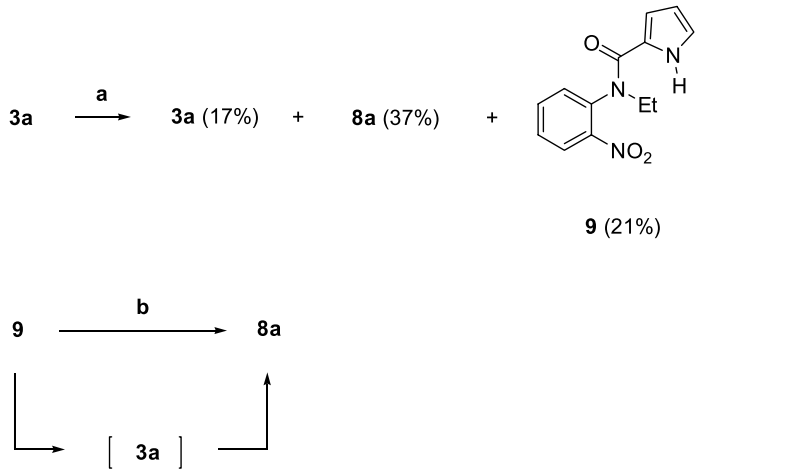
Scheme 3. Reagents (a) NaH (60% in oil), DMF.

of **9** with NaH in DMF for 4.5 h gave **8a** as sole product. TLC examination of this reaction after 0.5 h revealed three spots that corresponded to **3a**, **8a** and starting material **9**.

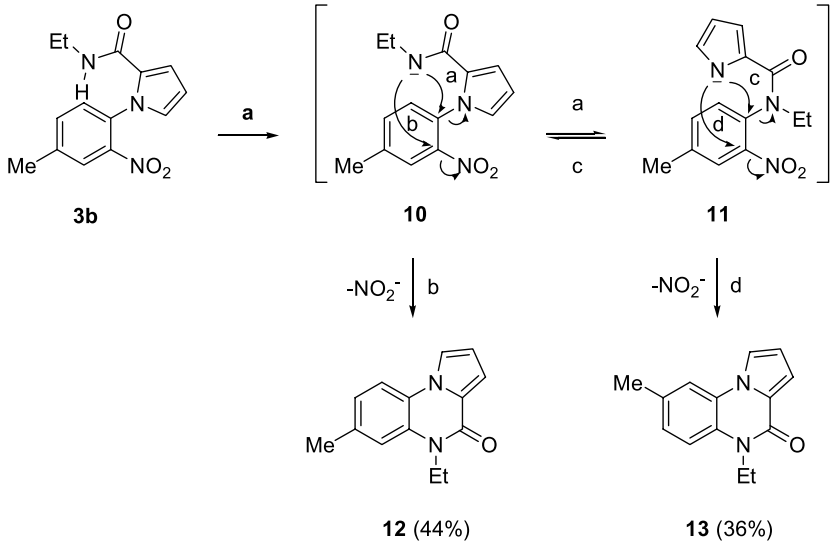
From the above observations we can confidently propose that carboxamide **3a** undergoes a Smiles rearrangement to give carboxamide **9**. However, although there is ample indication that the transformation of **3a** to **9** is reversible, there is no direct evidence as to whether **3a** or **9** or both lead to **8a**.

Further insight into the mechanism of 4-alkylpyrroloquinoxalinone formation was obtained by reacting carboxamide **3b** with NaH in DMF for 1.5 h. This gave a mixture containing pyrroloquinoxalinones **12** and **13** (Scheme 5). Since the separation of these two compounds by column chromatography was not possible, **12** was synthesised unambiguously by *N*-ethylating 7-methylpyrrolo[1,2-*a*]-quinoxalin-4(5*H*)-one[3] with ethyl iodide in DMF containing NaH. The ^1H NMR spectra of compound **12** and that of the mixture **12/13** were then compared and the peaks corresponding to **12** and **13** assigned. It turned out that **12** and **13** are in a ratio of about 44:36. Compounds **12** and **13** could only have been obtained from the corresponding anions of carboxamides **10** and **11** by denitrocyclisation through paths b and d. Compound **11** can only be obtained from **10** by a Smiles rearrangement that follows path a. Furthermore, based on previous observations (vide infra), it is quite reasonable to assume that the transformation of **10** to **11** is reversible through path c.

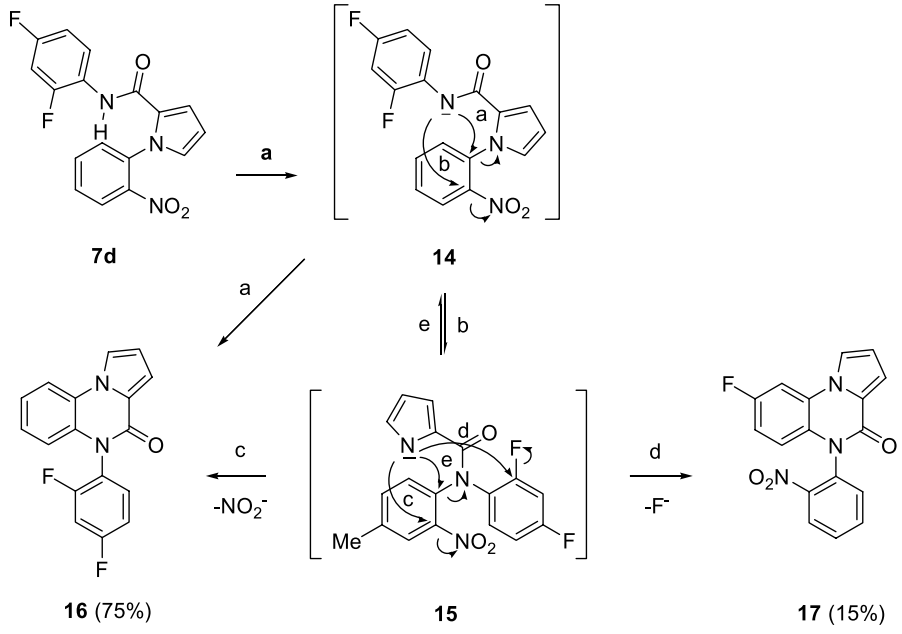
In order to verify whether a Smiles rearrangement occurred during the denitrocyclisation of aromatic carboxamides **7a–c**,**e** to pyrroloquinoxalinones **8c**,**e–g**, *N*-(2,4-difluorophenyl)carboxamide **7d** was employed as a potentially useful precursor. When **7d** was treated with NaH in DMF for 1.5 h, two products **16** and **17** were obtained in 75 and 15% yield, respectively. A proposed mechanism for this reaction is shown in Scheme 6. The initially formed carboxamide anion **14** could follow two paths a or b. Path a would lead to pyrroloquinoxalinone **16** by direct denitrocylisation whereas path b would lead to intermediate carboxamide **15** via a Smiles rearrangement. Taking into account previous observations (vide infra) it is reasonable to assume that **15** can reverse to **14** through path e and denitrocyclise to **16** through path c. On the other hand, pyrroloquinoxalinone **17** can only be formed through path d, that is, intramolecular nucleophilic displacement of fluoride anion by pyrrolyl anion of



Scheme 4. Reagents (a) NaH (60% in oil), DMF, 30 min; (b) NaH (60% in oil), DMF, 4.5 h.



Scheme 5. Reagents (a) NaH (60% in oil), DMF, 1.5 h.



Scheme 6. Reagents (a) NaH (60% in oil), DMF, 4.5 h.

intermediate **15**. The formation of **17** strongly suggests that intermediate **15** is its precursor. However, there is no substantial evidence to support that **16** is obtained directly from **14** or from intermediate **15** or from both.

3. Conclusion

In conclusion, we have shown that denitrocyclisation of *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides is a mild method that gives 5-alkyl(or aryl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones in high yields. For *N*-alkyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides there is direct evidence that reaction occurs through two pathways: (a) intramolecular nitro group displacement by the anion of *N*-alkyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides and (b) Smiles rearrangement of *N*-alkyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide anions into *N*-(2-nitrophenyl)-*N*-alkyl(or aryl)-1*H*-pyrrole-2-carboxamide anions, followed by intramolecular pyrrolyl anion displacement of the nitro group. It is highly probable that *N*-aryl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides give 5-arylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones by following similar pathways.

4. Experimental

4.1. General methods

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer, as Nujol mulls and liquids between sodium chloride discs. Elemental analyses were performed on a Perkin–Elmer 2400 or a Carlo Erba 1106 elemental analysers. Nuclear magnetic resonance spectra were measured at 360 MHz on a Brüker AM 360 spectrometer or at 400 MHz on a Brüker AMX 400 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained using a JEOL JMS-AX 505W or a Bruker Apex III high-resolution instruments. Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Preparative flash chromatography was carried out for all separations using Merck 9385 silica gel. Solvents and reagents were used as received from the manufacturers, except for dichloromethane, ethanol, ethyl acetate, hexane and methanol that were purified and dried according to recommended procedures.[14]

4.1.1. Preparation of 2-trichloroacetylpyrroles 2a,b: general procedure A. To a recently distilled solution of trichloroacetyl chloride (41.8 mL, 372 mmol) in dry 1,4-dioxane (140 mL), a solution of pyrrole **1a** or **1b** in (0.124 mol) in dry 1,4-dioxane (140 mL) was added dropwise. The reaction mixture was left to stir at room temperature for 6 days and then a saturated solution of potassium carbonate was slowly added until the pH was 7. Water (120 mL) was added and extracted with dichloromethane (3×80 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue, which on crystallisation from ethanol gave 2,2,2-trichloro-1-(1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)ethanone **2a** or 2,2,2-trichloro-1-(1-(4-methyl-2-nitrophenyl)-1*H*-pyrrol-2-yl)-ethanone **2b**.

4.1.1.1. 2,2,2-Trichloro-1-[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)]ethanone 2a. 4.20 g, 89%, as pale yellow needles (ethanol), mp 115–117 °C. [Found: C, 43.19; H, 2.15; N, 8.41. $C_{12}H_7Cl_3N_2O_3$ requires, 43.21; H, 2.12; N, 8.40%]; ν_{max} (Nujol) 1660, 1520, 1340 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.41 (t, J=3.8 Hz, 1H, H-4), 6.96 (s, 1H, H-3), 7.34 (d, J=7.8 Hz, 1H, H-6′), 7.54–7.60 (2H, m, H-5, H-4′), 7.65 (t, J=7.7 Hz, 1H, H-5′), 8.08 (d, J=8.1 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 111.60, 122.60, 124.76, 125.19, 130.13, 130.34, 133.65, 134.75, 135.03, 145.41, 171.73; *m*/*z* (EI) 332 (M^++1, 32), 215 (92), 187 (82), 171 (100%).

4.1.1.2. 2,2,2-Trichloro-1-[1-(4-methyl-2-nitrophenyl)-1*H*-pyrrol-2-yl)]ethanone 2b. 37.9 g, 88%, as pale yellow needles (ethanol), mp 122–124 °C. [Found: C, 45.03; H, 2.67; N, 8.01. $C_{13}H_9Cl_3N_2O_3$ requires C, 44.92; H, 2.61; N, 8.06%]; ν_{max} (Nujol) 3124, 1670, 1528, 1347 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.52 (s, 3H, Me), 6.47 (dd, J=4.3, 2.7 Hz, 1H, H-4), 7.02 (dd, J=2.6, 1.6 Hz, 1H, H-5), 7.29 (d, J=7.9 Hz, 1H, H-6′), 7.51 (dd, J=7.9, 1.3 Hz, 1H, H-5′), 7.66 (dd, J=4.4, 1.5 Hz, 1H, H-3), 7.96 (d, J=1.3 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 20.88, 95.44, 111.00, 123.64, 124.31, 125.61, 129.34, 131.71, 132.77, 134.44, 140.59, 145.09, 172.28; *m*/*z* (EI) 348 (M^++2, 6), 346 (M^+, 7), 302 (5) 300 (5), 283 (7), 265 (5), 229 (50), 201 (40), 183 (100), 154 (21), 84 (30%).

4.1.2. Preparation of 1*H*-pyrrole-2-carboxamides 3a,b: general procedure B. To a solution of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone **2a** or **2b** (9.04 mmol) in dichloromethane (40 mL) was added a solution of ethylamine 70% in water (3.5 mL, 54.225 mmol). The reaction mixture was stirred at room temperature for 18 h. Water was added (90 mL), the organic phase separated and the aqueous phase extracted with dichloromethane (3×30 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue which was triturated with toluene and filtered. The residue was purified by dissolving in ethyl acetate and precipitating by addition of hexane to afford *N*-ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **3a** or *N*-ethyl-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **3b**.

4.1.2.1. *N*-Ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3a. 2.16 g, 92%, as a pale-yellow solid (ethyl acetate/hexane); mp 93–95 °C; ν_{max} (CCl_4) 3450, 2980, 1665, 1350 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.05 (t, J=7.4 Hz, 3H, Me), 3.20 (q, J=6.9 Hz, 2H, CH_2), 5.79 (br, s, 1H, NH), 6.26 (t, J=3.3 Hz, 1H, H-4), 6.60 (d, J=3.9 Hz, 1H, H-3), 6.82 (s, 1H, H-5), 7.37 (d, J=7.9 Hz, 1H, H-6′), 7.47 (dd, J=8.0, 7.7 Hz, 1H, H-4′), 7.59 (dd, J=7.9, 7.7 Hz, 1H, H-5′), 7.98 (d, J=8.0 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 14.80, 34.03, 109.54, 112.24, 124.67, 127.01, 127.49, 128.67, 129.58, 133.31, 134.95, 145.02, 160.48; *m*/*z* (EI) 259 (M^+, 20), 213 (100), 188 (24), 171 (71) 169 (80), 155 (22), 143 (30), 118 (22%). HRMS (EI): (M^+), found 259.0961. $C_{13}H_{13}N_3O_3$ requires 259.0957.

4.1.2.2. *N*-Ethyl-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3b. 2.22 g, 90%, as a pale-yellow solid (ethyl acetate/hexane); mp 115–117 °C. [Found: C, 61.48; H, 5.47; N, 15.34; $C_{14}H_{15}N_3O_3$ requires C, 61.53; H,

5.53; N, 15.38%]; ν_{max} (Nujol) 3290, 1631, 1530, 1353 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.10 (t, $J=7.2$ Hz, 3H, Me), 2.47 (s, 3H, Me), 3.25 (q, $J=7.2$ Hz, 2H, CH_2), 5.92 (br, s, 1H, NH), 6.30 (dd, $J=3.9$, 2.8 Hz, 1H, H-4), 6.65 (dd, $J=3.9$, 1.6 Hz, 1H, H-3), 6.80 (dd, $J=2.8$, 1.6 Hz, 1H, H-5), 7.29 (d, $J=8.1$ Hz, 1H, H-6′), 7.45 (dd, $J=8.1$, 1.3 Hz, 1H, H-5′), 7.86 (d, $J=1.3$ Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 14.79, 20.80, 34.00, 109.26, 111.91, 125.03, 127.04, 127.49, 128.31, 132.31, 133.83, 139.38, 145.60, 160.49; *m/z* (EI) 273 (M^+, 10), 227 (100), 199 (16), 185 (46), 183 (27), 158 (19%).

4.1.3. *N*-Cyclohexyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3c. To a solution of 2,2,2-trichloro-1-(1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)ethanone **2a** (3 g, 9.04 mmol) in dry 1,4-dioxane (150 mL) under argon was added dropwise freshly distilled cyclohexylamine (5.17 mL, 45.18 mmol) and triethylamine (1.56 mL, 11.296 mmol) in dry 1,4-dioxane. The reaction mixture was stirred at 75 °C for 2 h and then the solvent removed under reduced pressure. Water was added (60 mL), the solution acidified with 2 N hydrochloric acid until the pH was 5 and then extracted with dichloromethane (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue which was photosensitive. The residue was suspended in toluene, filtered, and then purified from ethyl acetate/hexane to give the title compound **3c** as a pale-yellow solid (2.75 g, 97%); mp 98–100 °C; ν_{max} (Nujol) 3294, 1627, 1609, 1531, 1357 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.09–1.90 [m, 10H, $(CH_2)_5$], 3.67–3.74 (m, 1H, CH), 5.73 (s, 1H, NH), 6.32 (dd, $J=3.8$, 2.8 Hz, 1H, H-4), 6.66 (dd, $J=3.8$, 1.7 Hz, 1H, H-3), 6.82 (dd, $J=2.8$, 1.7 Hz, 1H, H-5), 7.44 (d, $J=7.8$ Hz, 1H, H-6′), 7.53 (dd, $J=8.0$, 7.6 Hz, 1H, H-4′), 7.66 (dd, $J=7.8$, 7.6 Hz, 1H, H-5′), 8.04 (d, $J=8.0$ Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 24.84, 25.44, 33.07, 47.91, 109.48, 111.93, 124.67, 126.98, 127.80, 128.64, 129.55, 133.26, 134.92, 146.01, 159.69; *m/z* (EI) 313 (M^+, 20), 267 (88), 215 (26), 185 (80), 171 (88) 169 (100), 155 (52), 143 (32), 118 (22%). HRMS (EI): (M^+), found 313.1422, $C_{17}H_{19}N_3O_3$ requires 313.1426.

4.1.4. 1-(2-Nitrophenyl)-1*H*-pyrrole-2-carboxylic acid 4. A suspension of 2,2,2-trichloro-1-[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)]ethanone **2a** (11.5 g, 35 mmol) in 10% aqueous sodium hydroxide (70 mL) was heated under reflux for 1.5 h. The resulting solution was allowed to cool and then acidified with 2 N hydrochloric acid to pH 4. The precipitate was filtered, washed with water, dried and recrystallised from propan-2-ol to give the title compound **4** as deep yellow microcrystals (6.81 g, 84%); mp 195.5–197 °C. [Found: C, 57.22; H, 3.52; N, 12.08; $C_{11}H_8N_2O_4$ requires C, 56.90; H, 3.47; N, 12.06%]; ν_{max} (Nujol) 3257, 3136, 1690, 1669, 1607, 1528, 1350 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.39 (t, $J=3.3$ Hz, 1H, H-4), 6.94 (s, 1H, H-3), 7.20 (d, $J=3.9$ Hz, 1H, H-5), 7.41 (d, $J=7.8$ Hz, 1H, H-6′), 7.59 (t, $J=7.7$ Hz, 1H, H-4′), 7.68 (t, $J=7.7$ Hz, 1H, H-5′), 8.09 (d, $J=8.0$ Hz, 1H, H-3′), 12.32 (s, 1H, COOH); δ_C (100 MHz; $CDCl_3$) 110.05, 118.67, 124.19, 124.18, 129.55, 129.93, 130.22, 134.07, 134.28, 145.93, 161.21; *m/z* (EI) 232 (M^+, 47), 187 (100), 171 (65), 159 (28) 143 (38), 131 (35), 102 (23), 83 (23), 77 (24%).

4.1.5. Preparation of 1*H*-pyrrole-2-carboxamides 7a–e: general procedure C. A suspension of 1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylic acid **4** (1.5 mmol) in freshly distilled thionyl chloride (8 mL) was heated to reflux under argon for 1 h. Removal of excess thionyl chloride, addition of dry benzene (7 mL) and then evaporation under vacuo gave a brownish oily residue. The residue was dissolved in dry benzene (7 mL) and then added dropwise under argon to a solution of the appropriate amine (1.5 mmol) in dry pyridine (7 mL). The reaction mixture was stirred at room temperature for 2 days. The solvents were evaporated in vacuo, a saturated solution of sodium bicarbonate (50 mL) was added and extracted with dichloromethane (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue that was purified by flash chromatography (25% ethyl acetate/hexane) to give 1-(2-nitrophenyl)-*N*-phenyl-1*H*-pyrrole-2-carboxamide **7a**, methyl 2-(1-(2-nitrophenyl)-1*H*-pyrrole-5-carboxamido)benzoate **7b**, *N*-(4-chlorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **7c**, *N*-(2,4-difluorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **7d**, or *N*-(4-methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **7e**.

4.1.5.1. 1-(2-Nitrophenyl)-*N*-phenyl-1*H*-pyrrole-2-carboxamide 7a. 387 mg, 84%, as a pale-yellow solid (ethyl acetate/hexane); mp 144–145 °C; ν_{max} (Nujol) 3320, 1637, 1540, 1355 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.17–6.20 (m, 1H, H-4), 6.66–6.68 (m, 2H, H-3, H-5), 6.84 (d, $J=7.1$ Hz, 1H, H-4″), 7.02–7.11 (m, 2H, H-3″, H-5″), 7.20–7.53 (m, 6H, H-2″, H-6″, H-6′, H-5′, H-4′, NH), 7.87 (d, $J=7.6$ Hz, 1H, H-3′); δ_C (100 MHz; DMSO-d_6) 109.60, 114.88, 120.36, 123.46, 124.75, 125.98, 128.70, 129.01, 129.19, 129.99, 134.15, 134.72, 139.11, 145.99, 158.79; *m/z* (EI) 307 (M^+, 33), 261 (22), 215 (32), 169 (100), 140 (17), 114 (12%); HRMS (EI): (M^+), found 307.0965, $C_{17}H_{13}N_3O_3$ requires 307.0957.

4.1.5.2. Methyl 2-(1-(2-nitrophenyl)-1*H*-pyrrole-5-carboxamido)benzoate 7b. 247 mg, 45%, as a pale-yellow solid (ethyl acetate/hexane); mp 166–168 °C. [Found: C, 62.31; H, 4.35; N, 11.45; $C_{19}H_{15}N_3O_5$ requires C, 62.46; H, 4.14; N, 11.50%]; ν_{max} (Nujol) 3257, 3136, 1690, 1669, 1607, 1528, 1350 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.45–6.48 (m, 1H, H-4), 7.08–7.16 (m, 2H, H-3, H-4″), 7.26–7.27 (m, 1H, H-5), 7.51–7.61 (m, 2H, H-6′, H-5″), 7.71 (t, $J=7.7$ Hz, 1H, H-4′), 7.84 (t, $J=7.6$ Hz, 1H, H-5′), 7.97 (d, $J=7.9$ Hz, 1H, H-6″), 8.16 (d, $J=8.0$ Hz, 1H, H-3″), 8.26 (d, $J=8.4$ Hz, 1H, H-3′), 11.41 (br, s, 1H, NH); δ_C (100 MHz; DMSO-d_6) 52.77, 110.15, 114.24, 116.00, 120.21, 122.85, 124.82, 126.73, 129.55, 129.89, 130.16, 130.86, 134.17, 134.26, 134.52, 140.56, 145.84, 158.21, 168.31; *m/z* (EI) 365 (M^+, 29), 319 (22), 287 (21), 215 (28), 188 (26), 169 (100), 145 (34%).

4.1.5.3. *N*-(4-Chlorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7c. 379 mg, 74%, as a pale-yellow solid (ethyl acetate/hexane); mp 136–137 °C; ν_{max} (Nujol) 3320, 1635, 1520, 1350 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.39 (dd, $J=3.8$, 2.8 Hz, 1H, H-4), 6.86–6.90 (m, 2H, H-3, H-5), 7.18–7.26 (m, 2H, H-3″, H-5″), 7.35–7.38 (d, m, 2H, H-2″, H-6″), 7.46 (dd, $J=7.7$, 1.5 Hz, 1H, H-6′), 7.57 (t, $J=7.6$ Hz 1H, H-4′), 7.65–7.70 (m, 2H, H-5′, NH), 8.07 (d, $J=$

7.9 Hz, 1H, H-3′); δ_C (100 MHz; DMSO-d_6) 107.51, 109.6, 115.09, 121.73, 124.74, 126.64, 126.98, 128.56, 129.24, 130.01, 134.16, 134.56, 138.07, 145.93, 158.73; *m/z* (EI) 343 ($M^+ + 2$, 8), 341 (M^+, 24), 297 (4), 295 (10), 215 (43), 171 (23), 169 (100), 140 (14), 114 (10%); HRMS (EI): (M^+), found 341.0557, $C_{17}H_{12}ClN_3O_3$ requires 341.0567.

4.1.5.4. *N*-(2,4-Difluorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7d. 443 mg, 86%, as a pale-yellow solid (ethyl acetate/hexane); mp 81–83 °C. [Found: C, 59.33; H, 3.29; N, 12.16;. $C_{17}H_{11}F_2N_3O_3$ requires C, 59.48; H, 3.23; N, 12.24%]; ν_{max} (Nujol) 3237, 1639, 1524, 1359 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.42 (t, J=3.3 Hz, 1H, H-4), 6.77 (dddd, J=9.2, 8.3, 2.8, 1.7 Hz, 1H, H-5″), 6.84 (ddd, J=11.3, 8.3, 2.8 Hz, 1H, H-3″), 6.91–6.92 (m, 2H, H-3, H-5), 7.47 (dd, J=7.8, 1.3 Hz, 1H, H-6′), 7.58 (td, J=8.1, 1.3 Hz, 1H, H-4′), 7.67–7.71 (m, 2H, H-5′, NH), 8.03 (td, J=9.2, 6.0 Hz, 1H, H-6″), 8.10 (dd, J=8.1, 1.4 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 103.47 (dd, J=26.6, 23.7 Hz), 110.13, 111.09 (dd, J=21.5, 3.7 Hz), 113.75, 122.40 (dd, J=10.4, 3.8 Hz), 122.95 (dd, J=9.0, 2.1 Hz), 124.99, 126.84, 128.63, 129.21, 129.81, 133.52, 134.47, 146.00, 153.77 (dd, J=246.2, 11.8 Hz), 158.29, 158.94 (dd, J=246.0, 11.4 Hz); δ_F (376 MHz; $CDCl_3$) −115.37 (tdd, J=8.3, 6.0, 4.6 Hz, 1F, F-4″), −126.27 (ddddd, J=11.0, 9.2, 4.6, 2.9, 1.7 Hz, 1F, F-2″); *m/z* (EI) 343 (M^+, 23), 215 (36), 169 (100), 119 (51), 105 (85%).

4.1.5.5. *N*-(4-Methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7e. 390 mg, 77%, as a pale-yellow solid (ethyl acetate/hexane); mp 107–109 °C;. ν_{max} (Nujol) 3315, 1630, 1510, 1345 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.75 (s, 3H, OMe), 6.37–6.39 (m, 1H, H-4), 6.79 (d, J=7.3 Hz, 2H, H-3″, H-5″), 6.83–6.87 (m, 2H, H-3, H-5), 7.30 (d, J=7.3 Hz, 2H, H-2″, H-6″), 7.46 (d, J=7.8 Hz, 1H, H-6′), 7.52–7.56 (m, 2H, H-4′, NH), 7.66 (t, J=7.8 Hz, 1H, H-5′), 8.05 (d, J=8.1 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 55.35, 109.53, 113.85, 114.42, 122.00, 124.71, 127.07, 128.71, 129.13, 129.95, 132.07, 134.13, 134.77, 145.99, 155.51, 158.51; *m/z* (EI) 337 (M^+, 85), 291 (14), 215 (40), 169 (100), 149 (30), 134 (15); HRMS (EI): (M^+), found 337.1060, $C_{18}H_{15}N_3O_4$ requires 337.1063.

4.1.6. Preparation of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones 8a,b: general procedure D. To a stirred solution of carboxamide **3a** or **c** (0.65 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 1.10 mmol) and left to stir at room temperature for 1.5 h. The reaction mixture was poured into water (50 mL), neutralised with 2 N HCl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. The oily residue was triturated with hexane, the solid collected and purified by flash chromatography (25% ethyl acetate/hexane) to afford 5-ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8a** or 5-cyclo-hexylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8b**.

4.1.6.1. 5-Ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8a. 119 mg, 85%, as a pale-yellow solid (ethyl acetate/hexane); mp 78–80 °C. [Found: C, 73.45; H, 5.63; N, 13.14;. $C_{13}H_{12}N_2O$ requires C, 73.56; H, 5.70; N, 13.20%]; ν_{max} (Nujol) 3118, 1638 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.29 (t, J=7.0 Hz, 3H, CH_3), 4.25, (q, J=7.2 Hz, 2H, CH_2), 6.58 (dd, J=3.6, 2.8 Hz, 1H, H-2), 7.12–7.19 (m, 2H, H-3, H-8), 7.24–7.27 (m, 2H, H-6, H-7), 7.57 (dd, J=2.8, 1.6 Hz, 1H, H-1), 7.61 (d, J=7.6 Hz, 1H, H-9); δ_C (100 MHz; $CDCl_3$) 13.19, 36.58, 112.85, 113.61, 115.19, 115.96, 116.21, 123.07, 123.75, 124.63, 125.98, 129.56, 155.59; *m/z* (EI) 212 (M^+, 79), 197 (39), 184 (100) 167 (25), 155 (17%).

4.1.6.2. 5-Cyclohexylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8b. 149 mg, 86%, as a pale-yellow solid (ethyl acetate/hexane); mp 109–111 °C. [Found: C, 76.38; H, 6.88; N, 10.46;. $C_{17}H_{18}N_2O$ requires C, 76.66; H, 6.81; N, 10.52%]; ν_{max} (Nujol) 3115, 1640, 1609 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.25–2.63 [m, 10H, $(CH_2)_5$], 4.75 (br, s, 1H, CH), 6.63–6.64 (m, 1H, H-2), 7.22–7.16 (m, 2H, H-3, H-8), 7.28 (t, J=7.3 Hz, 1H, H-7), 7.60–7.56 (m, 2H, H-1, H-6), 7.66 (d, J=7.8 Hz, 1H, H-9); δ_C (100 MHz; $CDCl_3$) 25.32, 26.51, 29.15, 55.98, 112.08, 113.03, 114.84, 115.30, 116.43, 122.43, 123.79, 124.31, 124.82, 129.76, 155.97; *m/z* (EI) 266 (M^+, 18), 184 (100), 155 (12), 129 (8%).

4.1.7. Preparation of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones 8c,d,f,g: general procedure E. To a stirred solution of the corresponding carboxamide **7a–c**,**e** (0.65 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 1.10 mmol) and left to stir at room temperature for 4.5 h. The reaction mixture was poured into water (50 mL), neutralised with 2 N HCl and the precipitate filtered, washed with water and dried to afford 5-phenylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8c**, 2-(4-oxo-pyrrolo[1,2-*a*]quinoxalin-5(4*H*)-yl)benzoic acid **8d**.

4.1.7.1. 5-Phenylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8c. 178 mg, 89%, as a pale-yellow solid (ethyl acetate/hexane); mp 168–170 °C. [Found: C, 78.10; H, 4.68; N, 10.74;. $C_{17}H_{12}N_2O$ requires C, 78.44; H, 4.65; N, 10.76%]; ν_{max} (Nujol) 3110, 1652 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.50 (dd, J=8.4, 1.1 Hz, 1H, H-6), 6.75 (dd, J=3.9, 2.6 Hz, 1H, H-2), 7.11 (dd, J=3.9, 1.4 Hz, 1H, H-3), 7.18 (td, J=7.8, 1.1 Hz, 1H, H-8), 7.26 (td, J=7.7, 1.2 Hz, 1H, H-7), 7.40 (d, J=7.2 Hz, 2H, H-2′, H-6′), 7.56 (t, J=7.3 Hz, 1H, H-4′), 7.63 (t, J=7.4 Hz, 2H, H-3′, H-5′), 8.16 (dd, J=8.1, 1.2 Hz, 1H, H-9), 8.29 (dd, J=2.6, 1.4 Hz, 1H, H-1); δ_C (100 MHz; $CDCl_3$) 112.40, 113.16, 115.26, 116.73, 118.22, 122.68, 122.99, 123.03, 125.46, 128.76, 129.57, 129.93, 130.98, 136.70, 154.32; *m/z* (EI) 260 (M^+, 100), 259 (100), 231 (6) 205 (7), 178 (6), 166 (7), 115 (8), 102 (8%).

4.1.7.2. 2-(4-Oxopyrrolo[1,2-*a*]quinoxalin-5(4*H*)-yl)benzoic acid 8d. 162 mg, 82%, as a pale-yellow solid (2 N NaOH/2 N HCl); mp 260–262 °C. [Found: C, 70.73; H, 4.03; N, 9.17; $C_{18}H_{12}N_2O_3$ requires C, 71.05; H, 3.97; N, 9.21%]; ν_{max} (Nujol) 2900, 3135, 1709, 1651 cm^{-1}; δ_H (250 MHz; DMSO-d_6) 6.43 (d, J=8.1 Hz, 1H, H-6), 6.73–6.76 (m, 1H, H-2), 7.11 (m, 1H, H-3), 7.17 (t, J=7.5 Hz, 1H, H-8), 7.25 (t, J=7.5 Hz, 1H, H-7), 7.49 (d, J=7.7 Hz, 1H, H-6′), 7.69 (t, J=7.6 Hz, 1H, H-4′), 7.86 (t, J=7.6 Hz, 1H, H-5′), 8.17 (d, J=7.7 Hz, 2H, H-9, H-3′), 8.29 (m, 1H, H-1), 12.80 (bs, 1H, CO_2H); δ_C (63 MHz; DMSO-d_6) 112.63, 113.32, 115.45, 116.63, 118.42, 123.07 (2C), 123.34, 125.76, 129.57, 130.56, 131.37, 131.68, 132.13, 134.13, 136.74, 154.70, 165.79; *m/z* (EI) 304 (M^+, 60), 259 (100%).

4.1.7.3. Methyl 2-(4-oxopyrrolo[1,2-*a*]quinoxalin-5(4*H*)-yl)benzoate 8e. 159 mg, 77%, as a pale-yellow solid (ethyl acetate /hexane); mp 159–161 °C. [Found: C, 71.40; H, 4.48; N, 8.77; $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 4.43; N, 8.80%]; ν_{max} (Nujol) 3148, 1724, 1660 cm^{-1}; δ_H (250 MHz; DMSO-d_6) 3.55 (s, 1H, Me), 6.41 (d, J=8.1 Hz, 1H, H-6), 6.74–6.77 (m, 1H, H-2), 7.09–7.11 (m, 1H, H-3), 7.16 (t, J=7.8 Hz, 1H, H-8), 7.26 (t, J=7.7 Hz, 1H, H-7), 7.54 (d, J=7.7 Hz, 1H, H-6′), 7.72 (t, J=7.6 Hz, 1H, H-4′), 7.88 (t, J=7.6 Hz, 1H, H-5′), 8.18 (d, J=7.7 Hz, 2H, H-9, H-3′), 8.30–8.31 (m, 1H, H-1); δ_C (63 MHz; DMSO-d_6) 52.26, 112.68, 113.12, 113.27, 115.45, 116.45, 118.52, 122.92, 123.13, 123.31, 125.73, 128.94, 129.68, 131.16, 131.84, 134.59, 136.92, 154.61, 164.37; *m/z* (EI) 318 (M^+, 56), 259 (100%).

4.1.7.4. 5-(4-Chlorophenyl)pyrrolo[1,2-*a*]quinoxalin-4-(5*H*)-one 8f. 182 mg, 82%, as a pale-yellow solid (ethyl acetate/hexane); mp 236–238 °C. [Found: C, 68.93; H, 3.82; N, 9.47; $C_{17}H_{11}ClN_2O$ requires C, 69.28; H, 3.76; N, 9.50%]; ν_{max} (Nujol) 3088, 1660 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.55 (dd, J=8.3, 1.1 Hz, 1H, H-6), 6.77 (dd, J=3.8, 2.8 Hz, 1H, H-2), 7.13 (dd, J=3.8, 1.4 Hz, 1H, H-3), 7.21 (td, J=7.8, 1.1 Hz, 1H, H-8), 7.29 (td, J=7.7, 1.2 Hz, 1H, H-7), 7.48 (d, J=8.6 Hz, 2H, H-2′, H-6′), 7.70 (d, J=8.6 Hz, 2H, H-3′, H-5′), 8.19 (dd, J=8.1, 1.2 Hz, 1H, H-9), 8.32 (dd, J=2.8, 1.4 Hz, 1H, H-1); δ_C (100 MHz; DMSO-d_6) 113.46, 114.11, 116.21, 117.62, 119.27, 123.45, 124.03, 126.47, 130.92, 131.66, 132.54, 134.32, 136.51, 155.20; *m/z* (EI) 294 (M^+, 100), 258 (18), 230 (11) 204 (6), 167 (7), 130 (12), 115 (9).

4.1.7.5. 5-(4-Methoxyphenyl)pyrrolo[1,2-*a*]quinoxalin-4-(5*H*)-one 8g. 208 mg, 95%, as a pale-yellow solid (ethyl acetate/hexane); mp 207–209 °C. [Found: C, 74.16; H, 4.90; N, 9.58; $C_{18}H_{14}N_2O_2$ requires C, 74.47; H, 4.86; N, 9.65%]; ν_{max} (Nujol) 3148, 1724, 1660 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 3.85 (s, 3H, Me), 6.55 (d, J=8.1 Hz, 1H, H-6), 6.74 (dd, J=3.8 Hz, 2.7 Hz, 1H, H-2), 7.09 (dd, J=3.8, 1.5 Hz, 1H, H-3), 7.20–7.14 (m, 3H, H-8, H-2′, H-6′), 7.25 (td, J=7.5, 1.1 Hz, 1H, H-7), 7.29 (d, J=8.8 Hz, 2H, H-3′, H-5′), 8.12 (d, J=8.1 Hz, 1H, H-9), 8.27 (dd, J=2.7, 1.5 Hz, 1H, H-1); δ_C (100 MHz; DMSO-d_6) 55.60, 112.55, 113.35, 115.33, 115.42, 117.09, 118.36, 123.01, 123.15, 123.27, 125.67, 128.25, 130.80, 131.52, 154.78, 159.39; *m/z* (EI) 290 (M^+, 100), 275 (11), 167 (18), 145 (8%).

4.1.8. Reaction of *N*-ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3a with NaH in DMF. To a stirred solution of carboxamide **3a** (170 mg, 0.65 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 44 mg, 1.10 mmol) and left to stir at room temperature for 30 min. The reaction mixture was added to a cold saturated aqueous sodium bicarbonate solution (50 mL), neutralised with 2 N HCl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. The oily residue was triturated with hexane, the solid collected and purified by flash chromatography (25, 50% ethyl acetate/hexane) to afford *N*-ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **3a**, 5-ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8a** and *N*-ethyl-*N*-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **9**.

4.1.8.1. *N*-Ethyl-*N*-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3a. 29 mg, 17%, as a pale-yellow solid (ethyl acetate/hexane), mp 93–95 °C, identical in all respects to an authentic sample (vide infra).

4.1.8.2. 5-Ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8a. 51 mg, 37%, as a pale-yellow solid (ethyl acetate/hexane), mp 78–80 °C, identical in all respects to an authentic sample (vide infra).

4.1.8.3. *N*-Ethyl-*N*-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 9. 36 mg, 21%, as a pale-yellow solid (ethyl acetate/hexane); mp 165.5–167.5 °C. [Found: C, 60.30; H, 5.26; N, 16.25; $C_{13}H_{13}N_3O_3$ requires C, 60.22; H, 5.05; N, 16.21%]; ν_{max} (Nujol) 3268, 1615 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.29 (t, J=7.2 Hz, 3H, Me), 3.60 (br, s, 1H, CH_2), 4.27–4.32 (m, 1H, CH_2) 4.94 (br, s, 1H, H-4), 5.96 (s, 1H, H-3), 6.87 (s, 1H, H-5), 7.50 (dd, J=7.8, 1.4 Hz, 1H, H-6′), 7.66 (td, J=7.6, 1.3 Hz, 1H, H-4′), 7.77 (td, J=7.7, 1.5 Hz, 1H, H-5′), 8.12 (dd, J=8.1, 1.5 Hz, 1H, H-3′), 9.69 (br, s, 1H, NH); δ_C (100 MHz; $CDCl_3$) 13.47, 46.00, 110.35, 112.99, 121.87, 125.05, 126.35, 129.83, 132.93, 134.55, 136.78, 147.67, 161.18; *m/z* (EI) 259 (M^+, 27), 213 (65), 184 (6) 166 (54), 151 (25), 131 (7), 106 (42), 94 (100), 66 (26%).

4.1.9. Preparation of 5-ethyl-7-methylpyrrolo[1,2-*a*]-quinoxalin-4(5*H*)-one 12. To a stirred solution of 7-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one[1] (300 mg, 1.51 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 65 mg, 1.61 mmol) and left to stir at room temperature for 1 h. Ethyl iodide (242 mg, 1.55 mmol) was added and the reaction mixture stirred for 15 min. Water (50 mL) was added and extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The oily residue was purified by flash chromatography (25% ethyl acetate/hexane) to afford 5-ethyl-7-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **12** (270 mg, 79%) as a colourless solid (propan-2-ol/hexane); mp 104–105 °C. [Found: C, 73.98; H, 6.29; N, 12.36; $C_{14}H_{14}N_2O$ requires C, 74.31; H, 6.24; N, 12.38%]; ν_{max} (Nujol) 3130, 1651 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.34 (t, J=7.2 Hz, 3H, CH_2CH_3), 2.42 (s, 3H, Me), 4.27 (q, J=7.2 Hz, 2H, CH_2CH_3), 6.60 (dd, J=3.9, 2.8 Hz, 1H, H-2), 6.97 (dd, J=8.2, 0.8 Hz, 1H, H-8), 7.06 (s, 1H, H-6), 7.17 (dd, J=3.9, 1.6 Hz, 1H, H-3), 7.50 (d, J=8.2 Hz, 1H, H-9), 7.55 (dd, J=2.8, 1.6 Hz, 1H, H-1); δ_C (100 MHz; $CDCl_3$) 12.65, 35.94, 68.54, 111.94, 112.75, 114.39, 115.50, 115.66, 121.85, 122.94, 123.27, 128.76, 135.38, 155.15; *m/z* (EI) 226 (M^+, 100), 211 (43), 198 (96), 181 (25), 169 (14%).

4.1.10. Reaction of *N*-ethyl-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3b with NaH in DMF. Following general procedure D carboxamide **3b** (0.65 mmol) in dry DMF (10 mL) and NaH (60% in oil, 1.10 mmol) at room temperature for 1.5 h gave a mixture (118 mg, 80%) of 5-ethyl-7-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **12** (44% in mixture from ^{1}H NMR) and 5-ethyl-8-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **13** (44% in mixture from ^{1}H NMR); δ_H (400 MHz; $CDCl_3$) 1.29–1.34 (m, 4H, 2×CH_2CH_3 of **12** and **13**), 2.41 (s, 3H, Me of **12**), 2.42 (s, 3H, Me of **13**), 4.24–4.30 (m, 4H, 2×CH_2CH_3 of **12** and **13**), 6.59–6.62 (m, 2H, 2×H-2 of **12** and **13**), 6.97

(d, $J=8.2$ Hz, 1H, H-8 of **12**), 7.06 (s, 1H, H-6 of **12**), 7.07 (d, $J=7.8$ Hz, H-7 of **13**), 7.14–7.18 (m, 3H, H-3 of **12** and **13**, H-6 of **13**), 7.45 (s, 1H, H-9 of **13**), 7.50 (d, $J=8.2$ Hz, 1H, H-9 of **12**), 7.55 (dd, $J=2.8$, 1.6 Hz, 1H, H-1 of **12**).

4.1.11. Reaction of *N*-(2,4-difluorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7d with NaH in DMF. Following general procedure E carboxamide **7d** (0.65 mmol) in dry DMF (10 mL) and NaH (60% in oil, 1.10 mmol) at room temperature for 4.5 h gave, after purification by flash chromatography (33% ethyl acetate/hexane), 5-(2,4-difluorophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **16** and 8-fluoro-5-(2-nitrophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **17**.

4.1.11.1. 5-(2,4-Difluorophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 16. 144 mg, 75%, as a pale-yellow solid (ethyl acetate/hexane); mp 200–202 °C. [Found: C, 69.07; H, 3.65; N, 9.35; $C_{17}H_{10}F_2N_2O$ requires C, 68.92; H, 3.40; N, 9.46%]; ν_{max} (Nujol) 3122, 1659 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.63 (d, $J=8.2$ Hz, 1H, H-6), 6.77 (dd, $J=3.9$, 2.8 Hz, 1H, H-2), 7.17 (dd, $J=3.9$, 1.5 Hz, 1H, H-3), 7.23 (td, $J=7.8$, 1.3 Hz, 1H, H-7), 7.31 (td, $J=7.8$, 1.3 Hz, 1H, H-8), 7.36 (ddd, $J=8.8$, 8.7, 2.8, Hz, 1H, H-5′), 7.61 (ddd, $J=10.1$, 9.2, 2.8 Hz, 1H, H-3′), 7.67 (td, $J=8.8$, 6.2 Hz, 1H, H-6′) 8.19 (dd, $J=8.1$, 1.3 Hz, 1H, H-9), 8.32 (dd, $J=2.8$, 1.5 Hz, 1H, H-1); δ_C (100 MHz; DMSO-d_6) 105.94 (dd, $J=27.1$, 24.2 Hz), 113.37 (dd, $J=22.5$, 3.5 Hz), 113.56, 113.78, 115.93, 116.52, 119.27, 120.62 (dd, $J=13.5$, 3.9 Hz), 122.49, 123.55, 124.01, 126.32, 130.34, 133.51 (d, $J=10.4$ Hz), 154.38, 158.90 (dd, $J=251.1$, 13.3 Hz), 162.80 (dd, $J=248.6$, 11.8 Hz); δ_F (376 MHz; DMSO-d_6) −107.70 (dddd, $J=9.2$, 8.7, 8.6, 6.2 Hz, 1F, F-4′), −117.05 (ddd, $J=10.1$, 8.8, 8.6 Hz, 1F, F-2′); *m/z* (EI) 296 (M^+, 100), 277 (57), 247 (6%).

4.1.11.2. 8-Fluoro-5-(2-nitrophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 17. 32 mg, 15%, as a pale-yellow solid (ethyl acetate/hexane); mp 264–265 °C. [Found: C, 63.32; H, 3.33; N, 12.86; $C_{17}H_{10}FN_3O_3$ requires C, 63.16; H, 3.12; N, 13.00%]; ν_{max} (Nujol) 1661, 1514, 1346 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.64 (dd, $J=9.0$, 5.1 Hz, 1H, H-6), 6.81 (t, $J=3.6$ Hz, 1H, H-2), 7.10 (td, $J=9.0$, 2.7 Hz, 1H, H-7), 7.16 (dd, $J=3.8$, 1.2 Hz, 1H, H-3), 7.77 (d, $J=7.8$ Hz, 1H, H-3′), 7.87 (td, $J=7.8$, 1.3 Hz, 1H, H-5′), 8.01 (td, $J=7.7$, 1.3 Hz, 1H, H-4′), 8.26 (dd, $J=9.8$, 2.7 Hz, 1H, H-9), 8.32–8.36 (m, 2H, H-1, H-6′); δ_C (100 MHz; DMSO-d_6) 103.31 (d, $J=28.4$ Hz), 112.84 (d, $J=22.8$ Hz), 113.91, 114.02, 118.35 (d, $J=9.6$ Hz), 119.88, 122.25, 124.25 (d, $J=11.4$ Hz), 126.16, 126.95, 129.86, 131.13, 132.65, 135.80, 147.26, 153.85, 158.36 (d, $J=240.3$ Hz); δ_F (376 MHz; DMSO-d_6) −118.25 (ddd, $J=9.8$, 9.0, 5.1 Hz, 1F, F-8); *m/z* (EI) 323 (M^+, 39), 277 (100), 247 (15), 222 (8%).

Acknowledgements

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Cycloaddition approach to benzo-annulated indane-based α-amino acid derivatives

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Abstract—Synthesis of various benzo-annulated indane-based α-amino acid (AAA) derivatives are reported via a [4+2] and [2+2+2] cycloaddition reactions as key steps. Here, *o*-xylylene based AAA moiety has been used as a reactive intermediate and by adopting this strategy various indane-based constrained AAA derivatives are prepared.

1. Introduction

During the past several years, research in our laboratory has focused on the synthesis of new building blocks which are suitable for the design of various constrained α-amino acid (AAA) derivatives.[1] These investigations are directed towards the preparation of α,α-dialkylated amino acid derivatives that are not accessible by conventional modes such as Bucherer–Berg (BB) method. Our efforts have led to the development of several building blocks, which are useful for the generation of various unusual AAA derivatives. Within this context, we proposed *o*-xylylene (or *o*-quinodimethane) intermediate **1** containing an AAA moiety as a versatile reactive intermediate for the generation of various benzo-annulated indane-based AAA derivatives (e.g., **5**) via a Diels–Alder (DA) strategy. It is hoped that introduction of new type of building blocks (e.g., **1**) as reaction partners in DA chemistry would significantly extend the impact of these methodologies in peptide-based drug design. Indane-based AAA derivatives such as **4**, are a special class of constrained phenylalanine (Phe) derivative **3**, used in several instances to modify various biologically active peptides.[2–5] Also, indane-based AAA are useful building blocks for the design of 'ladder-like' parallel tapes in crystal engineering studies.[6] Indanylglycine (Ind) **4** in which phenyl ring is covalently connected to the α-carbon through a C-methylene group and thereby providing the rigid aromatic ring lacking rotational freedom of the Phe-side chain. Compound **4**, a component of a potent ligand of angiotensin-II receptor with agonistic or antagonistic activity was extensively used in the synthesis of various biologically active peptides.[3] In this regard, Chasing and co-workers synthesized several 2-indanyl-glycine derivatives for analyzing the binding pockets of Phe$^{(7)}$ (S7) and Phe$^{(8)}$ (S8), two important aromatic residues for pharmacological properties of substance P (SP).[3] Cyclic analogues of phenylglycine, Ind, α-methyl-40-phosphonophenylglycine (MPPG) have been synthesized and exhibited interesting pharmacological properties towards glutamate receptors.[7]

Topographical consideration is the major approach to the rational design of peptide ligands to explore the side-chain interaction for binding to their receptors and for signal transduction. This aspect has been realized by incorporation of constrained AAA such as **5** (R=H) into the backbone of polypeptide and also in non-peptide templates.[8] When the C-terminal Phe residue in chemotactic agent HCO-Met-Leu-Phe-OH (FMLP) was replaced by Ind, the resulting modified analog has shown to be highly active in the superoxide production (Fig. 1).[4–5]

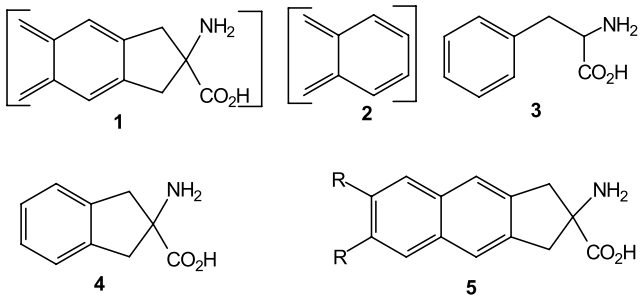

Figure 1.

Keywords: Amino acids and derivatives; Fullerenes; Sulfur heterocycles; Cycloadditions; Diels–Alder reactions.
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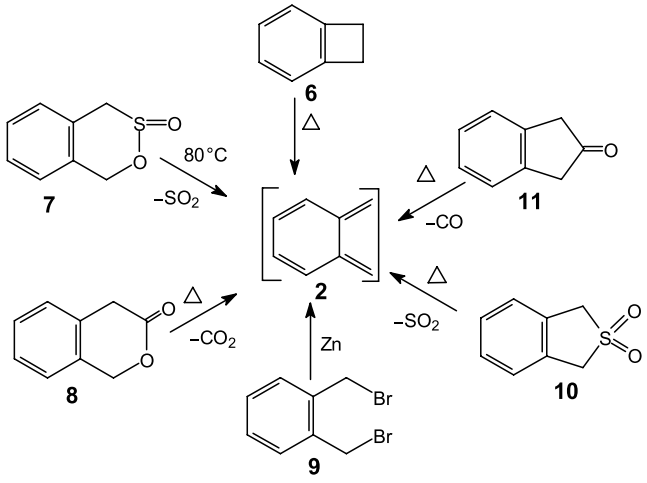
In addition, the indane moiety is an important structural element, which can fix the relative position of functional groups to impart a greater specificity for biological activity. Also, a number of indane-based derivatives have been synthesized and were shown to be pharmacologically active compounds.[9–16]

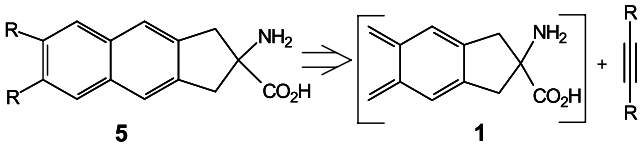
Several approaches towards the parent *o*-xylylene[17–18] or *o*-quinodimethane (*o*-QDM) **2** intermediate have been explored and these are summarized in Scheme 1. Thermal generation of **2** by various roots was realized at higher temperature except in case of sultine **7**. In 1991, Dittmer and co-workers had reported the syntheses of the sultine **7** from *o*-xylenedibromide **9** in high yield using PTC, tetrabutylammonium bromide (TBAB) conditions.[19] In this respect, sultine **7** was found to be a suitable precursor to generate the parent *o*-xylylene **2** at around 80 °C.



Scheme 1.

In a related study, Martin and co-workers explored several routes to generate the *o*-xylylene intermediate and they have reported various C_{60} fullerene adducts using sultine as a latent diene component (Scheme 2).[20] Later on, Chung and co-worker have reported various heterocyclic sultine derivatives capable of participating in DA chemistry.[21]

Realization of the proposition shown in Scheme 3 depends on finding suitable conditions to generate the key precursor related to **1**. Although, several methods are available for the generation of the parent *o*-xylylene **2**, these methods may not be applicable for the intermediates related to **1** due to the presence of two reactive functional groups, i.e., amino and carboxyl. Our initial experience to prepare *o*-xylylene



Scheme 3.

intermediates containing AAA moiety from benzocyclobutene intermediates was not favorable.[22] In the past, we had demonstrated that sultine intermediate can be trapped with a dienophile containing AAA moiety.[23] Therefore, the attention was focussed towards the generation of **1** via sultine intermediate. Compounds such as **5** may be prepared by BB[24] method starting from benzofused 2-indanone derivative, that involves drastic conditions for the hydrolysis of hydantoin intermediate. Due to this reason many sensitive substrates do not survive and only simple derivatives can be prepared by BB method.

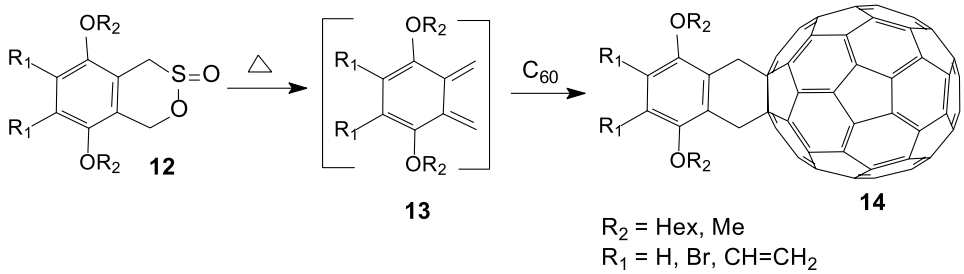
2. Strategy

In a program directed towards the synthesis of highly functionalized benzo-annulated indane-based (AAA) derivatives such as **5**, we identified [4+2]-cycloaddition (DA) strategy as a possible route (Scheme 3). Herein, we report the realization of this strategy to prepare various benzo-annulated indane-based AAA derivatives by trapping the reactive intermediate **1** with different dienophiles.

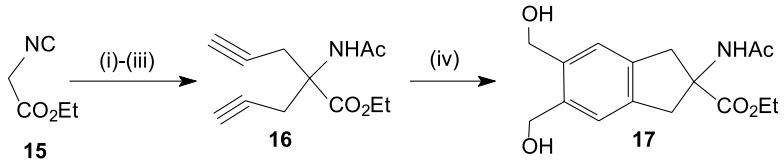
Approaches based on the DA strategy have been well established in the literature where the sultine derivatives were used as a latent diene equivalents.[20–21] However, there are no example known where the sultine derivative containing AAA moiety, and, in this regard we attempted to prepare various indane-based AAA derivatives by utilizing sultine methodology. To expand upon 'Building Block Approach' for highly functionalized benzo-annulated indane-based AAA derivatives, generation of **1** via sultine derivative **20** is an attractive proposition.

3. Results and discussion

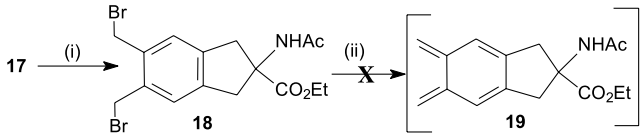
Towards the synthesis of compounds such as **5**, the required indane derivative **17** was synthesized according to the reported procedure via a four-step sequence starting from ethyl isocyanoacetate **15** (Scheme 4).[25] The dihydroxy indane derivative **17** was then converted to the corresponding dibromide **18** under PBr_3 conditions (Scheme 5).[26] The IR spectrum of compound **18** showed characteristic strong



Scheme 2.



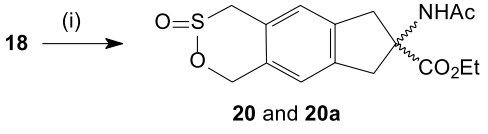
Scheme 4. (i) Propargyl bromide, K_2CO_3, TBAHS, CH_3CN, 80 °C; (ii) HCl, EtOH, rt; (iii) Ac_2O, DCM, rt; (iv) $Rh(PPh_3)_3Cl$, 2-butyne-1,4-diol, EtOH, 80 °C, 65%.



Scheme 5. (i) PBr_3, C_6H_6, rt, 81%; (ii) DMAD, Zn, ultrasound or NaI, DMF, or Bu_4NI or KI, 18-crown-6.

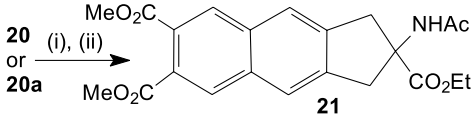
absorption bands at 3225, 1737 and 1654 cm^{-1}, indicating the presence of amino, ester and carbonyl functional groups, respectively. The M^+ peak at *m/z* 433 in its mass spectrum supported its structural formulation. The ^1H NMR spectrum of **18**, showed the absence of two hydroxyl protons. The two singlets at δ 4.65 and 6.03 are due to the methylene protons neighbouring the bromine atom and amide proton, respectively. It also exhibited a clear doublet at δ 3.25 ($J=16.8$ Hz) and another doublet at δ 3.61 ($J=16.8$ Hz) due to diastereotopic protons (H_a and H_b) present in the indane ring and a singlet at δ 7.21 accounts for aromatic protons. The 11-line ^{13}C NMR spectrum resonating indicated the symmetry present in the molecule **18**. Towards our objective, initially, various attempts to generate *o*-xylylene intermediate **19** from the corresponding dibromo derivative **18** were unsuccessful (Scheme 5).[27]

Next, the dibromo compound **18** was reacted with sodium hydroxy methanesulfinate (rongalite)[28] in presence of tetrabutylammonium bromide (TBAB) in DMF at 0 °C, the two isomeric sultine-based AAA derivatives **20** and **20a** were obtained in 72% combined yield (1:1) (Scheme 6). IR spectrum of the first isomer **20** (mp: 180–181 °C) showed absorption bands at 1453, 1169 cm^{-1} due to the presence of S=O and S–O functionalities suggesting the conversion of dibromide **18** into sultine derivative **20**. The absorption bands at 1668 and 1732 cm^{-1} are due to amide and ester carbonyl groups, respectively. The ^1H NMR spectrum of **20** showed doublets at δ 3.53 ($J=15.4$ Hz), δ 4.4 ($J=15.3$ Hz), δ 4.92 ($J=13.5$ Hz) and δ 5.27 ($J=13.2$ Hz) due to the presence of four diastereotopic protons in oxathiin-3-oxide (sultine) moiety. It further displayed an ABq at δ 3.30 (d, $J=16.8$ Hz) and δ 3.62 (d, $J=16.8$ Hz), due to diastereotopic $-CH_2$ protons (H_a and H_b) which are present in the indane ring system and singlets at δ 7.12 and 7.14 for the aromatic protons. The structure of compound **20** was further confirmed by its characteristic 16-line ^{13}C NMR spectrum and also supported the unsymmetrical nature of **20**. The ^{13}C NMR signals are assigned by reference to related literature examples.[29] The ^{13}C NMR spectrum of **20** showed two signals at δ 57.0 (CH_2S=O) and 63.9 (CH_2O-S) due to the presence of two characteristic carbons of oxathiin-3-oxide (sultine) moiety. The second isomer **20a** (mp: 198–199 °C) also displayed similar spectral parameters. Since these two isomers have very similar IR, ^1H NMR and ^{13}C spectra, it was not possible to assign the exact stereochemistry with the available data. Isomers **20** and **20a** are presumably diastereoisomers (each as a racemic mixture).



Scheme 6. (i) Rongalite, TBAB, DMF, 0 °C, 72%.

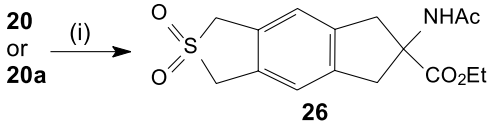
Having the sultines **20** and **20a** in hand, their DA chemistry with various dienophiles, was then explored. Subsequent oxidation of the DA adducts with DDQ[30] gave benzo-annulated derivatives (**21**–**25**). In a separate experiment both sultine derivatives **20** and **20a** were treated with dimethyl acetylenedicarboxylate (DMAD) in xylene at 120 °C to give the DA adduct which was contaminated with the aromatized product (Scheme 7). Therefore, isolation of the DA products was not attempted and they were treated with DDQ to give aromatized products **21**–**25**. In the ^1H NMR spectrum the presence of singlet at δ 7.67 and 8.11 are due to the presence of two different types of aromatic protons. The disappearance of four peaks at δ 3.53 ($J=15.4$ Hz), 4.4 ($J=15.3$ Hz), 4.92 ($J=13.5$ Hz) and 5.27 ($J=13.2$ Hz) indicated the absence of four diastereotopic protons in oxathiin-3-oxide (sultine) moiety and a strong absorption band at 1747 (C=O) cm^{-1} in the IR spectrum confirm the structure of **21**. The 13-line ^{13}C NMR spectrum resonating indicated the symmetry present in the molecule **21**.



Scheme 7. (i) DMAD, toluene, 120 °C; (ii) DDQ, C_6H_6, 80 °C, 78%.

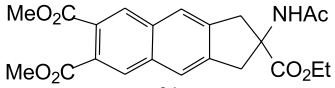
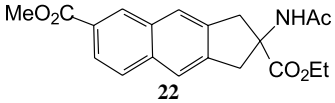
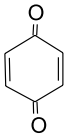
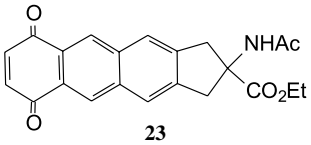
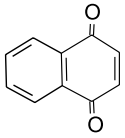
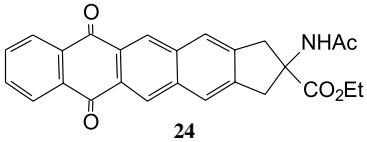
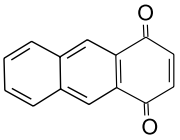
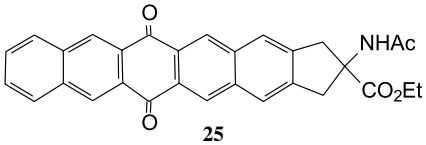
We were pleased to discover that the sultine **20** (or **20a**) on treatment with various dienophiles delivered highly functionalized indane derivatives, which on subsequent oxidation gave aromatized products. These products are characterized with the complementary spectral data (^1H and ^{13}C) and the results are summarized in Table 1.

During the DA sequence, we found that both the sultine derivatives **20** and **20a** gave the same sulphone **26** in refluxing toluene in the absence of a dienophile (Scheme 8).



Scheme 8. (i) Toluene, 120 °C, 88%.

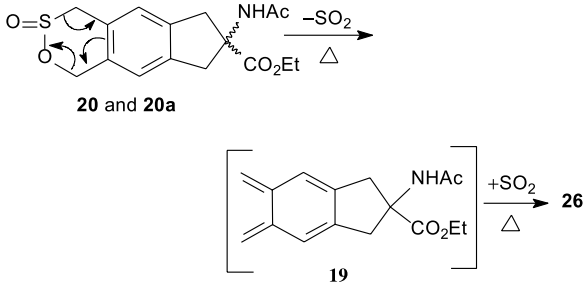
Table 1. List of various benzo-annulated indane-based AAA derivatives prepared by DA/DDQ oxidation strategy

S.No.	Dienophile	DDQ product	Yield[a] (%)
1		 **21**	78
2		 **22**	43
3		 **23**	90
4		 **24**	89
5		 **25**	92

[a] Yields refer to combined isolated yields for both the DA reaction and DDQ oxidation sequence.

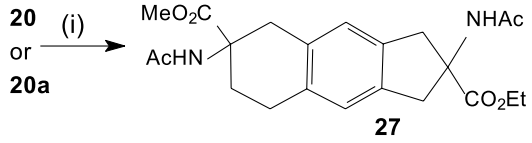
In the ^{1}H NMR spectrum of **26**, the methylene proton attached to the sulphone group appeared as a singlet at δ 4.32 and the M^+ peak at *m/z* 337 in its mass spectrum revealed its structural formulation. The 11-line ^{13}C NMR spectrum resonating indicated the symmetry present in the molecule **26**. In view of several functionalization reactions of sulfones,[31] availability of intermediate **26** can further expand the scope of the 'Building Block Approach'.[1]

A possible mechanism based on the earlier observation[32] for the formation of sulphone **26** from sultine derivatives **20** and **20a** under thermal condition is shown in Scheme 9. Under thermal conditions, retro Diels–Alder occurs to generate SO_2 and *o*-xylylene intermediate. Later on the in situ generated intermediate **19** react with SO_2 by a [4+1] cheletropic addition to form more stable sulphone **26**. Here, the formation of **19** is also supported by the formation of various DA products (**21**–**25**), which are shown in Table 1.



Scheme 9. Possible mechanism for the sulphone derivative **26**.

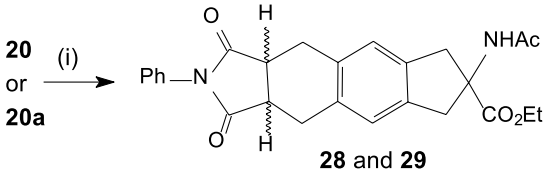
Next, the sultine **20** (or **20a**) was reacted with a dienophile such as methyl 2-acetamido acrylate at 120 °C in toluene to give the highly constrained bis AAA derivative **27**, in 33% isolated yield (Scheme 10).



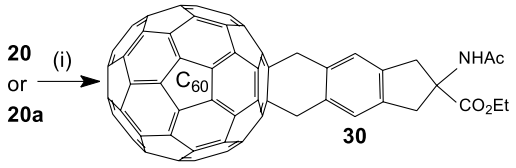
Scheme 10. (i) Methyl 2-acetamidoacrylate, 120 °C, 33%.

Along similar lines, the sultine **20** (or **20a**) was reacted with *N*-phenyl maleimide to give a pair of DA adducts **28** and **29** in 96% combined yield (Scheme 11). Both these compounds **28** (mp 162–164 °C) and **29** (mp 142–144 °C) gave almost identical ^{1}H, ^{13}C NMR and mass spectral data. Based on this data we concluded that they are diastereoisomeric compounds and stereochemistry of the individual isomers could not be determined.

In view of various applications of fullerene-based AAA derivatives in bioorganic chemistry,[33] we turned our



Scheme 11. (i) *N*-phenyl maleimide, toluene, 120 °C, 96% (combined).



Scheme 12. (i) C_{60}, toluene, 120 °C.

attention to incorporate the AAA moiety in fullerene system. For example the hydrophobic character and their ability to act as an electron sink make fullerene-based AAA derivatives an attractive building block for biological application. In this context sultine (or **20a**) was reacted with Buckminister fullerene (C_{60}) in toluene at reflux temperature to give the DA product **30** in 49% yield. The FAB mass spectral data (M+H, 994) of the DA product **30** is in agreement with the structure of the DA adduct **30** (Scheme 12).

4. Conclusions

General methods for cyclic AAA synthesis is an important stepping stone for the design of unnatural peptides and complex AAAs. In this respect, we have shown that *o*-xylylene derivative containing AAA moiety derived from sultine **20** (or **20a**) can be trapped with various dienophiles. It is worth mentioning that compounds, of the type **23**–**25**, are not accessible by the currently available BB method, due to the presence of the keto functionality. Moreover, the synthesis of the starting keto precursor required for BB method is not a trivial exercise. We believe that the methodology reported here can be extended to the synthesis of a new class of benzo-annulated AAA derivatives that may play an important role in combinatorial chemistry.

5. Experimental

5.1. General

Analytical thin layer chromatography (TLC) were performed on (10×5 cm) glass plate coated with Acme's silica gel G or GF 254 (containing 13% calcium sulfate as a binder). Visualization of the spots on TLC plate was achieved either by exposure to iodine vapor, or UV light. Flash chromatography was performed using Acme's silica gel (100–200 mesh) and the column was usually eluted by a ethyl acetate and petroleum ether mixture. Melting points are uncorrected. Infrared spectra (FT-IR) were recorded as KBr pellets unless otherwise mentioned. UV spectra were taken in dry chloroform as the solvent. Acetonitrile and carbon tetrachloride were distilled over phosphorous pentoxide. Dry THF and diethyl ether were obtained by distillation over sodium-benzophenone ketyl. For all the reactions, anhydrous magnesium sulfate was used as drying agent after worked up. Glycine ethyl ester hydrochloride, trimethylorthoformate, dimethyl acetylenedicarboxylate (DMAD), methyl propiolate, Wilkinson's catalyst, were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). Methyl 2-acetamidoacrylate was obtained from Lancaster Synthesis, Lancashire LA3 3BN, England (UK). ^{1}H and ^{13}C NMR samples were made in chloroform-d solvent and chemical shifts are reported in δ scale using tetramethylsilane as the internal standard. The standard abbreviation s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplets, respectively. 60 MHz ^{1}H NMR spectra were recorded on EM-300 spectrometer. 300, 400 MHz ^{1}H and 75.4, 100 MHz ^{13}C NMR spectra were recorded on Bruker spectrometer. Coupling constants (J) are in Hertz.

5.1.1. 2-Acetylamino-5,6-bis-bromomethyl-indane-2-carboxylic acid ethyl ester (18). To a stirred solution of the diol **17**[25] (800 mg, 2.6 mmol) in dry benzene (30 ml) was added phosphorous tribromide (1.6 g, 6.3 mmol) at 0 °C and the mixture was stirred at rt for 6 h. Then, the reaction mixture was poured into ice-cold water (40 ml) and then extracted with chloroform (3×100 ml). The combined organic extract was washed with water, brine, and then dried over magnesium sulfate. Evaporation of the solvent and purification of the crude product by a silica gel column using 30% ethyl acetate–hexane mixture as an eluent gave the dibromide **18** as colourless pellets (914 mg, 81%). Mp 172–174 °C. IR (KBr): ν_{max} 3225 (NH), 1737 (COOEt), 1654 (NCO) cm^{-1}. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 274 (1272), 243 (2764) nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.1 Hz, 3H), 1.96 (s, 3H), 3.25 (d, J=16.8 Hz, 2H), 3.61 (d, J=16.8 Hz, 2H), 4.22 (q, J=7.1 Hz, 2H), 4.65 (s, 4H), 6.03 (s, 1H), 7.21 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1, 23.2, 30.3, 43.2, 61.9, 65.9, 127.2, 135.6, 141.8, 170.2, 172.6. Anal.: for $C_{16}H_{19}NO_3Br_2$ Calcd: 44.36 (C), 4.42 (H), 3.23 (N)%; found: 44.57 (C), 4.43 (H), 3.01 (N)%.

5.1.2. 2-Acetylamino-7-oxo-1,2,3,5,7,8-hexahydro-6-oxa-7λ^6-thia-cyclopenta[b]naphthalene-2-carboxylic acid ethyl ester (20 and 20a). To a suspension of rongalite (710 mg, 0.43 mmol) in DMF (15 ml) was added dibromo compound **18** (200 mg, 0.46 mmol) and tetrabutylammonium bromide (TBAB) (148 mg, 0.43 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 3 h, and then at rt for 4 h. The reaction mixture was quenched with water (25 ml) and extracted with chloroform (3×150 ml), dried over magnesium sulfate and concentrated. The crude product was purified on a silica gel column. Elution with 60% ethyl acetate–hexane mixture gave the fast moving compound **20** as a white solid (56 mg, 36%). Mp: 180–181 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 240 (780), 276 (1092) nm. IR (KBr): ν_{max} 3324 (NH), 1732 (COOEt), 1668 (NCO), 1453, 1169 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.3 Hz, 3H), 1.95 (s, 3H), 3.30 (d, J=16.8 Hz, 2H), 3.53 (d, J=15.4 Hz, 1H), 3.62 (d, J=16.8 Hz, 2H), 4.22 (q, J=7.3 Hz, 2H), 4.40 (d, J=15.3 Hz, 1H), 4.92 (d, J=13.5 Hz, 1H), 5.27 (d, J=13.2 Hz, 1H), 6.11 (s, 1H), 7.12 (s, 1H), 7.14 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.2, 23.1, 43.2, 57.8, 61.7, 63.4, 65.7, 122.1, 125.5, 125.7, 133.1, 140.2, 141.1, 169.8, 172.6. HRMS (EI): m/z for $C_{16}H_{19}O_5S$ Calcd: (M+H): 338.1062; found: 338.1057.

Further elution of the column with the same solvent system gave **20a** as a white solid (56 mg, 36%). Mp: 198–199 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 240 (901), 276 (1224) nm. IR (KBr): ν_{max} 3329 (NH), 1735 (COOEt), 1658 (NCO), 1459, 1163 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.2 Hz, 3H), 1.95 (s, 3H), 3.27 (d, J=16.8 Hz,

2H), 3.54 (d, $J=15.3$ Hz, 1H), 3.63 (d, $J=16.8$ Hz, 2H), 4.21 (q, $J=7.2$ Hz, 2H), 4.31 (d, $J=15.2$ Hz, 1H), 4.92 (d, $J=13.5$ Hz, 1H), 5.23 (d, $J=13.5$ Hz, 1H), 6.15 (s, 1H), 7.07 (s, 1H), 7.10 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1, 23.0, 43.1, 43.2, 57.0, 61.8, 63.9, 65.8, 122.0, 124.8, 126.0, 132.5, 140.2, 140.8, 170.2, 172.6. HRMS (EI): *m/z* for $C_{16}H_{19}O_5S$ Calcd: (M+H): 338.1062; found: 338.1063.

5.2. General procedure for the DA reaction with sultine derivative with various dienophiles and subsequent DDQ oxidation of the DA adduct

A solution of the sultine (1 equiv) and dienophile (2–3 equiv) in toluene was refluxed until the starting materials have been disappeared. At the conclusion of the reaction (TLC monitoring), the solvent was removed at reduced pressure and the crude product was purified by silica gel column chromatography. Elution of the column with ethyl acetate/petroleum ether mixture gave the required DA adduct always mixed with small amount aromatized product. Subsequently, that DA adduct (1 equiv) and DDQ (1.5–2 equiv) in dry benzene was refluxed (22–48 h). The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with 2% KOH, water, brine, and dried with $MgSO_4$. The solvent was evaporated and the crude product was charged on a silica gel column. Elution of the column with ethyl acetate/petroleum ether mixture gave the desired product.

5.2.1. 2-Acetylamino-2,3-dihydro-1H-cyclopenta[b]-naphthalene-2,6,7-tricarboxylic acid ethyl ester dimethyl ester (21). A solution of the sultine **20** (15 mg, 0.04 mmol) and dimethyl acetylenedicarboxylate (DMAD) (20 mg, 0.14 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for 48 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave the required DA adduct (15 mg) as a semi-solid. Subsequently, the DA adduct and DDQ (22 mg, 0.08 mmol) in dry benzene (2 ml) was refluxed for 48 h. At the conclusion of reaction (TLC monitoring), the reaction mixture was worked up according to the general procedure. The crude product was purified by a silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave the desired product **21** (14.4 mg, 78%) as a semi-solid. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 254 (12,906) nm. IR (KBr): ν_{max} 3321 (NH), 1737 (COOR), 1631 (NCO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, $J=6.9$ Hz, 3H), 1.95 (s, 3H), 3.49 (d, $J=16.8$ Hz, 2H), 3.71 (d, $J=16.8$ Hz, 2H), 3.94 (s, 6H), 4.21 (q, $J=6.9$ Hz, 2H), 6.11 (s, 1H), 7.67 (s, 2H), 8.11 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.2, 23.2, 42.8, 52.6, 61.8, 66.1, 123.6, 128.2, 129.7, 133.2, 142.3, 168.0, 172.6. HRMS (EI): *m/z* for $C_{22}H_{23}NO_7$ Calcd: (M+H): 414.1552; found: 414.1548.

5.2.2. 2-Acetylamino-2,3-dihydro-1H-cyclopenta[b]-naphthalene-2,6,-dicarboxylic acid 2-ethyl ester 6-methyl ester (22). A solution of the sultine **20** (14 mg, 0.04 mmol) and methyl propiolate (17.5 mg, 0.20 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for 24 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by silica gel column chromatography. Elution of the column with 40% ethyl acetate/petroleum ether mixture gave the required DA adduct (6.5 mg) as a semi-solid. Subsequently, the DA adduct and DDQ (6 mg, 0.05 mmol) in dry benzene (2 ml) was refluxed for 48 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was worked up according to the general procedure. The crude product was purified by a silica gel column chromatography. Elution of the column with 40% ethyl acetate/petroleum ether gave the desired product **22** (6.4 mg, 43%) as a white solid. Mp: 102–104 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 250 (10,533), 288 (6021) nm. IR (KBr): ν_{max} 3428 (NH), 1729 (COOR), 1650 (NCO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, $J=7.3$ Hz, 3H), 1.95 (s, 3H), 3.49 (dd, $J=16.8$, 5.1 Hz, 2H), 3.71 (dd, $J=17.2$, 7.1 Hz, 2H), 3.97 (s, 3H), 4.23 (q, $J=7.3$ Hz, 2H), 6.0 (s, 1H), 7.69 (s, 1H), 7.75 (s, 1H), 7.8 (d, $J=8.4$ Hz, 1H), 8.0 (dd, $J=8.4$, 1.5 Hz, 1H), 8.53 (s, 1H). HRMS (EI): *m/z* for $C_{20}H_{21}NO_5$ Calcd: (M+H): 356.1497; found: 356.1495.

5.2.3. 2-Acetylamino-6,9-dioxo-2,3,6,9-tetrahydro-1H-cyclopenta[b]anthracene-2-carboxylic acid ethyl ester (23). A solution of the sultine **20** (20 mg, 0.059 mmol) and 1,4-benzoquinone (12.8 mg, 0.12 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for 14 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by a silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave the required DA adduct (20.5 mg) as a yellow solid. Subsequently, the DA adduct and DDQ (15.5 mg, 0.07 mmol) in dry benzene (2 ml) was refluxed for 30 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was worked up according to the general procedure. The crude product was purified by a silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave the desired product **23** (20 mg, 90%) as a yellow solid. Mp: >290 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 250 (20,416), 300 (18,053), 420 (5771) nm. IR (KBr): ν_{max} 3321 (NH), 1737 (COOR), 1668 (CO), 1629 (NCO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, $J=7.1$ Hz, 3H, ester CH_3), 1.98 (s, 3H, $NCOCH_3$), 3.55 (d, $J=17.4$ Hz, 2H), 3.77 (d, $J=17.4$ Hz, 2H), 4.23 (q, $J=7.1$ Hz, 2H), 6.16 (s, 1H), 7.04 (s, 2H), 7.85 (s, 2H), 8.52 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.0, 23.2, 42.0, 62.0, 65.9, 125.1, 127.9, 128.3, 134.6, 143.7, 139.9, 170.3, 172.5, 184.7. HRMS (EI): *m/z* for $C_{22}H_{19}O_5N$ Calcd: (M+H): 378.1341; found: 378.1334.

5.2.4. 2-Acetylamino-6,11-dioxo-2,3,6,11-tetrahydro-1H-cyclopenta[b]naphthacene-2-carboxylic acid ethyl ester (24). A solution of the sultine **20** (20 mg, 0.059 mmol) and 1,4-naphthoquinone (13.0 mg, 0.12 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for 14 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by a silica gel column chromatography. Elution of column with 50% ethyl acetate/petroleum ether gave the required DA adduct (17.5 mg) as a yellow solid. Subsequently, the DA adduct and DDQ (26.0 mg, 0.114 mmol) in dry benzene (2 ml) was refluxed for 48 h. At the

conclusion of reaction (TLC monitoring), the reaction mixture was worked up according to the general procedure. The crude product was purified by a silica gel column chromatography. Elution of column with 50% ethyl acetate/petroleum ether gave the desired product **24** (17 mg, 89%) as a yellow solid. Mp: 300–302 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 248 (38,982), 302 (32,233), 400 (4116) nm. IR (KBr): ν_{max} 3319 (NH), 1726 (COOR), 1665 (CO), 1621 (NCO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.3 Hz, 3H), 1.99 (s, 3H), 3.56 (d, J=17.2 Hz, 2H), 3.78 (d, J=17.2 Hz, 2H), 4.24 (q, J=7.2 Hz, 2H), 6.16 (s, 1H), 7.81–7.85 (m, 2H), 7.88 (s, 2H), 8.37–8.41 (m, 2H), 8.75 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.0, 23.2, 42.8, 62.0, 66.0, 125.0, 127.4, 129.0, 129.4, 134.1, 134.4, 135.0, 143.5, 170.3, 172.5, 184.7. HRMS:(EI) *m/z* for $C_{26}H_{21}O_5N$ Calcd: (M+H): 428.1497; found: 428.1499.

5.2.5. 2-Acetylamino-6,13-dioxo-2,3,6,13-tetrahydro-1H-cyclopenta[b]pentacene-2-carboxylic acid ethyl ester (25). A solution of the sultine **20** (15 mg, 0.044 mmol) and 1,4-anthraquinone (18.5 mg, 0.089 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for 24 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by a silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave the required DA adduct (22 mg) as a yellow solid. Subsequently, the DA adduct and DDQ (16.8 mg, 0.75 mmol) in dry benzene (2 ml) was refluxed for 48 h. At the conclusion of reaction (TLC monitoring), the reaction mixture was worked up according to the general procedure. The crude product was purified by a silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave the desired product **25** (19.5 mg, 92%) as a yellow solid. Mp: 216–218 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 248 (14,653), 306 (17,722), 410 (2443) nm. IR (KBr): ν_{max} 3328 (NH), 1736 (COOR), 1670 (CO), 1626 (NCO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J=7.3 Hz, 3H), 1.99 (s, 3H), 3.57 (d, J=17.2 Hz, 2H), 3.79 (d, J=17.2 Hz, 2H), 4.24 (q, J=7.2 Hz, 2H), 6.11 (s, 1H), 7.70–7.73 (m, 2H), 7.92 (s, 2H), 8.12–8.15 (m, 2H), 8.86 (s, 2H), 8.94 (s, 2H). FAB-MS (EI): *m/z* 419 (M-NHAc), 441 (M−NHAc+Na+H).

5.2.6. 6-Acetylamino-2,2-dioxo-1,2,3,5,6,7-hexahydro-2λ^6-thia-*s*-indacene-6-carboxylic acid ethyl ester (26). A solution of the sultine **20** (20 mg, 0.059 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for 24 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by a silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave the required compound **26** (14 mg, 88%) as a white solid. Mp: 210–211 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 278 (1905) nm. IR (KBr): ν_{max} 3440 (NH), 1689 (COOEt), 1629 (NCO), 1428, 1137 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, J=7.3 Hz, 3H), 1.97 (s, 3H), 3.31 (d, J=16.8 Hz, 2H), 3.60 (d, J=16.8 Hz, 2H), 4.23 (q, J=7.1 Hz, 2H), 4.32 (s, 4H), 6.03 (s, 1H), 7.14 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.0, 23.1, 43.1, 56.8, 61.9, 65.6, 122.1, 129.8, 141.1, 170.1, 172.6. MS (EI): *m/z* 437 (M^+). Anal.: for $C_{16}H_{19}SNO_5$ Calcd: 56.95 (C), 5.68 (H), 4.16 (N)%; found 57.20 (C), 5.79 (H), 3.69 (N)%.

5.2.7. 2,6-Bis-acetylamino-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalene-2,6,-dicarboxylic acid 2-ethyl ester 6-methyl ester (27). A solution of the sultine **20** (20 mg, 0.059 mmol) and methyl 2-acetamidoacrylate (17 mg, 0.2 mmol) in dry toluene (3 ml) was stirred at 120 °C in a sealed tube for 14 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by a silica gel column chromatography. Elution of the column with 60% ethyl acetate/petroleum ether gave the required DA adduct **27** (8 mg, 33%) as a white solid. Mp: 208–210 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 246 (32,956) nm. IR (KBr): ν_{max} 3303 (NH), 1750 (COOR), 1626 (NCO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.3 Hz, 3H), 1.93 (s, 3H), 1.95 (s, 3H), 1.99–2.16 (m, 1H), 2.51–2.56 (m, 1H), 2.74–2.94 (m, 3H), 3.20–3.28 (m, 3H), 3.56 (dd, J=16.8, 5.54 Hz, 2H), 3.76 (s, 3H), 4.21 (q, J=7.1 Hz, 2H), 5.69 (s, 1H), 6.13 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H). HRMS (EI): *m/z* for $C_{22}H_{28}NO_6$ Calcd: (M+H): 417.2025; found: 417.2022.

5.2.8. 7-Acetylamino-1,3-dioxo-2-pheny1,2,3,3a,4,6,7,8,10,10a-decahydro-2-aza-dicyclopenta[b,g]naphthalene-7-carboxylic acid ethyl ester (28 and 29). A solution of the sultine **20** (20 mg, 0.059 mmol) and *N*-phenyl maleimide (20 mg, 0.115 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for 12 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by a silica gel column chromatography. Elution of the column with 50% ethyl acetate/petroleum ether gave a fast moving DA adduct **28** (13 mg, 46%) as a white solid. Mp: 162–164 °C. UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 244 (1727), 274 (1826) nm. IR (KBr): 3317 (NH), 1734 (COOEt), 1668 (NCO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J=7.2 Hz, 3H), 1.93 (s, 3H), 2.93–2.98 (m, 2H), 3.17 (d, J=16.8 Hz, 2H), 3.19–3.24 (m, 2H), 3.44–3.45 (m, 2H), 3.59 (d, J=16.8 Hz, 2H), 4.20 (q, J=7.2 Hz, 2H), 5.91 (s, 1H), 6.93 (dd, J=7.9, 1.5 Hz, 2H), 7.03 (s, 2H), 7.28–7.38 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.1, 23.1, 30.0, 40.2, 43.2, 61.6, 65.9, 124.1, 126.1, 127.2, 128.5, 128.9, 133.8, 139.0, 170.0, 172.6, 178.5. HRMS (EI): *m/z* for $C_{26}H_{26}O_5N_2$ Calcd: (M+H): 447.1919; found: 447.1908.

Further elution of the column with the same solvent system gave another DA adduct **29** as a white solid (13 mg, 36%). Mp: 142–144 °C UV ($CHCl_3$): λ_{max} (ε M^{-1} cm^{-1}) 246 (1657), 274 (1808) nm. IR (KBr): ν_{max} 3321 (NH), 1732 (COOEt), 1667 (NCO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, J=7.3 Hz, 3H), 1.94 (s, 3H), 2.92–2.96 (m, 2H), 3.21 (d, J=16.8 Hz, 2H) 3.20–3.25 (m, 2H), 3.44–3.46 (m, 2H), 3.57 (d, J=16.8 Hz, 2H), 4.19 (q, J=7.3 Hz, 2H), 6.01 (s, 1H), 6.89 (dd, J=8.0, 1.8 Hz, 2H), 7.04 (s, 2H), 7.30–7.38 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.0, 23.2, 30.0, 40.2, 43.2, 61.6, 65.9, 124.1, 126.3, 128.5, 129.0, 131.6, 133.8, 139.1, 170.0, 172.8, 178.5. HRMS (EI): *m/z* for $C_{26}H_{26}O_5N_2$ Calcd: (M+H): 447.1919; found: 447.1915.

5.2.9. DA adduct of 2-acetylamino-2,2-dioxo-1,2,3,5,6,7-hexahydro-2λ^6-thia-*s*-indacene-6-carboxylic acid ethyl ester (20 and 20a) with C_{60} (30). A solution of the sultine **20** (14 mg, 0.041 mmol) and C_{60} (30 mg, 0.041 mmol) in dry toluene (2 ml) was stirred at 120 °C in a sealed tube for

10 h. At the conclusion of reaction (TLC monitoring), the solvent was removed at reduced pressure. The crude product was purified by a silica gel column chromatography. Elution of column with 25% ethyl acetate/petroleum ether gave the DA adduct **30** (20.4 mg, 49%) as a black solid. Mp: 246 °C. UV ($CHCl_3$): λ_{max} (ε $M^{-1}\,cm^{-1}$) 260 (44,760) nm. IR (KBr): ν_{max} 3423 (NH), 1723 (COOEt), 1648 (NCO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (brs, 3H), 2.03 (s, 3H), 3.47 (d, $J=16.0$ Hz, 2H), 3.79 (d, $J=16.0$ Hz, 2H), 4.26 (q, $J=7.3$ Hz, 2H), 4.40 (d, $J=14.1$ Hz, 2H), 4.78 (d, $J=14.2$ Hz, 2H), 6.14 (s, 1H), 7.51 (s, 2H). FAB-MS (EI): *m/z* 994 (M+H), 1017 (M+Na+H).

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Aluminum dodecatungstophosphate ($AlPW_{12}O_{40}$) as a non-hygroscopic Lewis acid catalyst for the efficient Friedel–Crafts acylation of aromatic compounds under solvent-less conditions

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Abstract—Stable and non-hygroscopic aluminum dodecatungstophosphate ($AlPW_{12}O_{40}$), which is prepared easily from cheap and commercially available compounds was found to be an effective catalyst for Friedel–Crafts acylation reactions using carboxylic acids, acetic anhydride and benzoyl chloride in the absence of solvent under mild reaction conditions.

1. Introduction

Heteropolyacids (HPAs) show very high catalytic activity for some acid-catalyzed reactions. They have been used for hydration of alkenes[1–3] and polymerization of tetrahydrofuran.[4–6] Strong Brønsted acidity[7,8] and the softness of the heteropoly anions are responsible for their high catalytic activities in these reactions.[9] HPAs are usually solids that are insoluble in non-polar solvents but highly soluble in polar ones. The use of HPAs in non-polar solvents improves product selectivity and also provides easy separation of them.[4] Heterogeneous catalysis has become attractive in view of the increasingly strict environmental legislation, in view of their isolation and separation from the reaction media. Solid acid catalysts are harmless to the environment with respect to corrosiveness, safety, quantity of waste, and separability with certainly some exceptions.

Cesium salts of HPAs are good examples of active and useful solid acid catalysts. They exhibit an excellent performance in several organic reactions owing to their high surface acidity and also probably to their unique basicity.[10,11] The catalytic activities of solid acids are usually suppressed significantly in the presence of water. Hence, although H-ZSM-5 has a high Si:Al ratio is known to have fair tolerance in aqueous solutions.[12] It has been demonstrated that the acidic cesium salts of HPAs are very water-tolerant catalysts for hydration of olefins[13] and hydrolysis of esters.[14] This nature was assigned to moderate hydrophobicity of the catalysts.[15]

We have recently started to study new catalytic applications of heteropoly acids in organic reactions.[16a–h]

Friedel–Crafts acylation of aromatic compounds is the most important and practical route for the synthesis of aromatic ketones that are used in manufacturing of fine chemicals as well as pharmaceuticals.[17] The acylating agents for the synthesis of aromatic ketones by Friedel–Crafts reactions are mostly acid anhydrides or acyl chlorides. For this purpose, varieties of catalysts have been reported.[18,19] A literature survey indicates that the use of carboxylic acids, as acylating agents, are scarcely reported.[20] Using carboxylic acids as acylating agents is a superior method with respect to the procedures utilizing acyl chlorides and anhydrides for the preparation of aryl ketones. Carboxylic acids are stable and more available compounds and their handlings are much easier than their corresponding acyl chlorides and anhydrides.

Now, we introduce aluminum dodecatungstophosphate ($AlPW_{12}O_{40}$) as a stable, non-hygroscopic, easily available, cheap and highly effective catalyst for Friedel–Crafts acylation of aromatic compounds using carboxylic acids, acetic anhydride and benzoyl chloride as acylating agents.

Keywords: Freidel–Crafts acylation; Poly oxometalate; Aluminum dodecatungstophosphate; Solvent-free.
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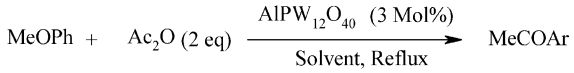
2. Results and discussion

2.1. Acylation of aromatic compounds with acetic anhydride catalyzed by $AlPW_{12}O_{40}$

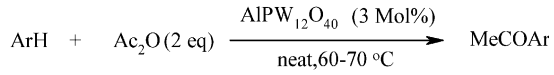
The reaction of acetic anhydride and aromatic compounds by Friedel–Crafts acylation reactions is the most practical route for the synthesis of methyl aryl ketones. Investigation of the application of $AlPW_{12}O_{40}$ as an easily available, cheap and non-hygroscopic Lewis acid for this purpose is of practical importance. In order to optimize the reaction conditions, acylation of anisole with acetic anhydride in the presence of different molar ratios of $AlPW_{12}O_{40}$ and various solvents were studied (Scheme 1).



Scheme 1.

The results of this investigation are shown in Table 1. The results indicate that the most suitable solvent for this purpose is *n*-hexane in which the catalyst reacts under completely heterogeneous conditions and the best result was obtained when no solvent was used.

The optimum ratio of the catalyst was found to be 3 mol% with respect to anisole for the reaction conducted in *n*-hexane or solvent-less conditions. The optimized molar ratio of acetic anhydride was found to be 2 mol equivalents with respect to 1 mol equivalent of anisole under similar reaction conditions (Scheme 2).



Scheme 2.

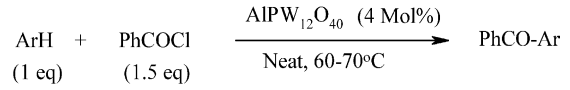
This reaction condition was applied for the preparation of different aryl ketones from electron rich aromatic compounds with success. The results of this study are tabulated in Table 2.

In order to show the efficiency and the catalytic activity of $AlPW_{12}O_{40}$ for the acylation of anisole with acetic anhydride, we have tabulated our results in Table 3 with some other recently used Lewis acids such as $Sc(OTf)_3$, $Bi(OTf)_3$ and $In(OTf)_3$.

The results show that aluminum dodecatungstophosphate is a more efficient and more effective catalyst than the triflates used for similar reaction and also does not require aqueous workup which makes the process of the isolation of the product much easier and not a time-consuming process.

2.2. Benzoylation of aromatic compounds with benzoyl chloride in the presence of $AlPW_{12}O_{40}$

We have studied optimization of the reaction conditions for the benzoylation of anisole under solvent-free conditions (Scheme 3).



Scheme 3.

It was found that the reaction was complete after 2 h by using of 4 mol% of the catalyst at 60–70 °C to produce *ortho* and *para* isomers (1:4 ratio). We applied similar reaction conditions for the preparation of other aryl ketones using different aromatic compounds. The reactions proceeded well and the desired products were isolated in excellent yields (Table 4). We have observed that the rate of acylation and benzoylation of 1,3-dimethoxy benzene was slower than anisole. Para acylation or benzoylation of anisole do not encounter that much steric resistance against the approach of bulky Lewis acid complex and acylium ions from the para position. However, in 1,3-dimethoxy benzene the situation is quiet different and the bulky complex should only approach from the ortho position of OMe groups which encounters ortho steric effects. This effect causes retardation in the rates of the reactions. Bezoylation of anthracene under solvent-free conditions was sluggish in the presence of this catalyst and gave a low yield. However, 9-benzoylanthracene was isolated in 88% yield when the reaction in *n*-hexane was heated under reflux conditions. We also applied similar reaction conditions for benzoylation of naphthalene. This reaction was not successful and a mixture of 1 and 2 substituted benzoyl naphthalenes in low yields plus unreacted starting material was isolated. Benzoylation of benzene under similar reaction conditions failed. However, this reaction was successful in a sealed tube at 120 °C overnight with 10 mol% of $AlPW_{12}O_{40}$ (97% GC yield).

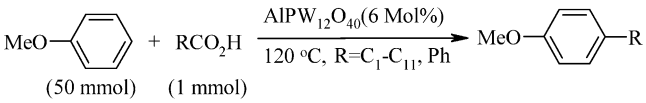
2.3. Direct acylation of anisole with carboxylic acids in the presence of $AlPW_{12}O_{40}$ as a reusable catalyst

We have also studied acylation of anisole with carboxylic acids in the presence of 6 mol% of $AlPW_{12}O_{40}$ at 120 °C (Scheme 4).

Table 1. Effect of solvents upon Friedel–Crafts acylation of anisole catalyzed by $AlPW_{12}O_{40}$

Entry	Solvent	Temp. (°C)	*T* (h)	Conv. (%)[a]
1	CH_2Cl_2	40	5	63
2	$CHCl_3$	62	3	76
3	CH_3CN	82	3	38
4	CH_3NO_2	100	4	63
5	*n*-Hexane	69	2.5	93
6	None	60	1	100

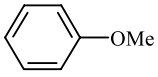
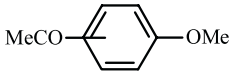
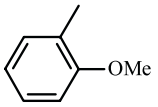
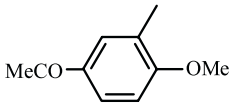
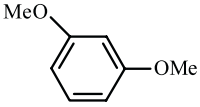
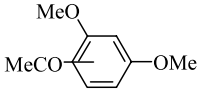
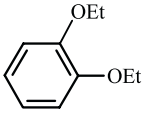
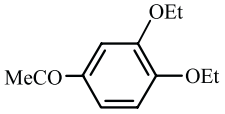
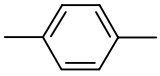
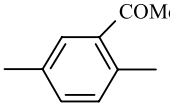
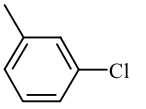
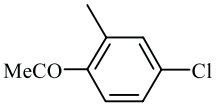
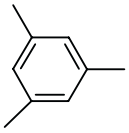
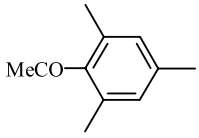
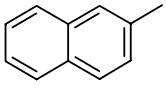
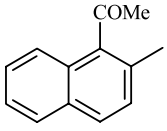
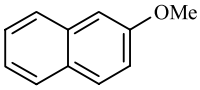
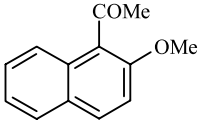
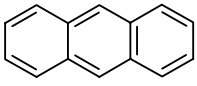
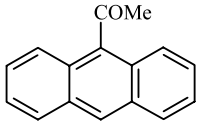
[a] Conversion was determined by GC analysis.



Scheme 4.

This acylation was carried out with different carboxylic acids (C_2–C_{12}) in good yields (Table 5). In this study, it was observed that by increasing the chain length of the carboxylic acids from C_2 to C_{12} the regioselectivity of the reactions increased and *p*-isomers were mostly produced. We have not also observed any ester formation in any of the reactions we conducted in the presence of $AlPW_{12}O_{40}$. We have found that this catalyst is reusable for these reactions and can be easily recovered from the reaction mixture by simple filtration followed by washing the mixture by *n*-hexane/EtOAc (1:1). Drying of the catalyst was performed at 120 °C under vacuum overnight. We have used the recovered catalyst for the reaction of anisole with hexanoic acid with success five times without noticeable change in its catalytic activity. In Table 6, the results are compiled in order to show the effectiveness of $AlPW_{12}O_{40}$ with respect to the recently reported catalysts $Cs_{2.5}H_{0.5}PW_{12}O_{40}$ and HZSM-5 for acylation of anisole with different carboxylic acids. The results show that $AlPW_{12}O_{40}$ promotes the reactions more effectively than the reported catalysts.

Table 2. Acylation of aromatic compounds with acetic anhydride catalyzed by $AlPW_{12}O_{40}$

Entry	ArH	Time (h)	Product	Yield[a] (%)	Ref.
1		0.75		94 (*Ortho*:*Para*=12:88)	18p,t
2		0.25		95	18k,y
3		2		88[b]	18k
4		0.6		93	19a
5		6		91	18n
6		2.5		92[c]	18f
7		5.5		90	18l
8		4		85	18j
9		1.6		91	18i
10		2.6		90[d]	18i

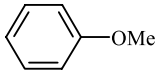
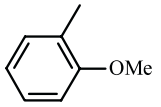
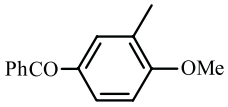
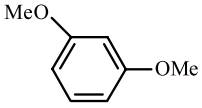
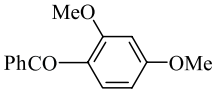
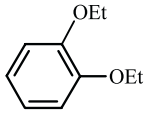
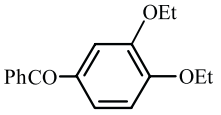
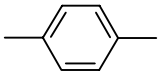
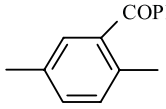
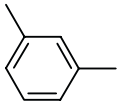
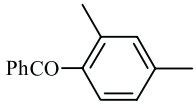
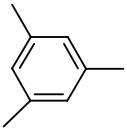
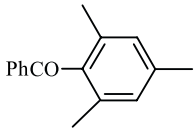
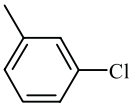
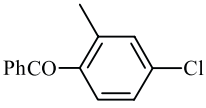
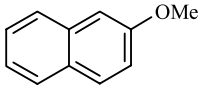
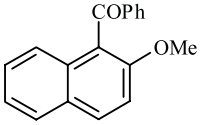
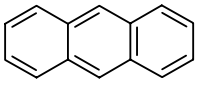
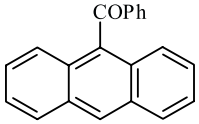
[a] Isolated yields and the purity of the products were determined by ^1H NMR spectroscopy and the ratio of the isomers was determined by GC.
[b] 2,6-Dimethoxyacetophenone was also detected in 12% yield.
[c] Other regioisomers were detected in 8%.
[d] Ac_2O (4 equiv/mol) was used.

Table 3. Comparison of the results used for the acylation of anisole with acetic anhydride catalyzed by $AlPW_{12}O_{40}$ and some other catalysts

Entry	Catalyst	Mol%	Temp. (°C)	*T* (h)	Yield (%)	Ref.
1	$Sc(OTf)_3$	20	50	18	99	18l
2	$Sc(OTf)_3$	20	50	2[a]	90	18n
3	$Bi(OTf)_3$	5	50	2	80	18p
4	$In(OTf)_3$	1	50	1[b]	96	18w
5	$AlPW_{12}O_{40}$	3	60	0.8	94	—[c]

[a] 2 equiv of $LiClO_4$ was used as an additive.
[b] 1 equiv of $LiClO_4$ was used as an additive.
[c] Results are shown in Table 2.

Table 4. Benzoylation of aromatic compounds with benzoyl chloride catalyzed by $AlPW_{12}O_{40}$

Entry	ArH	Time (h)	Product	Yield[a]	Ref.
1		2		94 (*Ortho*:*Para*=1:4)	18p,t
2		1		97	18k
3		3.5		90[b]	18d
4		2		90	19b
5		4.5		91	18u
6		3.5		92[c]	18q,v
7		2.5		91	18q
8		3		92[d]	18f
9		1.7		94	18a
10		4		88[e]	18x

[a] Isolated yields and the purity of the products were determined by ^1H NMR spectroscopy and the ratio of the isomers was determined by GC.
[b] Formation of 2,6-dimethoxybenzophenone was detected in 10%.
[c] Formation of 2,6-dimethylbenzophenone was detected in 8%.
[d] Other regioisomers were detected in 7%.
[e] Reaction was carried out in 2 mL of *n*-hexane under reflux conditions.

Table 5. Acylation of anisole with carboxylic acids catalyzed by reusable $AlPW_{12}O_{40}$ at 120 °C[a]

Entry	Acid	Time (h)	Yield (%)[b] Ref. [20b]
1	Acetic	3	85[c]
2	Propionic	3.5	88[d]
3	Butyric	5	87
4	Hexanoic	3	0[e]
5	Hexanoic	1.5	91
6	Octanoic	4	85
7	Dodecanoic	8	90
8	Benzoic	10	92

[a] The catalyst was filtered, washed with *n*-hexane: ethyl acetate, dried at 120 °C/(−20) Torr/overnight and reused.
[b] Isolated yield based on carboxylic acid conversion determined by ^1H NMR spectroscopy and GC analysis.
[c] 12% regioisomer was determined.
[d] 8% regioisomer was detected.
[e] Reaction was carried out in the presence of 1 g silica gel.

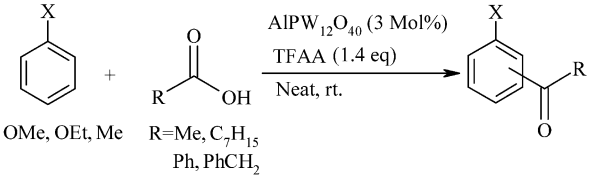
Table 6. Comparison of some of the results obtained using $AlPW_{12}O_{40}$ with some other catalysts used for acylation of anisole with carboxylic acids[a]

Acid	Cat.	Yield (%) (*para*-product)
Acetic	HZSM-5	0.025
	40%CsPW/SiO_2	62
	$AlPW_{12}O_{40}$	73
Hexanoic	HZSM-5	19.92
	40%CsPW/SiO_2	63.2
	$AlPW_{12}O_{40}$	91
Octanoic	HZSM-5	4
	40%CsPW/SiO_2	32.9
	$AlPW_{12}O_{40}$	85
Dodecanoic	HZSM-5	0
	40%CsPW/SiO_2	24.8
	$AlPW_{12}O_{40}$	91

[a] The results were extracted from Ref. 20b,c.

2.4. Acylation of aromatic compounds with carboxylic acids in the presence of trifluoroacetic anhydride catalyzed with $AlPW_{12}O_{40}$ at room temperature

In this part of our studies, we have found that with 3 mol% of $AlPW_{12}O_{40}$ in the presence of trifluoroacetic anhydride (1.4 equiv) acylation of anisole proceeded easily in 0.25 h in an excellent yield (Scheme 5).



Scheme 5.

In order to show the effect of the catalyst in this reaction, we performed acylation of anisole with acetic acid in the presence of trifluoroacetic anhydride (1.4 equiv) at room temperature in the absence of the catalyst. We have observed that the corresponding ketone was produced in 88% yield (GC) after 4 h (Table 7, entry 1) whereas the desired ketone was isolated in 94% yield after 0.25 h in the presence of the catalyst (Table 7, entry 2). We also tried the reaction of anisole with TFAA in the presence of the catalyst. We observed that the reaction did not proceed at all even after 24 h. We have found that this is a general method and can be applied easily to a wide range of liquid and crystalline carboxylic acids. Therefore, acylation of anisole was conducted with acetic acid, octanoic acid, phenyl acetic acid and benzoic acid in the presence of $AlPW_{12}O_{40}$ (3 mol%) and trifluoroacetic anhydride in excellent yields (Table 7, entries 1–5). 2-Methylanisole was also acylated with these acids in the presence of this catalyst and the anhydride in excellent yields (90–96%) with high regioselectivity (Table 7, entries 9–12). 1,2-Diethoxybenzene reacted with the above acids under similar reaction conditions to give the desired compounds as the sole products of these reactions in 91–94% yields (Table 7, entries 13–16). We also tried acylation of anthracene with acetic acid, phenyl acetic acid and benzoic acid. The reactions were slow and needed higher temperatures therefore, the reactions were performed at 50 °C and the desired ketones were isolated in 69–78% yields (Table 7 entries 17–19). The reaction of 2-methylnaphthalene with acetic acid was also conducted at 50 °C in the presence of the catalyst and trifluoroacetic anhydride. This reaction was sluggish and after prolonged reaction times the desired ketone was isolated in only 53% yield (Table 7 entry 20). The reaction of 2-methoxynaphthalene with acetic acid, octanoic acid, phenyl acetic acid and benzoic acid went smoothly at room temperature in excellent yields (Table 7, entries 21–24). Acylation of furan and pyrrole is not a straightforward reaction and usually in the presence of acid catalysts undergo polymerization reactions. We found that $AlPW_{12}O_{40}$ is a suitable catalyst for such important acylation reactions.

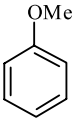
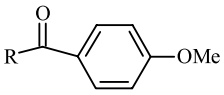
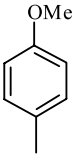
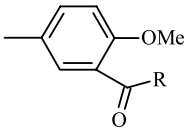
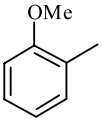
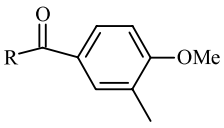
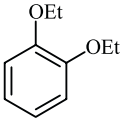
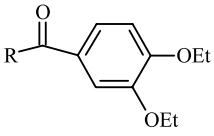
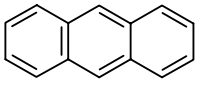
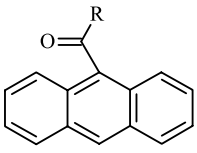
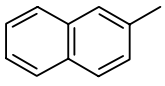
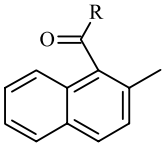
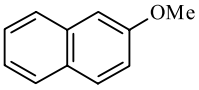
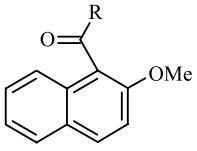
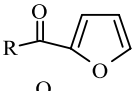
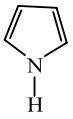
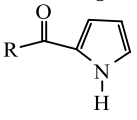
Acylation of furan with acetic acid, phenyl acetic acid and benzoic acid was conducted in the presence of TFAA and $AlPW_{12}O_{40}$ at 0 °C successfully in 94–98% isolated yield (Table 7, entries 25–27).

Acylation of pyrrole also conducted smoothly in the presence of TFAA, $AlPW_{12}O_{40}$ with acetic and benzoic acids at −23 °C. The desired pyrrole ketones were isolated in 92–98% yield (Table 7, entry 28–29). The formation of any polymeric materials was not observed in these reactions.

3. Conclusion

$AlPW_{12}O_{40}$ is a cheap, easily available, non-hygroscopic, heterogeneous, non-corrosive and environmentally benign compound. In this work it has been used as an effective catalyst for the efficient preparation of ketones via Friedel–Crafts acylation reactions with acetic anhydride, benzoyl chloride and with a range of easily available caboxylic acids in the presence of triflouroacetic anhydride. This general method can be applied easily to a wide range of liquid and crystalline carboxylic acids. The method has many advantages such as cheapness and availability of reactants and also non-aqueous and easy work-up of the reaction due to the heterogeneous conditions. The isolation of products was easily accomplished by a simple extraction and evaporation of the organic solvent.

Table 7. $AlPW_{12}O_{40}$ catalyzed acylation of aromatic compounds with compounds with carboxylic acids in the presence of trifluoroacetic anhydride

Entry	ArH	RCO_2H	Product	Time (h)	Yield (%)[a]	Ref.
1		R=Me		4	88[b,c]	18p,t
2		R=Me		0.25	94[c]	18p,t
3		$R=C_7H_{15}$		1.5	91	20b,d
4		$R=PhCH_2$		2	94	18w
5		R=Ph		2.5	96	18p,t
6		R=Me		2	97	18y
7		$R=PhCH_2$		2.5	90	18c
8		R=Ph		3.75	91	18k
9		R=Me		0.12	96	18y
10		$R=PhCH_2$		0.4	92	18c
11		$R=C_7H_{15}$		0.34	93	—
12		R=Ph		0.75	90	18k
13		R=Me		0.65	93	19a
14		$R=C_7H_{15}$		1.5	94	—
15		$R=PhCH_2$		2.5	91	—
16		R=Ph		3.5	91	19b
17		R=Me		2.5	78[d]	18i
18		$R=PhCH_2$		10	71[d]	18b
19		R=Ph		8.5	69[d]	18x
20		R=Me		2	53[e]	18j
21		R=Me		0.25	98	18i
22		$R=C_7H_{15}$		0.34	95	18m
23		$R=PhCH_2$		2	90	18m
24		R=Ph		8	88	18a
25		R=Me		1.25	94[f]	18n
26		$R=PhCH_2$		1.5	95[f]	19c
27		R=Ph		2.5	98[f]	18g
28		R=Me		0.25	92[g,h]	18h
29		R=Ph		0.4	98[g]	18h

[a] Isolated yields and the purity of the products were determined by ^1H NMR spectroscopy, ^{13}C NMR spectroscopy and GC.
[b] Reaction was performed without using $AlPW_{12}O_{40}$.
[c] 8% of regioisomer was detected.
[d] Reaction was carried out in 2 mL *n*-hexane at 50 °C.
[e] Reaction was carried out at 50 °C.
[f] Reaction was carried out at 0 °C with 2 equiv of furan.
[g] Reaction was carried out in 2 mL *n*-hexane at −23 °C.
[h] 8% 3-acetyl pyrrole was detected by GC.

4. Experimental

4.1. General remarks

Chemicals were purchased from Fluka or Merck and $AlPW_{12}O_{40}$ was prepared from $H_3PW_{12}O_{40}$ and aluminium nitrate according to the literature method.[21] Aromatic compounds, carboxylic acids, acetic anhydride and acyl chloride were purified by distillation or recrystallization before use. The purity determination of the products was accomplished by GC on a Shimadzu model GC-14A instrument or by TLC on silica gel polygram SIL G/UV 254 plates. The FTIR spectra were recorded on a Shimadzu model 8300 instrument. The NMR spectra were recorded on

a Bruker Advance DPX 250 MHz spectrometer and in all cases $CDCl_3$ was used as a solvent and TMS as an internal standard.

4.2. Typical procedure for acylation of anisole with acetic anhydride; a

Anisole (2 mmol, 0.216 g), acetic anhydride (4 mmol, 0.408 g) and $AlPW_{12}O_{40}$ (0.06 mmol, 0.232 g) were combined, and the mixture was stirred at 60–70 °C for 45 min (Table 3). After completion of the reaction (monitored by TLC and GC), Et_2O (10 mL) and powder of sodium hydrogen carbonate (0.8 g) was added to the mixture in order to destroy the unreacted acetic anhydride. The solid phase was isolated and washed with Et_2O (2× 5 mL). Evaporation of the combined ethereal solutions afforded the almost pure product in 94% yield (0.504 g).

4.3. Typical procedure for benzoylation of anisole with benzoyl chloride

Anisole (2 mmol, 0.216 g), benzoyl chloride (3 mmol, 0.421 g) and $AlPW_{12}O_{40}$ (0.08 mmol, 0.232 g) were combined and the mixture was stirred at 60–70 °C for 2 h (Table 4, entry 1). After completion of the reaction (monitored by TLC and GC), Et_2O (10 mL) and powder of sodium hydrogen carbonate (0.8 g) was added to the reaction mixture in order to destroy the unreacted benzoyl chloride. The solid phase was recovered by filtration and was washed with Et_2O (2×5 mL). Evaporation of the combined ethereal solutions afforded the almost pure product in 94% yield (0.796 g).

4.4. General procedure for acylation of anisole with carboxylic acids

To a mixture of carboxylic acid (2 mmol) and anisole (100 mmol), $AlPW_{12}O_{40}$ (12 mol%, 0.362 g) was added and the reaction mixture was stirred at 120 °C for the appropriate reaction times (Table 5). After completion of the reaction (monitored by TLC and GC), the catalyst was filtered. The unreacted anisole was separated by vacuum distillation and the desired ketone was isolated with high purity (GC) in good yield.

4.5. General procedure for acylation of aromatic compounds using carboxylic acids and triflouroacetic anhydride (TFAA) catalyzed with $AlPW_{12}O_{40}$

Aromatic compound (2 mmol), carboxylic acid (2 mmol), trifluoroacetic anhydride (2.8 mmol, 0.39 mL) and $AlPW_{12}O_{40}$ (0.03 mmol, 0.174 g) were mixed together and stirred by a magnetic stirrer at room temperature for the appropriate reaction times (Table 7). After completion of the reaction (monitored by TLC and GC), Et_2O (10 mL) and powder of sodium hydrogen carbonate (1.2–1.5 g) was added to destroy the unreacted TFAA or carboxylic acid. The solid phase was recovered by filtration and was washed with Et_2O (2×5 mL). Evaporation of the combined ethereal solutions afforded the highly pure product.

4.6. Spectral data of the unknown ketones prepared by the presented protocol

4.6.1. Table 7 entry 11: R=C_7H_{15}. Colourless viscous oil, [Found: C, 77.38; H, 9.65. $C_{16}H_{24}O_2$ requires C, 77.41; H, 9.65%]. Bp (*P*/32 mmHg)=218 °C IR (KBr) (ν C=O)= 1610, 1691 cm^{-1} δ_H (250 MHz, $CDCl_3$) 7.83–7.77 (2H, m, Ph), 6.83 (1H, d, J=8.4 Hz), 2.92 (t, 2H, $^2J_{HH}$=12 Hz, –$COCH_2CH_2$), 2.25 (s, 3H), 1.67 (m, 2H), 1.56 (m, 2H), 1.42 (m, 2H), 1.36 (m, 2H), 1.21 (m, 2H), 0.88 (t, 3H, $^2J_{HH}$= 7.5 Hz, CH_3CH_2). ^{13}C NMR: δ (ppm)=199.53, 161.59, 130.7, 129.72, 128.1, 126.6, 109.15, 55.4, 38.2, 31.7, 29.4, 24.7, 22.6, 16.2, 14.1. MS (20 eV): *m/z* (%)=248 (M^+, 3.1), 177 (6.9), 164 (71.5), 150 (10.1), 149 (100), 91 (23.5), 41 (16.2).

4.6.2. Table 7 entry 14: R=C_7H_{15}. Light yellow solid, mp=43 °C, [Found: C, 73.94; H, 9.57. $C_{18}H_{28}O_3$ requires C, 73.97; H, 9.58%] **IR** (KBr) (ν C=O)=1677 cm^{-1}, δ_H (250 MHz, $CDCl_3$) 6.5–7.4 (m, 3H, Ph), 4.08 (q, 4H), 2.9 (t, 2H, $^2J_{HH}$=12 Hz, –$COCH_2CH_2$), 1.5 (t, 6H, $^2J_{HH}$=15 Hz, OCH_2CH_3), 1.71 (m, 2H), 1.41 (m, 2H), 1.3 (m, 2H), 1.18 (m, 2H), 0.98 (m, 2H), 0.81 (t, 3H, $^2J_{HH}$=7.5 Hz, CH_3CH_2). δ_C (63 MHz, $CDCl_3$)=196.6, 153.2, 148.8, 144, 130.4, 122.9, 120, 115, 112.4, 64, 42, 32, 30, 23, 15, 14, MS (20 eV): *m/z* (%)=292 (M^+, 10.8), 221 (8.6), 208 (100), 193 (73.2), 180 (14.8), 165 (38.4), 137 (36.3), 109 (17.5), 81 (14), 57 (16.1).

4.6.3. Table 7 entry 15: R=$PhCH_2$. Yellow solid, mp= 82 °C, [Found: C, 76.1; H, 7.02. $C_{18}H_{20}O_3$ requires C, 76.05; H, 7.04%] IR (KBr) (ν C=O)=1700, 1596 cm^{-1} δ_H (250 MHz, $CDCl_3$) 7.34–7.2 (5H, m, Ph), 7.62 (1H, d, J= 8.37 Hz), 7.46 (1H, s),6.86 (1H, d, J=8.4 Hz), 4.22 (2H, s), 4.08–4.19 (4H, m, –OCH_2CH_3), 1.5–1.41 (6H, m, OCH_2CH_3). δ_C (63 MHz, $CDCl_3$)=196.3, 148, 144, 135.1, 131, 130, 129.3, 128, 126, 120, 114, 64.4, 45.13, 14.6. MS (20 eV): *m/z* (%)=284 (M^+, 3.3), 194 (12.5), 193 (100), 165 (32.1), 137 (27.3), 109 (10.4), 91 (19.5).

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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.2004.09.049

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Efficient synthesis of CCR5 antagonist, 2,3-dihydro-1-benzothiepine derivatives by improved intramolecular Claisen type reaction using dialkylcarbonate

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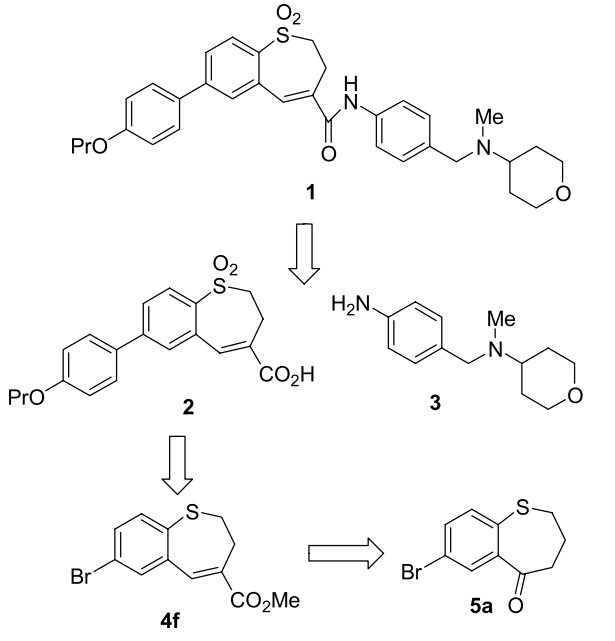
Abstract—The efficient synthesis of 2,3-dihydro-1-benzothiepine derivatives **4** has been developed. The intramolecular Claisen type reaction of the new products, 4-(*o*-formylphenylthio)butyrate **9**, with alcoholate in dialkylcarbonate as a solvent afforded **4** in good yields. According to this new procedure, we have accomplished the practical preparation of CCR5 antagonist **1** as a candidate for oral HIV-1 therapy.

1. Introduction

Recently, various small-molecular nonpeptide compounds have been reported as CC chemokine receptor 5 (CCR5) antagonist, because CCR5 was found to be a coreceptor for the entry of macrophage-tropic human immunodeficiency virus type 1 (HIV-1) into host cells.[1,2] Shiraishi et al. previously reported that TAK-779 as a CCR5 antagonist appeared to be a candidate for the therapy of HIV-1 infected individuals.[3] Furthermore, *N*-[4-[*N*-methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxamide **1** showed CCR5 antagonistic activity when orally administered.[4] Hence, an efficient preparation of **1** on a large scale was required to support pharmacological and toxicological evaluations. In the early report,[4] the oxidation of 2,3-dihydro-1-benzothiepine **4f** with H_2O_2 followed by arylation and hydrolysis gave the acid **2**, which was amidated with the aniline **3** to provide the desired **1** (Scheme 1). For the preparation of 2,3-dihydro-1-benzothiepine **4**, there have been some syntheses based on the same generation (Scheme 2).[4,5] Compound **4** was led from β-oxo-ester **6** prepared from the ketone **5**. These methods via **6**, however, had some drawbacks, for example, the production of over-reduced compound **8** in the reduction of **7**, and the requirement of several processes to **4** from **5**. There were similar problems in the preparation of **4f** via β-oxo-ester. There has been no report of synthesis of **4** based on an other generation to the best of our knowledge. On the other hand, 2,3-dihydro-1-benzoxepine and 2,3-dihydro-1-benzazepine could be synthesized from the analogues of **9** with alcoholate according to the Claisen type reaction.[4,5a,6] The



Scheme 1.

Keywords: 2,3-Dihydro-1-benzothiepine; Claisen type condensation; Dialkylcarbonate; CCR5 antagonist.
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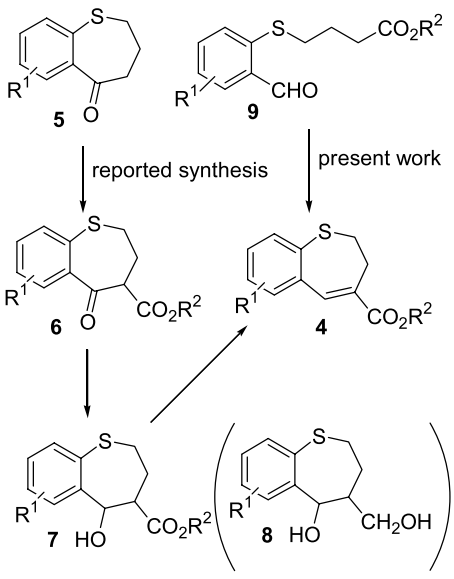


Scheme 2.

preparation of **4** from **9** attracted our interest regarding large-scale preparations because of its simple and wasteless protocol, even though the yields based on this generation were not sufficiently high. In this paper, we announce the facile and efficient synthesis of **4**, and the application for **1**.

2. Results and discussion

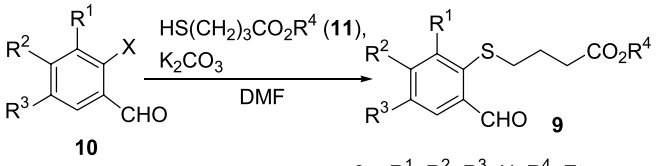
2.1. Development of new preparation of 2,3-dihydro-1-benzothiepines

We synthesized **9**, having various substituted groups, to develop a new synthetic procedure for **4**. The synthesis of new products **9a–e** was accomplished by thioalkylation of *o*-halogenobenzaldehyde **10** with 4-mercaptobutyrate **11**[7] and K_2CO_3 in DMF overnight at room temperature (Table 1), although there has been no report about the synthesis of **9**. Most thioalkylations of **10** gave **9** in good to excellent yields, while **10d** having an electron-donating group at the *p*-position of the halogen gave lower yields (entry 5).

To optimize the reaction conditions, the intramolecular cyclization of **9a** for producing **4a** was examined (Table 2). First, the conditions for synthesizing benzoxepines[5] were applied to the cyclization of **9a**. The treatment of **9a** was conducted with NaOEt in EtOH to give many products. After the workup, the chromatographic purification provided the desired **4a** in 27% yield and the hydrolyzed **12** in 18% yield (entry 1). The combinations of NaOEt and 1,2-dimethoxyethane (DME) or NaH and THF decreased the hydrolysis to increase the yields of **4a** (entries 2 and 3). However, these reactions could neither depress the production of impurities of which the structures were unknown, nor increase the total yields of cyclization (**4a**+**12**). It was thought that the value of pK_a at the α carbon of ester was insufficient for cyclization of **9a**, resulting in the production of impurities.[8] To decrease the value of pK_a, the reaction of **9a** was performed with the combination of NaOEt and diethylcarbonate as a solvent, which was converted to the malonate derivatives.[9] Surprisingly, this treatment made a breakthrough in the yield of cyclization, giving **4a** in 71% yield without detection of the malonate derivative and **12** (entry 4). For this reaction, 1.2 equiv of diethylcarbonate affected the cyclization to increase the yield of **4a** (entry 6 vs 1). Moreover, the same reaction of **9a** with NaOEt using ethyl formate as a solvent, expected to produce a similar effect, gave a slightly higher yield of **4a** than that using DME as a solvent (entry 2 vs 5).[10]

For research into the scope and limitation of the intramolecular Claisen type reaction, a variety of **9** reactions were next performed under the conditions of alcoholate/dialkylcarbonate (Table 3). The use of dimethylcarbonate

Table 1. Thioalkylation of *o*-halogenobenzaldehydes[a]

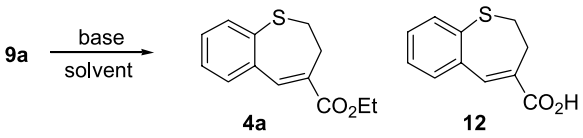


9a: R^1=R^2=R^3=H, R^4=Et
9b: R^1=R^2=R^3=H, R^4=Me
9c: R^1=R^2=H, R^3=Br, R^4=Et
9d: R^1=Cl, R^2=R^3=H, R^4=Et
9e: R^1=H, R^2=R^3=OMe, R^4=Et

Entry	Substrates		Yield (%)[b]
	10	**11**	
1	**10a** (R^1=R^2=R^3=H, X=F)	**11a** (R^4=Et)	**9a**: 67
2	**10a**	**11b** (R^4=Me)	**9b**: 95
3	**10b** (R^1=R^2=H, R^3=Br, X=F)	**11a**	**9c**: 78
4	**10c** (R^1=Cl, R^2=R^3=H, X=Cl)	**11a**	**9d**: 70
5	**10d** (R^1=R^2=H, R^3=OMe, X=Br)	**11a**	**9e**: 27

[a] *General procedure.* To a suspension of **10** (1.0 g, 1.0 equiv), K_2CO_3 (2.0 equiv) and DMF (3 v/w) was added **11** (2 equiv), and the whole suspension was stirred overnight at room temperature.
[b] Isolated yield.

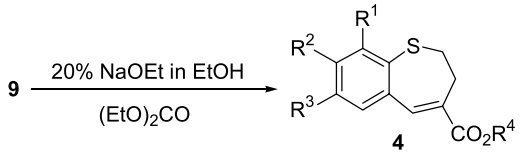
Table 2. Optimization of reaction conditions[a]



Entry	Solvent	Base	Conditions	Isolated yield (%)		
				9a	**4a**	**12**
1	EtOH	20% NaOEt in EtOH	rt, 3 h, then refluxed, 1 h	ND	27	18
2	DME	20% NaOEt in EtOH	rt, 45 min	ND	37	6
3	THF	NaH	rt, 1 h, then refluxed, 0.5 h	ND	44	6
4	$(EtO)_2CO$	20% NaOEt in EtOH	rt, 2 h	ND	71	ND
5	HCO_2Et	20% NaOEt in EtOH	rt, 4 h	26	58	ND
6	EtOH, $(EtO)_2CO$ (1.2 eqiv)	20% NaOEt in EtOH	rt, 3 h, then refluxed, 1 h	ND	53	4

[a] The mixture of **9a** (1.0 g, 1.0 equiv), base (1.2 equiv) and solvent (20 v/w) was reacted.

Table 3. The intramolecular Claisen type reaction[a]



Entry	Substrate	Time (h)	Isolated yield (%)
1[b]	**9b**	15	**4b** ($R^1=R^2=R^3=H$, $R^4=Me$): 71
2	**9c**	2	**4c** ($R^1=R^2=H$, $R^3=Br$, $R^4=Et$): 32
3	**9d**	7	**4d** ($R^1=Cl$, $R^2=R^3=H$, $R^4=Et$): 46
4	**9e**	6	**4e** ($R^1=H$, $R^2=R^3=OMe$, $R^4=Et$): 70

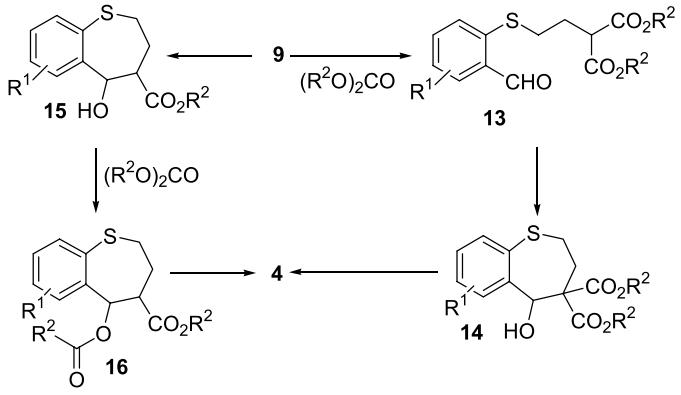
[a] To a solution of **9** (1.0 g) and diethyl carbonate (20 v/w) was added 20% NaOEt in EtOH (1.2 equiv), and the whole mixture was stirred at room temperature.
[b] 28% NaOMe in MeOH (1.2 equiv) and $(MeO)_2CO$ (20 mL) were used.

instead of diethylcarbonate as a solvent also affected the intramolecular condensation of **9b** to give **4b** in 71% yield (entry 1). The yields of **4** were decreased by the electron-withdrawing groups at the *o*- or *p*-position of thiobutyrate, while the treatment of **9e** having an electron donor group at the *p*-position of the sulfur atom afforded **4e** in 70% yield (entries 2, 3 and 4).

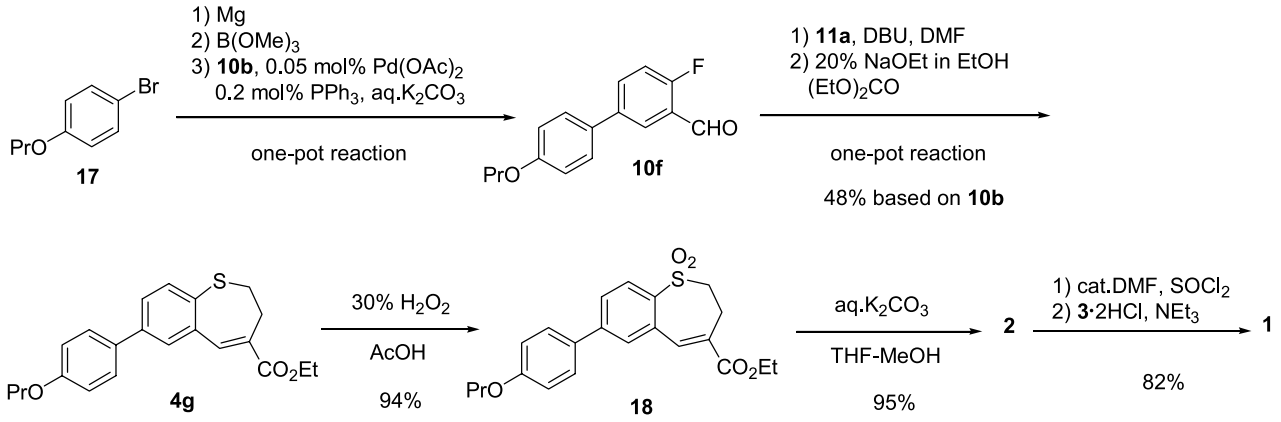
The reaction mechanism to **4** from **9** was not clear, although the addition of dialkylcarbonate was required for improvement in these reactions. We deduced that the treatment of **9** with alcoholate and dialkylcarbonate converted it to the malonate derivative **13**, which smoothly afforded the cyclization to give **4**. However, the role of dialkylcarbonate in the intramolecular cyclization also might be thought to the acceleration of dehydration of **16** (Scheme 3).

2.2. Large-scale preparation of 1 as a candidate for orally administered HIV-1 therapy

According to the new procedure for 2,3-dihydro-1-benzothiepines, we tried to develop a large-scale preparation of the desired **1** (Scheme 4). The biarylaldehyde **10f** was selected as an intermediate, because the intramolecular condensation of **9c** as a substrate afforded a lower yield, as mentioned. Although there were many syntheses of biaryl compounds, the preparation of **10f** was attempted using the convenient procedure of the Suzuki–Miyaura reaction in one-pot for large-scale preparation.[11,12] The treatment of **17** was conducted with magnesium in THF under the refluxing condition, followed by cooling to −10 °C and boronation with trimethoxyborane, which was reacted with **10b**, aqueous K_2CO_3, and a catalytic amount of $Pd(PPh_3)_4$ under the refluxing condition to give **10f** in excellent yield. The coupling reaction also proceeded smoothly when 0.05 mol% of $Pd(OAc)_2$ and 0.2 mol% of PPh_3 instead of $Pd(PPh_3)_4$ were employed. As a result, all reactions from the Grignard reaction of **17** to the cross-coupling reaction were performed in one-pot to give **10f** almost quantitatively. After workup followed by extraction and concentration, **10f** was used without further purification. The thioalkylation of crude **10f** with **11a** using K_2CO_3 in DMF as a base, followed



Scheme 3.



Scheme 4.

by cyclization with the combination of NaOEt in EtOH solution and diethyl carbonate at room temperature provided 1-benzothiepine **4g** in one-pot. However, it was difficult to adopt these conditions for a large-scale preparation, because the reaction time was unstable in the thioalkylation when the reaction was scaled up to multi-decade grams. It was thought that the thioalkylation of **10f** with **11a** proceeded heterogenously. The use of DBU instead of K_2CO_3 afforded a stable reaction time, because the salt was dissolved in DMF. The reactions to **4g** in two steps afforded 48% yield using only the crystallization procedure.

The preparation of **2** from **4g** was conducted using two methods. The hydrolysis of **4g** with 2 N NaOH gave carboxylic acid, which was oxidated with H_2O_2 in AcOH. However, the oxidation was not completed, giving **2** containing the sulfoxide. The oxidation from the sulfide **4g** to the sulfone **18** was accomplished in 94% yield by the reaction of 30% hydrogen peroxide in acetic acid. The sulfone **18** was hydrolyzed with aqueous K_2CO_3 solution in a mixture of THF and MeOH under the refluxing condition to give **2** in 95% yield. The hydrolysis using NaOH as a base provided some by-products, and the hydrolysis of **18** also was not completed under the acidic conditions.

Finally, the acid-chloride generated from **2** was amidated with the amine **3**·2HCl (**3** dihydrochloride)[13] to give **1**. The reaction in *N*,*N*-dimethylacetamide (DMAc) proceeded smoothly, although the acid **2** was left in **1** when DMF or 1-methyl-2-pyrrolidone was used. After the reaction was completed, the addition of water to the reaction mixture caused crystallization to give the high-quality target product **1** in 82% yield.

3. Conclusion

We have developed a facile and novel synthetic preparation of 2,3-dihydro-1-benzothiepine derivatives **4**. The new compound, alkyl 4-(*o*-formylphenylthio)butyrate **9**, was prepared from *o*-halogenobenzaldehyde **10** and mercapto-butylate **11**. The improved intramolecular Claisen type reaction of **9** with alcoholate in dialkylcarbonate as a solvent provided **4** in good yields.

Furthermore, the practical preparation of **1** as a candidate for orally administered HIV-1 therapy was accomplished by employing the new method, and did not require any chromatographic purification. This synthetic route was consisted of five steps in 35% yield, as compared with the previous nine steps.

4. Experimental

4.1. General

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer. ^{1}H NMR spectra are reported as follows: chemical shifts in ppm (δ) downfield from tetramethylsilane as an internal standard, multiplicity (s, singlet; d, doublet; t, triplet and m, mutiplet), coupling constants spectra (Hz) and integration. ^{13}C NMR spectra recorded in ppm (δ) relative to the central line for $CDCl_3$ at 77 ppm and DMSO-d_6 at 39.7 ppm. The column chromatography was performed on BW820 (Fuji Silysia Chemical Ltd) Elemental and HRMS analyses were performed at Takeda Analytical Research Laboratories, Ltd.

4.1.1. General procedure for the preparation of 9. Compound **11** (2 equiv) was added to a suspension of **10** (1.0 g) and K_2CO_3 (2 equiv) in DMF (3 v/w), and stirred overnight at room temperature. The reaction mixture was diluted in AcOEt, and washed successively with water, 0.5 N HCl, and brine. The organic layer was dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica-gel with *n*-hexane–AcOEt.

4.1.2. Ethyl 4-(2-formylphenylthio)butyrate (9a), from 10a and 11a. A pale yellow oil; yield: 67%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 3H), 1.95–2.07 (m, 2H), 2.49 (t, J=7.2 Hz, 2H), 3.02 (t, J=7.1 Hz, 2H), 4.13 (q, J=7.1 Hz, 2H), 7.27–7.34 (m, 1H), 7.45–7.53 (m, 2H), 7.83–7.86 (m, 1H), 10.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.9, 32.4, 33.0, 60.5, 125.5, 128.3, 132.1, 134.0, 134.2, 141.3, 172.7, 191.4; IR (neat) 1731, 1695,

1196 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}O_3S$ ($[M]^+$) 252.0820; Found 252.0820.

4.1.3. Methyl 4-(2-formylphenylthio)butyrate (9b), from 10a and 11b. A pale yellow oil; yield: 95%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.96–2.06 (m, 2H), 2.50 (t, $J=7.2$ Hz, 2H), 3.01 (t, $J=7.1$ Hz, 2H), 3.68 (s, 3H), 7.27–7.34 (m, 1H), 7.46–7.55 (m, 2H), 7.81–7.84 (m, 1H), 10.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 32.3, 32.7, 51.6, 125.5, 128.2, 132.1, 134.0, 134.1, 141.3, 173.1, 191.3; IR (neat) 1735, 1693, 1197 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{14}O_3S$ ($[M]^+$) 238.0664; Found 238.0664.

4.1.4. Ethyl 4-(4-bromo-2-formylphenylthio)butyrate (9c), from 10b and 11a. A pale yellow solid; yield: 78%; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J=7.1$ Hz, 3H), 1.95–2.05 (m, 2H), 2.48 (t, $J=7.1$ Hz, 2H), 3.00 (t, $J=7.2$ Hz, 2H), 4.13 (q, $J=7.1$ Hz, 2H), 7.35 (d, $J=8.5$ Hz, 1H), 7.60–7.64 (m, 1H), 7.94 (d, $J=2.3$ Hz, 1H), 10.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 23.9, 32.7, 32.9, 60.6, 119.6, 130.4, 134.1, 135.5, 136.7, 140.3, 172.6, 189.8; IR (KBr) 1732, 1678, 1458, 1178 cm^{-1}; mp 48–49 °C; HRMS (FAB) calcd for $C_{13}H_{16}O_3BrS$ ($[MH]^+$) 331.0004; Found 331.0004. Anal. Calcd for $C_{13}H_{15}O_3SBr$: C, 47.14; H, 4.56; S, 9.68; Br, 24.12. Found: C, 47.19; H, 4.48; S, 9.58; Br, 24.23.

4.1.5. Ethyl 4-(2-chloro-6-formylphenylthio)butyrate (9d), from 10c and 11a. A pale yellow oil; yield: 70%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, $J=7.2$ Hz, 3H), 1.84–1.94 (m, 2H), 2.43 (t, $J=7.2$ Hz, 2H), 2.95 (t, $J=7.2$ Hz, 2H), 4.11 (q, $J=7.2$ Hz, 2H), 7.42 (dd, $J=7.9$, 7.2 Hz, 1H), 7.71 (d, $J=7.9$ Hz, 1H,), 7.84 (d, $J=7.7$ Hz, 1H), 10.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 24.7, 32.8, 36.0, 60.5, 126.9, 129.8, 135.0, 136.8, 140.2, 141.2, 172.5, 192.0; IR (neat) 1739, 1685, 1037 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{16}O_3ClS$ ($[MH]^+$) 287.0509; Found 287.0509.

4.1.6. Ethyl 4-(3,4-dimethoxy-6-formylphenylthio)butyrate (9e), from 10d and 11a. A pale yellow solid; yield: 27%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, $J=7.1$ Hz, 3H), 1.80–2.07 (m, 2H), 2.43 (t, $J=7.1$ Hz, 2H), 2.92 (t, $J=7.4$ Hz, 2H), 3.93 (s, 3H), 3.99 (s, 3H), 4.12 (q, $J=7.1$ Hz, 2H), 7.02 (s, 1H),7.41 (s, 1H), 10.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 23.9, 32.2, 35.1, 55.5, 55.8, 60.0, 110.0, 114.4, 129.2, 133.3, 148.3, 153.3, 172.1, 189.7; IR (nujol) 1718, 1671, 1272 cm^{-1}; mp 87–88 °C; HRMS (FAB) calcd for $C_{15}H_{20}O_5S$ ($[M]^+$) 312.1031; Found 312.1031. Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; S, 10.26; O, 25.61. Found: C, 57.50; H, 6.47; S, 10.37.

General procedure for the preparation of **4**. 20% NaOEt (1.2 equiv) in EtOH (or 28% NaOMe in MeOH) was added to a solution of **9** (1.0 g) and diethyl carbonate (20 v/w) (or dimethyl carbonate), and stirred at room temperature. After cooling to 0 °C, the reaction mixture was neutralized with 1 N HCl. The resulting solution was extracted with AcOEt, and the organic layer was washed with water, dried by Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica-gel with *n*-hexane–AcOEt.

4.1.7. Ethyl 2,3-dihydro-1-benzothiepin-4-carboxylate (4a). A yellow oil; yield: 71%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.96–3.00 (m, 2H), 3.16–3.21 (m, 2H), 4.28 (q, $J=7.1$ Hz, 2H), 7.18–7.27 (m, 2H), 7.36–7.48 (m, 2H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 32.8, 35.3, 61.1, 127.0, 128.5, 132.2, 133.4, 134.4, 136.8, 138.8, 139.4, 168.1; IR (neat) 1703, 1267, 1240 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{14}O_2S$ ($[M]^+$) 234.0715; Found 234.0715.

4.1.8. Methyl 2,3-dihydro-1-benzothiepin-4-carboxylate (4b). A white solid; yield: 71%; ^1H NMR (300 MHz, $CDCl_3$) δ 2.96–3.00 (m, 2H), 3.16–3.21 (m, 2H), 3.83 (s, 3H), 7.18–7.27 (m, 2H), 7.36–7.48 (m, 2H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9, 35.2, 52.2, 127.0, 128.6, 132.2, 133.0, 134.5, 136.7, 138.8, 139.7, 168.5; IR (KBr) 1706, 1631, 1428 cm^{-1}; mp 52–54.3 °C; HRMS (FAB) calcd for $C_{12}H_{12}O_2S$ ($[M]^+$) 220.0558; Found 220.0558. Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.57; H, 5.43; F, 14.32.

4.1.9. Ethyl 7-bromo-2,3-dihydro-1-benzothiepin-4-carboxylate (4c). A yellow solid; yield: 32%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.95–2.99 (m, 2H), 3.15–3.20 (m, 2H), 4.28 (q, $J=7.1$ Hz, 2H), 7.26–7.34 (m, 2H), 7.51–7.52 (m, 1H), 7.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 33.1, 35.8, 61.7, 121.1, 131.6, 134.1, 135.3, 136.9, 138.2, 138.3, 139.2, 168.0; IR (KBr) 1704, 1629, 1465 cm^{-1}; mp 82–83 °C; HRMS (FAB) calcd for $C_{13}H_{13}O_2SBr$ ($[M]^+$) 311.9820; Found 311.9820. Anal. Calcd for $C_{13}H_{13}O_2SBr$: C, 49.85; H, 4.18; S, 10.24; Br, 25.51. Found: C, 50.13; H, 4.12; S, 10.11; Br, 25.55.

4.1.10. Ethyl 9-chloro-2,3-dihydro-1-benzothiepin-4-carboxylate (4d). A yellow oil; yield: 46%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.99–3.03 (m, 2H), 3.15–3.20 (m, 2H), 4.28 (q, $J=7.1$ Hz, 2H), 7.12–7.27 (m, 1H), 7.26–7.36 (m, 2H), 7.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 33.2, 34.3, 61.2, 126.9, 129.3, 133.5, 134.1, 135.6, 137.9, 138.6, 138.9, 167.8; IR (neat) 1712, 1631 cm^{-1}. HRMS (FAB) calcd for $C_{13}H_{13}O_2ClS$ ($[M]^+$) 268.0325; Found 268.0325.

4.1.11. Ethyl 7,8-dimethoxy-2,3-dihydro-1-benzothiepin-4-carboxylate (4e). A yellow oil; yield: 70%; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, $J=7.1$ Hz, 3H), 2.95–2.98 (m, 2H), 3.16–3.21 (m, 2H), 3.88 (s, 3H), 3.89 (s, 3H), 4.28 (q, $J=7.1$ Hz, 2H), 6.86 (s, 1H), 6.96 (s, 1H), 7.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 32.8, 35.7, 55.9, 60.9, 114.7, 116.6, 129.4, 130.9, 131.8, 139.2, 147.8, 148.8, 168.1; IR (neat) 1700, 1594, 1502 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{18}O_4S$ ($[M]^+$) 294.0926; Found 294.0926.

4.1.12. Ethyl 7-(4-propoxyphenyl)-2,3-dihydro-1-benzothiepin-4-carboxylate (4g). Under an argon atmosphere, a solution of **17** (37.1 g, 172.4 mmol) and THF (90 mL) was added dropwise to a suspension of magnesium (4.3 g, 177.3 mmol) and THF (270 mL) under a refluxing condition, and the whole was stirred for 1.5 h under the same conditions. After cooling to −11 °C, a solution of trimethoxyborane (17.9 g, 172.4 mmol) and THF (90 mL) was added dropwise to the reaction mixture and stirred for 1 h at −10 °C. After warming to room temperature,

palladium (II) acetate (11 mg, 0.049 mmol) and triphenylphosphine (52 mg, 0.197 mmol) were added to the resulting mixture, and stirred for 30 min at room temperature. Compound **10b** (20.0 g, 98.5 mmol), K_2CO_3 (71.5 g, 517.2 mmol) and distilled water (85 mL) were added to the resulting mixture, and the whole was refluxed for 4 h. After cooling to room temperature, 2 N HCl (450 mL) was added dropwise to the reaction mixture at 20–30 °C and separated. The aqueous solution was extracted with toluene (450 mL), and the combined organic solution was washed successively with 2 N HCl (300 mL), 2 N NaOH (300 mL×2), 2 N HCl (300 mL) and 20% NaCl solution (300 mL×2). Activated charcoal (1.0 g) was added to the organic solution, and the mixture was stirred for 20 min at room temperature. The charcoal was filtered off and washed with toluene (50 mL). The filtrate and washing were concentrated in vacuo to give crude 2-fluoro-5-(4-propoxyphenyl)benzaldehyde (**10f**, 30.5 g) as a brown oil. An analytically pure sample of **10f** was obtained by chromatography on silica-gel as a white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.77–1.90 (m, 2H), 3.96 (t, J=6.6 Hz, 2H), 6.95–6.98 (m, 2H), 7.18–7.25 (m, 1H), 7.46–7.50 (m, 2H), 7.74–7.78 (m, 1H), 8.00–8.04 (m, 1H), 10.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.6, 70.0, 115.0, 116.7, 117.0, 124.1, 126.3, 128, 131.1, 134.3, 137.8, 159.2, 162.1, 165.6, 187.2; IR (KBr) 2875, 1691, 1608, 1484, 1216 cm^{-1}; mp 42–43 °C; HRMS (FAB) calcd for $C_{16}H_{15}O_2F$ ($[M]^+$) 258.1056; Found 258.1056. Anal. Calcd for $C_{16}H_{15}O_2F$: C, 74.40; H, 5.85; F, 7.36. Found: C, 74.66; H, 5.67; F, 7.28.

DBU (34.4 mL, 229.9 mmol) was added dropwise to a solution of the above crude **10f** and **11a** (32.6 mL, 229.9 mmol) in DMF (59 mL) at 0–10 °C under an argon atmosphere, and the whole was stirred for 1 h at 20–30 °C. After diethyl carbonate (590 mL) was added the reaction mixture, 20% NaOEt in EtOH (156.0 g, 459.8 mmol) was added dropwise to the resulting mixture, and the whole was stirred for 3 h at 20–30 °C. After cooling to 5 °C, 2 N HCl (338 mL) was added dropwise to the reaction mixture, and separated. The aqueous solution was extracted with AcOEt (290 mL), and the combined organic layer was washed successively with water (300 mL), 5% $NaHCO_3$ solution (300 mL) and 5% NaCl solution (300 mL). Activated charcoal (3.5 g) and tri-*n*-butylphosphine (4 mL) were added to the organic solution, and the mixture was stirred for 20 min. The charcoal was filtered off, and washed with AcOEt (60 mL). After the filtrate and washing was concentrated in vacuo, the resulting residue was dissolved in diisopropyl ether (60 mL) under a refluxing condition. After cooling to room temperature, stirring for 1.5 h at room temperature and stirring for 2 h at 0 °C, the resulting crystals were collected by filtration, washed with cold diisopropyl ether (60 mL) and dried in vacuo to give **4g** (20.3 g, yield, 48% based on **10b**) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.36 (t, J=7.1 Hz, 3H), 1.77–1.90 (m, 2H), 3.00 (t, J=5.3 Hz, 2H), 3.22 (t, J=5.6 Hz, 2H), 3.96 (t, J=6.6 Hz, 2H), 4.29 (q, J=7.1 Hz, 2H), 6.94–7.00 (m, 2H), 7.36–7.57 (m, 5H), 7.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 14.4, 22.6, 32.7, 35.6, 61.1, 69.6, 114.9, 126.7, 127.9, 132.0, 132.5, 132.7, 133.6, 136.7, 137.2, 139.6, 139.7, 159.1, 168.1; IR (KBr) 2927, 1704, 1240, 819 cm^{-1}; mp 87–88 °C; HRMS (FAB) calcd for $C_{22}H_{24}O_3S$ ($[M]^+$) 368.1446; Found 368.1446. Anal. Calcd for $C_{22}H_{24}O_3S$: C, 71.71; H, 6.56; S, 8.70. Found: C, 71.72; H, 6.77; S, 8.64.

4.1.13. Ethyl 7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxylate (18). After **4g** (15.0 g, 40.7 mmol) was dissolved in acetic acid (135 mL) at 56 °C, 30% H_2O_2 (9.5 g, 83.5 mmol) in acetic acid (15 mL) was added dropwise to a solution at the same temperature and stirred for 3 h at 65–70 °C. Water (15 mL) and 5% Na_2SO_3 solution (60 mL) were added dropwise to the reaction mixture, and then the whole was cooled to room temperature and stirred for 2 h at the same temperature. The resulting crystals were collected by filtration, washed successively with acetic acid/water (3/2, 15 mL) and water (150 mL), and dried in vacuo to give **18** (15.4 g, yield, 94%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.38 (t, J=7.2 Hz, 3H), 1.78–1.90 (m, 2H), 3.14 (t, J=6.3 Hz, 2H), 3.64 (t, J=7.1 Hz, 2H), 3.98 (t, J=6.6 Hz, 2H), 4.32 (q, J=7.2 Hz, 2H), 6.99–7.02 (m, 2H), 7.53–7.57 (m, 2H), 7.65–7.69 (m, 2H), 7.89 (s, 1H), 8.18 (d, J=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 14.3, 22.6, 25.0, 55.8, 61.7, 69.7, 115.2, 126.7, 127.9, 128.4, 130.5, 131.8, 132.6, 132.9, 137.9, 138.3, 146.1, 160.0, 166.6; IR (KBr) 2933, 1706, 1606, 1517, 1243 cm^{-1}; mp 139–140 °C; HRMS (FAB) calcd for $C_{22}H_{24}O_5S$ ($[M]^+$) 400.1344; Found 400.1344. Anal. Calcd for $C_{22}H_{24}O_5S$: C, 65.89; H, 6.04; S, 8.01. Found: C, 65.72; H, 5.87; S, 7.96.

4.1.14. 7-(4-Propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxylic acid (2). A solution of K_2CO_3 (342 g, 2.47 mol) and water (4.2 L) was added dropwise to a solution of **18** (495 g, 1.24 mol), THF (4.95 L) and MeOH (2.48 L), and the whole was refluxed for 6.5 h. Under the same condition, 3 N HCl (1.85 L) was added dropwise to the reaction mixture and the whole was cooled to room temperature. Under the same temperature, 6 N HCl (84 mL) was added dropwise to the resulting mixture and stirred for 1 h with ice-bathing. The resulting crystals were collected by filtration, washed with THF/MeOH/water (1/1/3, 2.97 L), and dried in vacuo to give **2** (443 g, yield, 96%) as a light white-yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (t, J=7.4 Hz, 3H), 1.70–1.78 (m, 2H), 2.95 (t, J=6.2 Hz, 2H), 3.73 (t, J=6.4 Hz, 2H), 3.98 (t, J=6.5 Hz, 2H), 7.05 (d, J=8.7 Hz, 2H), 7.75 (d, J=8.7 Hz, 2H), 7.86–7.88 (m, 2H), 8.02–8.05 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.6, 22.2, 25.4, 53.9, 69.3, 115.3, 126.4, 127.1, 128.6, 129.9, 132.1, 132.4, 134.0, 136.8, 138.8, 144.9, 160.0, 168.5; IR (KBr) 3500, 1673, 1608, 1519, 1294, 1251 cm^{-1}; mp 271–272 °C; HRMS (FAB) calcd for $C_{20}H_{20}O_5S$ ($[M]^+$) 372.1031; Found 372.1031. Anal. Calcd for $C_{20}H_{20}O_5S$: C, 64.50; H, 5.41; S, 8.61. Found: C, 64.40; H, 5.47; S, 8.55.

4.1.15. *N*-[4-[*N*-Methyl-*N*-(tetrahydropyran-4-yl)aminomethyl]phenyl]-7-(4-propoxyphenyl)-1,1-dioxo-2,3-dihydro-1-benzothiepin-4-carboxamide (1). Thionyl chloride (0.70 g, 5.91 mmol) was added dropwise to a suspension of **2** (2.0 g, 5.37 mmol) in *N*,*N*-dimethylacetoamide (10 mL) at room temperature, and the whole was stirred for 2 h at room temperature. The reaction mixture was added dropwise to a suspension of **3**·2HCl (1.9 g, 6.44 mmol) and NEt_3 (5.8 mL, 41.87 mmol) in

N,*N*-dimethylacetamide (10 mL) at 0–10 °C, and stirred for 1 h at room temperature. Water (20 mL) was added to the resulting mixture at room temperature and stirred for about 1 h at the same temperature. The resulting crystals were collected by filtration, washed with water (5 mL) and MeOH (5 mL), and dried in vacuo to give **1** (2.5 g, yield, 82%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J=7.4 Hz, 3H), 1.64–1.88 (m, 6H), 2.20 (s, 3H), 2.60–2.67 (m, 1H), 3.13 (t, J=6.6 Hz, 2H), 3.33–3.41 (m, 2H), 3.56 (s, 2H), 3.69 (t, J=6.3 Hz, 2H), 3.95–4.07 (m, 4H), 6.98 (d, J=8.7 Hz, 2H), 7.29–7.34 (m, 3H, 7.48–7.61 (m, 6H), 8.08–8.16 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.6, 25.0, 29.2, 37.5, 57.3, 57.5, 59.6, 67.7, 69.7, 115.2, 120.3, 126.3, 128.1, 128.4, 129.4, 130.4, 130.6, 132.0, 133.2, 136.4, 136.5, 137.3, 139.3, 146.1, 160.1, 166.6; IR (KBr) 3485, 2948, 1654, 1635, 1606, 1519, 1315, 1292, 1130 cm^{-1}; mp 239.6–240.8 °C; HRMS (FAB) calcd for $C_{33}H_{39}N_2O_5S$ ($[MH]^+$) 575.2580; Found 575.2580. Anal. Calcd for $C_{33}H_{38}N_2O_5S$; C, 68.96; H, 6.66; N, 4.87; S, 5.58. Found: C, 68.79; H, 6.56; N, 4.95; S, 5.66.

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Synthesis of polyhydroxy cavitands and intramolecular inclusion of their octaester derivatives

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Abstract—A facile and efficient synthesis of novel cavitands containing eight hydroxyl groups was accomplished in eight steps beginning from commercially available resorcinol and the corresponding aldehydes. The synthesis combines two classical approaches to cavitand chemistry and yields the target octol cavitand molecules in gram quantities with no chromatographic separations. A variety of octaester cavitand derivatives were then prepared from the parent octols and their spectral properties are reported.

1. Introduction

The acid-catalyzed condensation of resorcinol and aldehydes produces resorcinarenes such as compound **1** (Fig. 1). Resorcinarenes are known to posses hydrophilic (upper rim) and hydrophobic (lower rim) regions and a cavity, which can accommodate small organic molecules.[1] Cavitands of the general structure **2** (Fig. 1) are synthesized from resorcinarenes via bridging reactions of the hydroxyl groups.[2] The bridges serve to impart conformational rigidity to the existing aryl skeleton and form the concave cavity of the cavitand.[3] As a result of these structural motifs resorcinarenes and cavitands have enjoyed use as surfactants and liquid crystals, in the complexation of metals, ammonium compounds, alcohols, diols, sugars, amino acids and carboxylic acids.[2b] The introduction of functional groups onto cavitand scaffolds has been the focus of intensive research, to elucidate various structural features that provide valuable insight into factors governing host–guest chemistry.[2d] Functionalized cavitand substrates offer interesting molecular platforms for metal ligand exchange complexes,[2,4] polymeric materials,[5] self-assembled systems,[2d] and as prospective reaction sites, and unique catalytic platforms.[2b,d] The availability of such material will be useful in synthesis of a wide array of novel materials and applications such as metal complexing agents,[6] sensors,[7] water soluble cavitands,[8] in phase transfer extraction of heavy metals,[9] for complexation of fullerenes[10] and related molecules,[11,12] for new bioorganic and biomimetic chemistries,[13] for self assembled systems,[14] for cavitand based crown ethers,[15] as stationary phases,[16] and as novel cavitand polymers.[5,17]

However, functionalized cavitands have largely been unexplored because of their unavailability stemming from the difficult synthesis. The main difficulties associated with the functionalization of cavitands are solubility related, which are manifested in two ways. First, the poor solubility of cavitand compounds leads to problems in chromatographic separations as tedious column separations, render lengthy synthetic sequences cumbersome. Second, the solubility of cavitands in reaction media is limited and thus reaction yields are not uniformly high.[2c] One method for the introduction of functional groups onto cavitands is a stepwise manner[2c] beginning from tetrabromocavitands such as compound **2** in (Fig. 1). The bromo atoms are substituted via lithium exchange and subsequent quenching with an appropriate electrophilic reagent introduces hydroxyl, thiol, or carboxylic ester functionalities respectively.[2d] An alternative synthetic method for the introduction of functional groups onto cavitands is known as the modular approach, which consists of coupling reactions of resorcinarenes with a suitable bridging component and then further synthetic elaboration on the bridging component to introduce the functional moieties.[2c]

In our laboratories, we are interested in the design and synthesis of polyhydroxy cavitands with well-defined structures.[18a,b] We sought to blend the stepwise and modular approaches to create polyhydroxy cavitands **3** and **4**, that are reminiscent of their parent compounds the resorcinarenes, and to which various functional groups can be appended through phosphorylation, sulfonylation, acylation, alkylation, halogenation, and oxidation reactions on the eight hydroxyl groups. The combination of the synthetic

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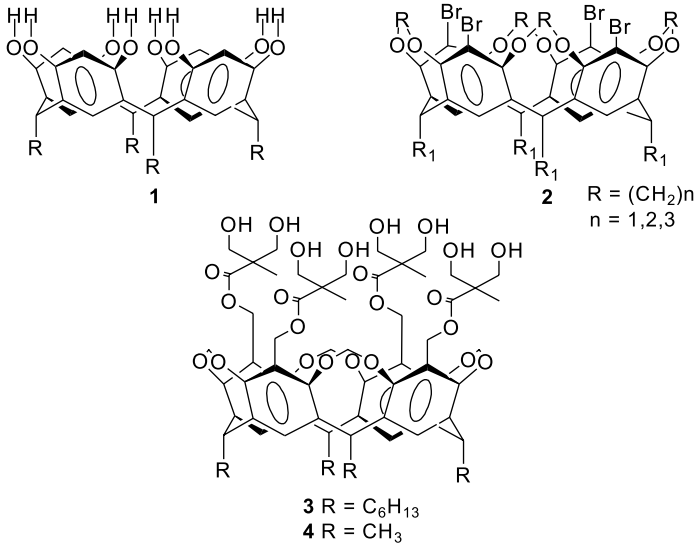


Figure 1. Resorcinarenes, cavitands, polyhydroxy cavitands.

approaches towards synthesis of functionalized cavitands proved highly effective in our hands. We, thus, secured the target molecules in gram quantities while performing no chromatographic separations throughout the entire synthetic sequence. We subsequently synthesized several octaester derivatives of the octols **3** and **4**, including acetate, mesylate, isopropionate, *p*-anisoate, and *p*-phenylbenzoate in excellent yields. In this article we report on a simple and efficient synthesis of well defined polyhydroxy cavitands, their derivatives, and spectral properties.

2. Results and discussion

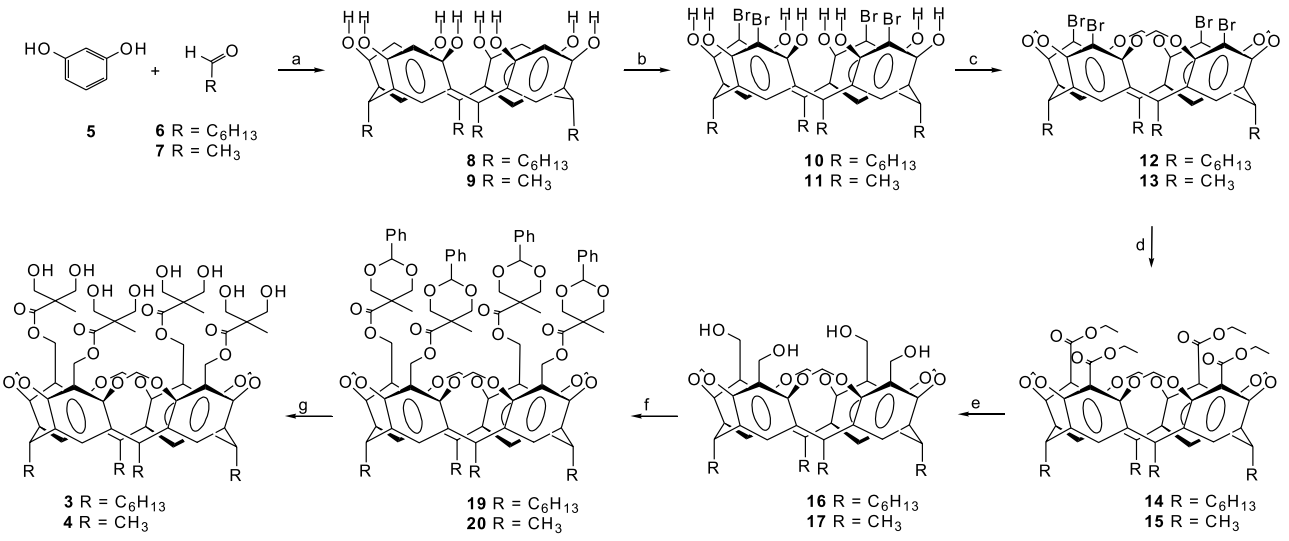
Our studies began by utilizing heptaldehyde or acetaldehyde, as the two alkyl aldehydic components for the condensation reactions with resorcinol to produce the resorcinarenes.[1] Aromatic bromination reactions resulted in the formation of the tetrabromides which served to introduce a suitable functionality for the stepwise approach.[3] Cavitand formation using Kaifer's sealed tube method on the brominated resorcinarenes yielded the desired tetrabromide tetramethylene bridged cavitands.[19] The aryl bromide positions were further functionalized to the esters and subsequently reduced to give the tetrol cavitands.[20] Further functionization of the tetrol was conceived through a modular coupling approach using 2,2-bis(phenyldioxymethyl)propionic acid,[21] a well established synthetic building block in the synthesis of macromolecules.[22] However, this proved difficult, as we screened several DCC and DMAP mediated coupling, procedures. Additionally, the reactions mixtures were complicated by the formation of urea, which presented difficulty in the purification, and identification of the product. However, employing a Mitsunobu protocol, using a triphenylphosphine and DIAD mediated coupling in THF, we were able to isolate the product in quantitative yield by precipitation of the reaction mixture into cold methanol. Moreover, we envisioned that catalytic hydrogenolysis to remove the protected alcohols would secure the target molecules (Scheme 1). Thus, we coupled the tetrol cavitands with a benzyl ketal protected acid, and subsequently removed the benzyl-protecting group to give the polyhydroxy cavitands **3** and **4** in excellent yields with no need of column chromatography.

2.1. Synthesis of octol cavitands 3 and 4

Synthesis of octol cavitand **3** (Scheme 1) began from acid catalyzed condensation of resorcinol **5** and heptaldehyde **6** in equal molar quantities in a refluxing solution of 95% ($EtOH/H_2O$), which afforded resorcinarene **8** in 96% yield. Subsequent aromatic bromination using *N*-bromosuccinamide in a solution of 2-butanone gave tetrabromide **10** in 75% yield. Cs_2CO_3 catalyzed cavitand formation with bromochloromethane as the bridging reagent in 1:1 DMF/DMSO using a sealed tube reaction vessel afforded after recrystallization from CH_2Cl_2/hexanes bromo-substituted cavitand **12** in 89% yield. (CAUTION: the reaction vessel must be able to tolerate an internal pressure of several atmospheres). Metal–halogen exchange between bromo cavitand **12** and *n*-butyllithum and subsequent nucleophilic attack on ethylchloroformate afforded tetraester **14** in 80% yield, after recrystallization from 80% EtOAc/EtOH. Reduction of the tetraester **14** using lithium aluminum hydride afforded tetrol **16** in 85% yield. Mitsunobu esterification protocol of tetrol **16** with 2,2-bis(phenyldioxymethyl)propionic acid **18** afforded tetrabenzylketal **19** in 96% yield. Palladium catalyzed hydrogenation of tetrabenzylketal **19** afforded octol cavitand **3** in 94% yield. Using the same protocol we synthesized octol cavitand **4** from resorcinol **5** and acetaldehyde **7** (Scheme 1). We confirmed the structure of **3** and **4** by ^1H NMR, ^{13}C NMR, MALDI analysis, and ^1H–^1H COSY.

2.2. Synthesis of octaester cavitands 21 and 22

In order to test the viability of the octols **3** and **4** to further modification utilizing esterification protocols, we synthesized octaacetate cavitands **21** and **22** (Scheme 2) upon reaction of cavitands **3** and **4**, respectively, with acetic anhydride in dry THF at rt using triethylamine and a

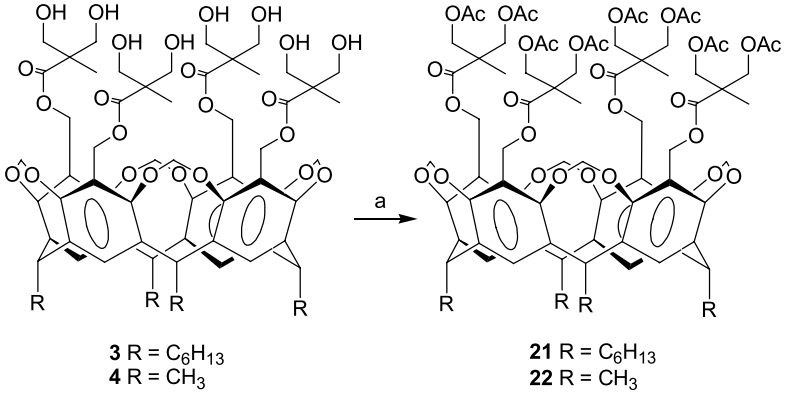


Scheme 1. Synthesis of polyhydroxy cavitands **3** and **4**. Reagents and conditions: (a) 95% EtOH/H_2O, HCl, reflux, **8**=96%, **9**=82%. (b) NBS, 2-butanone, rt, **10**=75%, **11**=71%. (c) $BrCH_2Cl$, Cs_2CO_3, 1:1 DMF/DMSO, 88 °C, sealed tube, **12**=89%, **13**=94%. (d) *n*-BuLi, ethylchloroformate, THF, −78 °C, **14**=80%, **15**=89%. (e) $LiAlH_4$, THF, rt, **16**=85%, **17**=87%. (f) **18**, triphenylphosphine, DIAD, THF, rt, **19**=96%, **20**=98%. (g) Pd/C, H_2, EtOAc, THF, **3**=94%, **4**=95%. Yields correspond to pure compounds.

catalytic amount of DMAP. Upon completion of the reaction, removal of the solvent under reduced pressure gave a residue, which was partitioned between methylene chloride and water. Evaporation of the methylene chloride yielded **21** in 98% and **22** in 97% as white solids.

2.3. ^{1}H NMR spectra of 21 and 22

Before recording spectra we ensured that the samples were free of solvents used during the synthesis and crystallization such as DMSO, MeOH, CH_2Cl_2, H_2O, etc. This was accomplished by repeatedly dissolving the compound in solutions of dry THF and dry toluene and then distillation of the solvent through a vigreux column followed by drying under heated vacuum overnight. The ^{1}H NMR spectrum of **21** recorded in $CDCl_3$ at 20 °C (Fig. 2) showed a singlet corresponding to the four aromatic protons (H_1) of the resorcinarene rings at 7.2 ppm. A double doublet characteristic of methylene-bridged protons[3] is observed at 5.7 ppm (four outer protons, H_2), and at 4.1 ppm (four inner protons, H_3). A 8H singlet corresponding to the methylene protons (H_4) adjacent to the resorcinarene rings at 5.0 ppm, a triplet at 4.7 ppm corresponding to four benzylic protons (H_7), and a singlet corresponding to the methylene groups (H_6) adjacent to the prochiral center at 4.0 ppm were also observed. Further upfield, were three separate resonances for the alkyl chains; a quartet for the methylene groups (H_8) at 2.2 ppm, a broad multiplet at 1.5–1.2 ppm for the methylene groups (H_9–H_{12}), and a triplet at 0.88 ppm for the terminal methyl groups (H_{13}). Also observed was a 12H singlet corresponding to the methyl groups (H_5) adjacent to the prochiral center at 1.1 ppm. Interestingly, acetate group resonances that would have been consistent with literature at around 2.1 ppm were not present in the ^{1}H NMR spectrum of **21**.[23] Similarly, the ^{1}H NMR spectrum of **22** recorded in $CDCl_3$ at 20 °C (Fig. 2) showed proton resonances at expected chemical shift values but did not exhibit acetate signals at chemical shift values consistent with literature.[23] Instead, a signal upfield at 1.5 ppm that integrated to twenty-four protons was observed for the acetate groups. In ^{1}H NMR spectra of **21** and **22**, the upfield signal shifts in the acetate methyl resonances are characteristic of aromatic shielding and we suspected that intramolecular inclusion of the acetate groups within the



Scheme 2. Synthesis of octaacetate cavitands **21** and **22**. Reagents and conditions: (a) acetic anhydride, TEA, DMAP, THF, rt, **21**=98%, **22**=97%. Yields correspond to pure compounds.

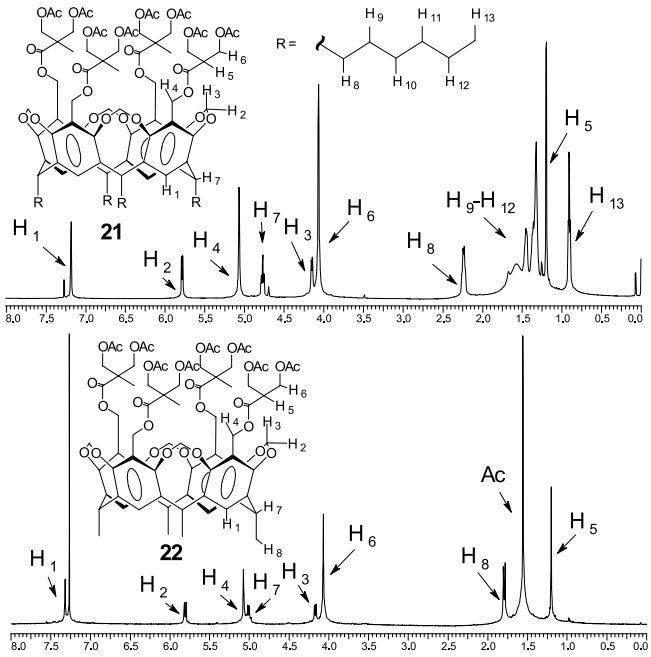


Figure 2. ^{1}H NMR spectra of octaacetates **21** and **22** in $CDCl_3$ at 20 °C at 360 MHz.

cavitand cavity was responsible. The inclusion is believed to be intramolecular as evidenced by the fact that ^{1}H NMR spectra recorded at 5, 10, 15, 20 and 25 mM concentrations resulted in no change of the spectra. Additionally, ^{1}H NMR spectral data of **21** and **22** recorded in deuterated solvents of different polarity, viz., benzene-d_6, 1,2-dichlorobenzene-d_4, dimethylsulfoxide-d_6, and methanol-d_4, resulted in no change of the spectrum.[4,24a–d]

2.4. Variable temperature ^{1}H NMR spectra of 21 and 22

The ^{1}H NMR spectra of **21**, recorded at different probe temperatures in $CDCl_3$ at 360 MHz (Fig. 3), showed a downfield shift of 0.7 ppm (from 1.5 to 2.2 ppm) in acetate methyl resonance upon cooling from 20 to −50 °C for octaacetate **21**. Similarly, the spectra of **22** also show a downfield field shift for the acetate resonances upon cooling to −50 °C (Fig. 3). This suggests that at 20 °C there is a higher percentage of the 'bound' species present, however exchange is fast on the NMR timescale and an averaged signal is observed at 1.5 ppm. At intermediate temperature, i.e. −20 °C broad signals are observed, which correspond to both the free and bound species being present and in intermediate-rate exchange. At −50 °C, the acetyl groups are mostly uncomplexed and a higher percentage of the 'free' species is favored giving rise to a single signal at 2.2 ppm.

Importantly, when octaacetate **21** was heated in DMSO-d_6, inside the 5 mm probe of a 360 MHz spectrometer, a sharpening of the acetate signals at 1.5 ppm was observed in the temperature range of 300–380 K, which arises from a higher rate of exchange between the bound and the free species at higher temperatures (Fig. 4).

2.5. Synthesis of octaester cavitands 23–26

In order to examine the intramolecular inclusion phenomenon further, we treated the octol cavitand **3** with a series of electrophiles that afforded the octaester cavitands **23**–**26** (Scheme 3). We selected octol **3** as the starting material due to its higher solubility in organic solvents than octol **4**, which we attribute to increased chain length, i.e. hexyl chains versus methyl chains. Acyl halides were of different size and steric bulk, including mesyl chloride (as the sulfur analogue of the acetates) and isobutyryl chloride. Additionally we examined aromatic esters of *p*-anisoyl chloride and *p*-biphenylcarbonyl chloride. The reactions were performed in dry THF at rt using triethylamine and catalytic amount of DMAP. Each of the electrophiles reacted quantitatively and afforded the desired products with no need of column chromatography.

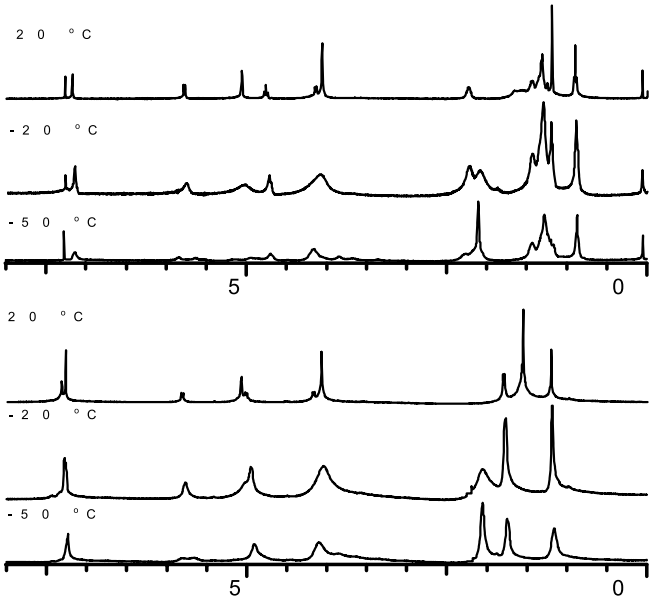


Figure 3. Variable temperature ^{1}H NMR spectra of octaacetates **21** and **22** in $CDCl_3$ at 360 MHz.

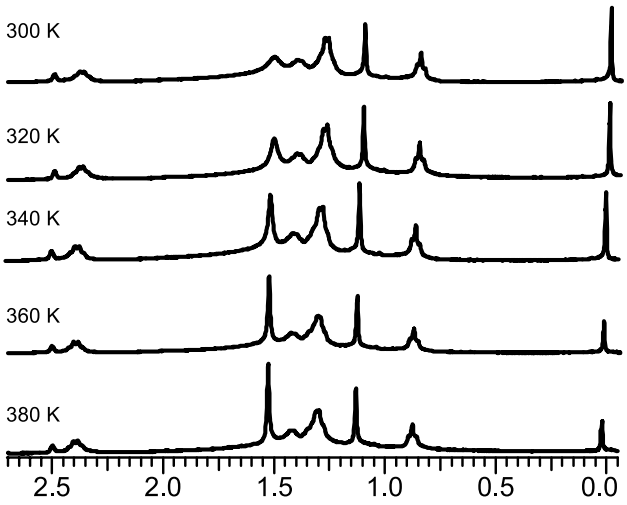


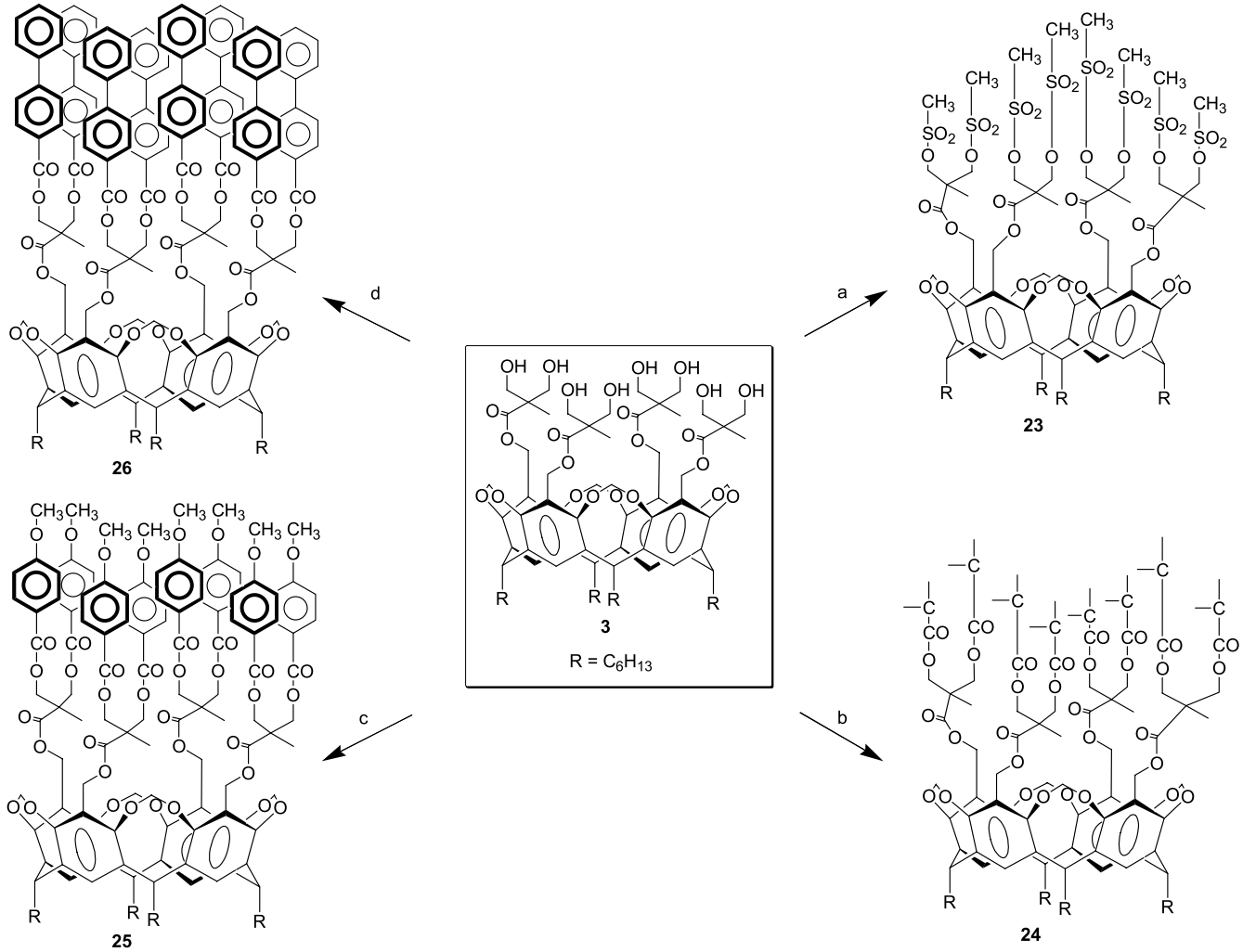
Figure 4. Parts of the variable temperature ^{1}H NMR spectra of octaacetate **21** in DMSO at 360 MHz.

2.6. ^{1}H NMR spectra of 23 and 24

Similar to octaacetates **21** and **22**, the ^{1}H NMR spectrum of octamesylate **23** recorded in $CDCl_3$ at 360 MHz showed most resonances at expected chemical shift values[23] however, the mesylate methyl signal was shifted upfield at 1.5 ppm. Variable temperature ^{1}H NMR experiments on **23** revealed a downfield shift in the mesylate resonance upon cooling from 20 to −50 °C. In contrast, the octaisopropionate **24** (Fig. 5) showed most resonances at expected chemical shift values[23] and only a small upfield resonance shift ($\Delta\delta=0.07$) to 1.06 ppm for the methyl protons in the isopropyl esters was observed, compared to literature value of 1.13 ppm. Interestingly, the isopropyl methyls were observed in a double doublet-splitting pattern (Fig. 6), suggesting chemical non-equivalence of the two-methyl groups. Although the upfield ^{1}H NMR shift is fairly small excluding total encapsulation of the isopropyl group, however, influence of the aromatic cavity such that the methyl groups are oriented towards and away from it cannot be discounted for the non-equivalence of the isopropyl groups.

2.7. Variable temperature ^{1}H NMR of 24

During acquisition of the ^{1}H NMR spectra of **24**, cooling from 20 to −20 °C (Fig. 6), the isopropyl group signals began to merge while shifting downfield. The merging and



Scheme 3. Synthesis of octaester cavitands **23**–**26**. Reagents and conditions: (a) mesyl chloride, TEA, DMAP, THF, rt, **23**=98%. (b) Isobutyryl chloride, TEA, DMAP, THF, rt, **24**,=98%. (c) *p*-Anisoyl chloride, TEA, DMAP, THF, rt, **25**=97%. (d) *p*-Biphenylcarbonyl chloride, TEA, DMAP, rt, **26**=95%. Yields correspond to pure compounds.

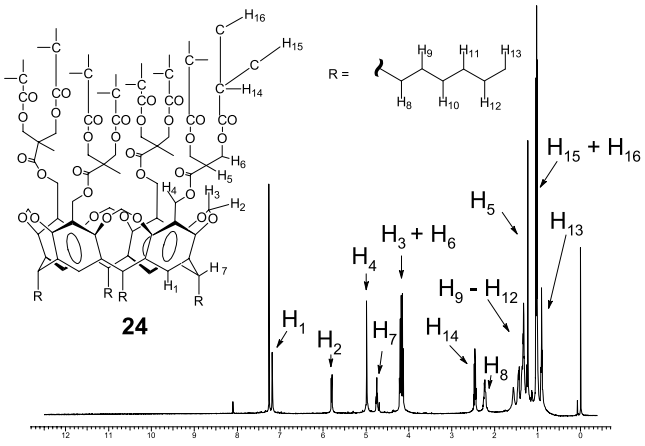


Figure 5. ^{1}H NMR spectra of octaisopropionate **24** in $CDCl_3$ at 500 MHz.

shifting of the signals at lower temperatures was consistent with our previous findings for the octaesters **21**, **22**, and **23** although not as pronounced, which we attribute to the larger size of the isopropyl moiety.

2.8. ^{1}H NMR spectra of 25 and 26

Figure 7 shows the spectrum of octaanisoate **25** here we observed all resonances at expected values[23] with no intramolecular inclusion of the methoxy signal. Finally, in octaphenylbenzoate compound **26** interactions of the cavitand cavity and the phenylbenzoate group was not observed. From these results one can glean certain information about the intramolecular inclusion phenomenon in these novel cavitand esters. It is apparent from the spectral data obtained in this study that the intramolecular inclusion is directly related to size of the ester moiety or 'guest'. When the ester moiety is 'small' such as the acetate and mesylate, the cavitand is able to accommodate the guest. The cavity contains aromatic rings that effectively shield the acetate signals causing upfield shifts in the ^{1}H NMR spectra. When one substitutes a larger ester group such as the isopropyl, the intramolecular inclusion is only

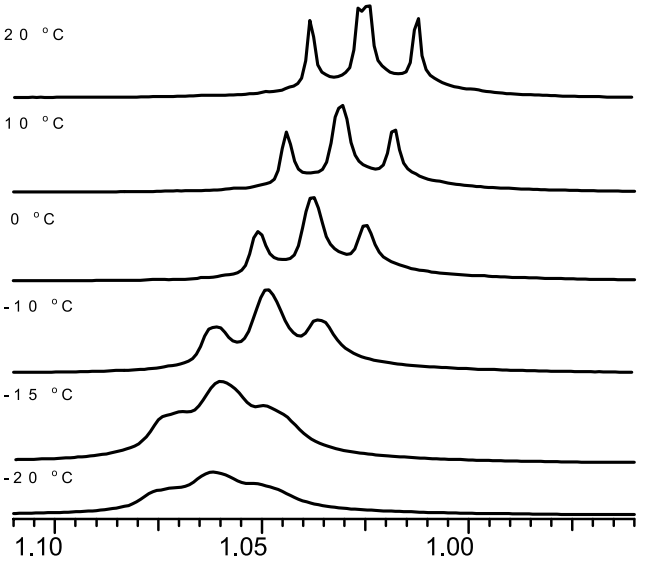


Figure 6. Parts of the variable temperature ^{1}H NMR spectra of octaisopropionate **24** in $CDCl_3$ at 500 MHz.

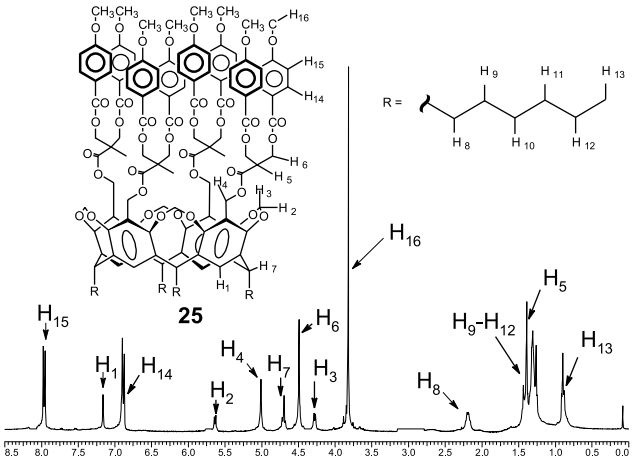


Figure 7. ^{1}H NMR spectra of octaanisoate **25** in $CDCl_3$ at 360 MHz.

partial as a direct result the larger size of the ester moiety. When the ester size is increased to the aromatic system no inclusion was observed within our detection limits.

3. Conclusion and outlook

We have demonstrated a highly efficient and facile methodology for the synthesis of polyhydroxy functionalized cavitands and their octaester derivatives. The synthetic strategy relied upon the combination of classical methods of stepwise and modular approaches for the synthesis of the target molecules, which proceeded in excellent yield without the need of column chromatography. ^{1}H NMR experiments showed that intramolecular inclusion of the ester moieties is directly related to their size and steric bulk. Increasing the steric bulk or size of the ester moiety resulted in partial or no intramolecular inclusion. Such cavitands offer unique molecular platforms for host–guest chemistries, sensor development, metal complexation, as well as new polymers and self-assembled systems, and as potential reaction sites, and novel catalytic platforms.

4. Experimental

4.1. General

Synthesis of the requisite starting tetrol cavitand **17** has been reported elsewhere.[3,19,20] All reactions were carried out under a nitrogen atmosphere in flame-dried glassware.

Commercially available reagents were purchased from Acros Chemical Co. or Aldrich Chemical Co. and were used without further purification. Cs_2CO_3 was dried by heating to 250 °C for 24 h and then cooled to ambient temperature in a vacuum desiccator. *N*-bromosuccinimide (NBS) was recrystallized from boiling water 1 g to 100 mL. Triphenylphosphine was recrystallized from boiling MeOH. 2,2-Bis(phenyldioxymethyl)propionic acid **18** was prepared from 2,2-bis(hydroxymethyl)propionic acid and benzaldehyde dimethyl acetal according to literature procedures.[20] Triethylamine was distilled from potassium hydroxide under a nitrogen atmosphere and stored over potassium

hydroxide. DMF and DMSO were stored over molecular sieves (3 Å) for 24 h and degassed prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl under a nitrogen atmosphere.

Thin layer chromatography was performed using Whatman silica gel 60 Å with fluorescent indicator on 250-micrometer thickness glass backed with hexanes/ethyl acetate as the mobile phase. NMR spectra were recorded on a Bruker 250 and 360 MHz, and an Inova 500 MHz spectrometers in $CDCl_3$ or DMSO containing 0.03% TMS. Chemical shifts are listed downfield in ppm relative to tetramethylsilane. Coupling constants are given in Hz. Mass spectrometric analysis was performed on a Bruker Autoflex MALDI-TOF MS with DHB as the matrix. HRESIMS data were obtained using either PEG (polyethylene glycol) or the PPG (polypropylene glycol) as internal standard. Data were obtained on JEOL Model JMS-T100LC (The AccuTOF) by spraying in MeOH.

4.1.1. Resorcinarene (8).[2b] Resorcinol **5** (20 g, 0.181 mol) was dissolved in 120 mL of 95% ethanol/water, and 36 mL of 37% aqueous HCl. The solution was cooled in an ice bath and 25.3 mL (0.181 mol) of heptaldehyde **6** was added drop wise over a period of 1 h with an addition funnel. The mixture was allowed to slowly warm to rt. The reaction mixture was then maintained at 80 °C for 12 h, and the yellow needles that separated were collected by filtration and washed with cold 1:1 ethanol–water until the material was pale yellow, and neutral to pH paper. Drying under vacuum at 100 °C for 16 h afforded 35.9 g (96%) of **8**: ^{1}H NMR (250 MHz, DMSO) δ 0.829 (t, 12H, CH_3), 1.21 (m, 32H, $CH_2CH_2CH_2CH_2$), 2.07 (m, 8H, CH_2 α to methine), 4.23 (t, 4H, methine, J=7.3 Hz), 6.13 (s, 4H, ArH), 7.12 (s, 4H, ArH), 8.85 (s, 8H, Ar-OH); MALDI-TOF m/z 847 ($M+Na^+$).

4.1.2. Tetrabromide resorcinarene (10).[2b] To a stirred orange solution of resorcinarene **8** (30 g, 0.036 mol) in 181 mL of 2-butanone was added 38.5 g (0.216 mol) of *N*-bromosuccinimide in portions. After 5 min, the product began to precipitate. The mixture was stirred for an additional 3 h, and the product was collected by filtration and washed with cold 2-butanone, drying under vacuum at 100 °C for 12 h afforded 30.9 g (75%) of **10** as a white solid: ^{1}H NMR (250 MHz, DMSO) δ 0.818 (t, 12H, CH_3), 1.28 (m, 32H, $CH_2CH_2CH_2CH_2$), 2.13 (m, 8H, CH_2 α to methine), 4.34 (t, 4H, methine, J=7.1 Hz), 7.31 (s, 4H, ArH), 9.06 (s, 8H, Ar-OH); MALDI-TOF m/z 1159 ($M+Na^+$).

4.1.3. Tetrabromide cavitand (12).[2b] To a sealed tube (Ace Glass Co., pressure tube, 200 ml volume) was added tetrabromide resorcinarene **10** (3 g, 0.0026 mol) and 26 mL of degassed dry DMF and 26 mL of degassed dry DMSO and (5.74 g, 0.0415 mol) of dry Cs_2CO_3. After stirring at rt for 1 h the solution developed a deep purple color. Then was added 2.7 mL (0.415 mol) of CH_2BrCl in one portion. The reaction was then heated to 88 °C for 3 h. (CAUTION: modifications of the reaction conditions may result in much larger internal pressures.) The sealed tube was then cooled in an ice bath for 2 h and poured into (600 ml of 2% HCl), the solid was filtered and slowly recrystallized from CH_2Cl_2/hexanes, drying under vacuum at 100 °C for 12 h afforded 2.78 g (89%) of **12** as off white needles: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, 12H, CH_3), 1.39 (m, 32H, $CH_2CH_2CH_2CH_2$), 2.24 (m, 8H, CH_2 α to methine), 4.40 (d, 4H inner OCH_2, J=7.31 Hz), 4.88 (t, 4H, methine, J=7.8 Hz), 5.97 (d, 4H outer OCH_2, J=7.31 Hz), 7.03 (s, 4H, ArH); MALDI-TOF m/z 1207 ($M+Na^+$).

4.1.4. Tetraester cavitand (14).[2b] Before metal–halo exchange it was important to drive off reactive solvents such as CH_2Cl_2 trapped within the crystal lattice, this was most easily accomplished by repeatedly dissolving the material in solutions of dry THF and dry toluene and then distillation of the solvent through a vigreux column. Tetrabromide cavitand **12** (10 g, 0.0084 mol) was dissolved in 844 mL of dry THF and cooled to −78 °C in a dry ice-acetone bath, then was added 52.5 mL of *n*-butyllithium, 1.6 M solution in hexanes. The mixture was stirred for 2 h at −78 °C and then was added 8.02 mL (0.065 mol) of ethyl chloroformate all in one portion. The mixture was allowed to warm to rt over a 12 h period after which time was added 22 mL of water. The THF was removed in vacuo and the residue was partitioned between methylene chloride (250 mL) and water (100 mL). The aqueous layer was extracted twice with methylene chloride (250 ml) and the combined organic layers were washed with brine (200 ml) dried over sodium sulfate and concentrated in vacuo. Overnight recrystallization from 80% EtOAc/EtOH and drying under vacuum at 100 °C for 12 h afforded 8.17 g (80%) of **14** as white needles: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, 12H, CH_3), 1.09–1.49 (m, 44H, $CH_2CH_2CH_2CH_2$, and OCH_2CH_3), 2.20 (m, 8H, CH_2 α to methine), 4.29 (q, 8H, OCH_2CH_3), 4.59 (d, 4H inner OCH_2, J=7.31 Hz), 4.88 (t, 4H, methine, J=7.8 Hz), 5.97 (d, 4H outer OCH_2, J=7.31 Hz), 7.03 (s, 4H, ArH); MALDI-TOF m/z 1183 ($M+Na^+$).

4.1.5. Tetrol cavitand (16). Tetraester cavitand **14** (5 g, 0.0041 mol) was dissolved in 130 mL of dry THF and transferred via canula to a flask containing 1.55 g (0.041 mol) of $LiAlH_4$ in 16 mL of dry THF. The mixture was stirred at rt for 12 h and then was carefully added 2 mL of water followed by 2 mL of 10% NaOH. The mixture was filtered through celite, concentrated in vacuo, and the residue was partitioned between methylene chloride (150 mL) and water (50 mL). The aqueous layer was extracted twice with methylene chloride (100 mL) and the combined organic layers were washed with brine (100 mL) dried over sodium sulfate and concentrated in vacuo. Drying under vacuum at 100 °C for 12 h afforded 3.46 g (85%) of **16** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 12H, CH_3), 1.17 (s, 12H, CH_3 α to prochiral center), 1.31 (m, 32H, $CH_2CH_2CH_2CH_2$), 1.43–1.54 (m, 24H, $OCOCH_3$), 2.23 (m, 8H, CH_2 α to methine), 4.04 (s, 16H, CH_2 α to prochiral center), 4.14 (d, 4H inner OCH_2, J=7.32 Hz), 4.78 (t, 4H, methine, J=7.8 Hz), 5.04 (s, 8H, CH_2OCO), 5.78 (d, 4H outer OCH_2, J=7.32 Hz), 7.16 (s, 4H, ArH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3, 17.9, 20.1, 22.84, 27.9, 29.6, 32.0, 37.0, 46.3, 56.9, 65.6, 100.2, 121.4, 122.7, 138.4, 154.4, 170.6, 172.6; MALDI-TOF m/z 1015 ($M+Na^+$). HRESIMS m/z: 1015.5547 $[M+Na]^+$ (Calcd for $C_{60}H_{80}O_{12}Na$, 1015.5558).

4.1.6. Tetrabenzyl ketal cavitand (19). Tetrol cavitand **16** (1 g, 0.0010 mol) was dissolved in 5 mL of dry THF, then was added 1.37 g (0.006 mol) of 2,2-bis(phenyldioxymethyl)propionic acid **18** and 2.12 g (0.008 mol) of triphenylphosphine. Then was added, drop wise at rt, 1.6 mL of diisopropyl diazodicarboxylate. The reaction was stirred for 24 h and precipitated into cold methanol, the product was collected and washed with cold methanol. Drying under vacuum at 100 °C for 12 h afforded 1.73 g (96%) of **19** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.91 (t, 12H, CH_3), 1.17 (s, 12H, CH_3 α to prochiral center), 1.31 (m, 32H, $CH_2CH_2CH_2CH_2$), 1.43–1.54 (m, 24H, $OCOCH_3$), 2.23 (m, 8H, CH_2 α to methine), 4.04 (s, 16H, CH_2 α to prochiral center), 4.14 (d, 4H inner OCH_2, J=7.32 Hz), 4.78 (t, 4H, methine, J=7.8 Hz), 5.04 (s, 8H, CH_2OCO), 5.78 (d, 4H outer OCH_2, J=7.32 Hz), 7.16 (s, 4H, ArH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3, 17.9, 20.1, 22.8, 27.9, 29.6, 32.0, 36.9, 46.3, 56.9, 65.6, 100.2, 121.4, 122.7, 138.4, 154.4, 170.6, 172.6; MALDI-TOF *m/z* 1831 ($M+Na^+$). HRESIMS *m/z*: 1831.8692 $[M+Na]^+$ (Calcd for $C_{108}H_{128}O_{24}Na$, 1831.8693).

4.1.7. Octol cavitand (3). Tetrabenzyl ketal cavitand **19** (1 g, 0.0005 mol) was dissolved in 7.8 mL of dry THF, and 71 mL of EtOAc then was added (0.100 g, $Pd(OH)_2$ 10%). The apparatus for catalytic hydrogenolysis was evacuated and filled with H_2(g) to 40 psi. The reaction mixture was then stirred for 24 h, and the $Pd(OH)_2$ was removed by filtration through celite. The filtrate was concentrated in vacuo to a volume of about 5 mL and was precipitated into cold methanol, the product was collected and washed with cold methanol, drying under vacuum at 100 °C for 12 h afforded (0.728 g, 94%) of **3** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.91 (t, 12H, CH_3), 1.17 (s, 12H, CH_3 α to prochiral center), 1.31 (m, 32H, $CH_2CH_2CH_2CH_2$), 1.43–1.54 (m, 24H, $OCOCH_3$), 2.23 (m, 8H, CH_2 α to methine), 4.04 (s, 16H, CH_2 α to prochiral center), 4.14 (d, 4H inner OCH_2, J=7.32 Hz), 4.78 (t, 4H, methine, J=7.8 Hz), 5.04 (s, 8H, CH_2OCO), 5.78 (d, 4H outer OCH_2, J=7.32 Hz), 7.16 (s, 4H, ArH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.3, 17.9, 20.07, 22.8, 27.9, 29.6, 32.0, 37.0, 46.3, 56.9, 65.6, 100.2, 121.4, 122.7, 138.4, 154.4, 170.6, 172.6; MALDI-TOF *m/z* 1479 ($M+Na^+$). HRESIMS *m/z*: 1479.7513 $[M+Na]^+$ (Calcd for $C_{80}H_{112}O_{24}Na$, 1479.7441).

4.1.8. Tetrabenzyl ketal cavitand (20). Tetrol cavitand **17** (0.450 g, 6.23×10^{-4} mol) was dissolved in 3.16 mL of dry THF, then was added 0.842 g (3.7×10^{-3} mol) of 2,2-bis(phenyldioxymethyl)propionic Acid **18** and 1.24 g (5.08×10^{-3} mol) of triphenylphosphine. Then was added, drop wise at rt, 1.0 mL of diisopropyl diazodicarboxylate, the reaction was then stirred for 24 h and precipitated into cold methanol, the product was collected and washed with cold methanol. Drying under vacuum at 100 °C for 12 h afforded 1.73 g (98%) of **20** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.10 (s, 12H, CH_3 α to prochiral center), 1.78 (d, 12H, CH_3 chain), 3.62 (d, 8H, CH_2 α to prochiral center), 4.25 (d, 4H inner OCH_2, J=7.32 Hz), 4.62 (d, 8H, CH_2 α to prochiral center), 5.04 (s, 8H, CH_2OCO), 5.12 (t, 4H, methine, J=7.8 Hz), 5.49 (s, 4H CH benzyl), 5.78 (d, 4H outer OCH_2, J=7.32 Hz), 7.25–7.69 (m, 24H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.3, 15.6, 30.9, 39.1, 39.5, 39.5, 39.7, 39.9, 40.1, 53.8, 57.3, 99.7, 119.1, 127.5, 138.9, 152.8, 156.8; MALDI-TOF *m/z* 1551 ($M+Na^+$). HRESIMS *m/z*: 1551.5488 $[M+Na]^+$ (Calcd for $C_{88}H_{88}O_{24}Na$, 1551.5563).

4.1.9. Octol cavitand (4). Tetrabenzyl ketal cavitand **20** 1 g (6.1×10^{-4} mol) was dissolved in 8.6 mL of dry THF and 86 mL of EtOAc and 0.100 g of 10% $Pd(OH)_2$ was added. The apparatus for catalytic hydrogenolysis was evacuated and filled with H_2(g) to 40 psi. The reaction mixture was then stirred for 24 h, and the $Pd(OH)_2$ was removed by filtration through celite. The filtrate was concentrated in vacuo to a volume of about 5 mL and was precipitated into cold methanol, the product was collected and washed with cold methanol, drying under vacuum at 100 °C for 12 h afforded 0.728 g (95%) of **4** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.05 (s, 12H, CH_3 α to prochiral center), 1.79 (d, 12H, CH_3 chain), 3.63 (m, 16H, CH_2 α to prochiral center), 4.13 (d, 4H inner OCH_2, J=7.32 Hz), 5.00 (q, 4H, methine, J=7.8 Hz), 5.08 (s, 8H, CH_2OCO), 5.83 (d, 4H outer OCH_2, J=7.32 Hz), 7.23 (s, 4H, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.1, 59.4, 95.4, 96.7, 99.1, 103.3, 111.9 126.6 135.3, 195.7, 196.2, 197.0; MALDI-TOF *m/z* 1200 ($M+Na^+$). HRESIMS *m/z*: 1199.4334 $[M+Na]^+$ (Calcd for $C_{60}H_{72}O_{24}Na$, 1199.4311).

4.2. Synthesis of the octaester cavitands

4.2.1. Octaacetate cavitand (21). To a solution of octol **3** 0.100 g (6.7×10^{-5} mol) in 6.86 mL of dry THF was added 0.075 mL of triethylamine, 0.054 mL of acetic anhydride, and a few crystals of DMAP (15 mg). The reaction mixture was stirred for 1 h, after which time TLC analysis (hex/EtOAc 1:1) showed complete consumption of the starting material. The THF was removed in vacuo and the residue was partitioned between methylene chloride (30 mL) and water (10 mL). The aqueous layer was extracted with methylene chloride (2×30 mL) and the combined organic layer was washed with brine (30 mL) dried over sodium sulfate and concentrated in vacuo to give 0.122 g (99%) of **21** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, 12H, CH_3), 1.17–1.31 (m, 44H, CH_3 α to prochiral center and $CH_2CH_2CH_2CH_2$), 1.43–1.54 (m, 24H, $OCOCH_3$), 2.23 (m, 8H, CH_2 α to methine), 4.04 (s, 16H, CH_2 α to prochiral center), 4.14 (d, 4H inner OCH_2, J=7.32 Hz), 4.78 (t, 4H, methine, J=7.8 Hz), 5.04 (s, 8H, CH_2OCO), 5.78 (d, 4H outer OCH_2, J=7.32 Hz), 7.16 (s, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 17.9, 20.1, 22.8, 27.9, 29.6, 32.0, 36.9, 46.2, 56.8, 65.6, 100.1, 121.3, 122.7, 138.4, 154.4, 170.5, 172.5; MALDI-TOF *m/z* 1816 ($M+Na^+$). HRESIMS *m/z*: 1815.8290 $[M+Na]^+$ (Calcd for $C_{96}H_{128}O_{32}Na$, 1815.8286).

4.2.2. Octaacetate cavitand (22). Following a procedure similar to the one described above, a solution of 0.1 g, (8.3×10^{-5} mol) of octol **4** in 8.31 mL of dry THF, 0.094 mL of triethylamine, 0.067 mL of acetic anhydride, and DMAP (15 mg) gave 0.122 g (97%) of **22** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (s, 12H, CH_3 α to prochiral center) 1.52 (m, 24H, $OCOCH_3$) 1.78 (d, 12H, CH_3 chain), 4.04 (s, 16H, CH_2 α to prochiral center) 4.14 (d, 4H inner OCH_2, J=7.32 Hz) 4.78 (t, 4H, methine, J=7.8 Hz) 5.04 (s, 8H, CH_2OCO) 5.78 (d, 4H outer OCH_2,

J=7.32 Hz) 7.16 (s, 4H, ArH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 15.9, 17.6, 31.1, 46.1, 56.7, 65.4, 99.7, 99.9, 120.6, 122.4, 136.1, 153.9, 170.4, 172.4; MALDI-TOF *m/z* 1536 ($M+Na^+$). HRESIMS *m/z*: 1535.5108 $[M+Na]^+$ (Calcd for $C_{76}H_{88}O_{32}Na$, 1535.5156).

4.2.3. Octamesylate cavitand (23). Following a procedure similar to the one described above, a solution of 0.050 g (3.3×10^{-5} mol) of octol **3** in 3.43 mL of dry THF, 0.037 ml of triethylamine, 0.023 mL of methanesulfonyl chloride, and DMAP (5 mg), gave 0.07 g (98%) of **23** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.92 (t, 12H, CH_3), 1.19–1.31 (m, 44H, CH_3 α to prochiral center and $CH_2CH_2CH_2CH_2$), 1.39–1.54 (m, 24H, $OSOCH_3$) 2.22 (m, 8H, CH_2 α to methine), 4.06 (s, 16H, CH_2 α to prochiral center), 4.13 (d, 4H inner OCH_2, J=7.2 Hz), 4.74 (t, 4H, methine, J=7.2 Hz), 5.06 (s, 8H, CH_2OCO), 5.77 (d, 4H outer OCH_2, J=7.2 Hz), 7.10 (s, 4H, ArH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.9, 17.3, 22.5, 27.7, 29.3, 29.8, 31.7, 36.5, 36.8, 46.6, 57.1, 69.0, 99.7, 121.0, 122.7, 138.6, 154.2, 170.8; MALDI-TOF *m/z* 2105 ($M+Na^+$). HRESIMS *m/z*: 2103.392 $[M+Na]^+$ (Calcd for $C_{88}H_{128}O_{40}S_8Na$, 2103.564).

4.2.4. Octaisopropanoate cavitand (24). Following a procedure similar to the one described above, a solution of 0.050 g, (3.3×10^{-5} mol) of octol **3** in 3.43 mL of dry THF, 0.043 ml of triethylamine, 0.032 mL of isobutyryl chloride, and DMAP (5 mg), gave 68 mg (99%) of **24** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 12H, CH_3), 1.03 and 1.01 (2d, 48H, $CH(CH_3)_2$), 1.22–1.31 (m, 44H, CH_3 α to prochiral center and $CH_2CH_2CH_2CH_2$), 2.24 (m, 8H, CH_2 α to methine), 2.45 (sep, 8H, CH α to $CH_3)_2$), 4.12–4.20 (m, 16H, CH_2 α to prochiral center, 4H inner OCH_2), 4.68 (t, 4H, methine, J=7.7 Hz), 5.04 (s, 8H, CH_2OCO), 5.79 (d, 4H outer OCH_2, J=7.0 Hz), 7.18 (s, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 17.4, 18.3, 22.2, 27.3, 29.0, 29.6, 29.8, 31.34, 33.4, 36.3, 45.9, 56.6, 64.6, 99.2, 120.9, 120.9, 137.8, 153.8, 172.3, 175.9; MALDI-TOF *m/z* 2040 ($M+Na^+$). HRESIMS *m/z*: 2040.072 $[M+Na]^+$ (Calcd for $C_{112}H_{160}O_{32}Na$, 2040.0790).

4.2.5. Octaanisoate cavitand (25). Following a procedure similar to the one described above, a solution of 0.050 g, (3.3×10^{-5} mol) of octol **3** in 3.43 mL of dry THF, 0.037 ml of triethylamine, 0.052 g of *p*-anisoyl chloride, and DMAP (5 mg) gave 0.085 g (98%) of **25** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, 12H, CH_3), 1.25–1.50 (m, 44H, CH_3 α to prochiral center, and $CH_2CH_2CH_2CH_2$), 2.18 (m, 8H, CH_2 α to methine), 3.82 (s, 24H, $ArOCH_3$), 4.27 (d, 4H inner OCH_2, J=7.13 Hz), 4.49 (s, 16H, CH_2 α to prochiral center), 4.78 (t, 4H, methine, J=8.0 Hz), 5.01 (s, 8H, CH_2OCO), 5.62 (d, 4H outer OCH_2, J=7.27 Hz), 6.87 (d, 16H, ArH, J=8.9 Hz), 7.16 (s, 4H, ArH), 7.95 (d, 16H, ArH, J=8.61 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.7, 17.6, 22.3, 27.4, 28.9, 29.3, 30.0, 31.4, 36.5, 46.5, 55.1, 57.2, 65.4, 99.3, 113.3, 131.0, 137.8, 146.2, 154.0, 163.3, 165.8, 172.5; MALDI-TOF *m/z* 2552 ($M+Na^+$). HRESIMS *m/z*: 2552.0413 $[M+Na]^+$ (Calcd for $C_{144}H_{160}O_{40}Na$, 2552.0383).

4.2.6. Octa *p*-phenyl benzoate cavitand (26). Following a procedure similar to the one described above, a solution of 0.050 g (3.3×10^{-5} mol) of octol **3** in 3.43 mL of dry THF, 0.037 ml of triethylamine, 0.065 g of *p*-biphenyl carbonyl chloride, and DMAP (5 mg) gave 0.094 g (95%) of **26** as a white solid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.88 (t, 12H, CH_3), 1.25–1.50 (m, 44H, CH_3 α to prochiral center, and $CH_2CH_2CH_2CH_2$), 2.18 (m, 8H, CH_2 α to methine), 3.82 (s, 24H, $ArOCH_3$), 4.27 (d, 4H inner OCH_2, J=7.13 Hz), 4.49 (s, 16H, CH_2 α to prochiral center), 4.78 (t, 4H, methine, J=8.0 Hz), 5.01 (s, 8H, CH_2OCO), 5.62 (d, 4H outer OCH_2, J=7.27 Hz), 6.87 (d, 16H, ArH, J=8.9 Hz), 7.16 (s, 4H, ArH), 7.95 (d, 16H, ArH, J=8.61 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.7, 17.6, 22.3, 27.4, 29.0, 29.3, 30.0, 31.4, 36.5, 46.5, 55.1, 57.2, 65.4, 99.3, 113.3, 131.0, 137.8, 146.2, 154.0, 163.3, 165.8, 172.5; MALDI-TOF *m/z* 2920 ($M+Na^+$). HRESIMS *m/z*: 2920.2148 $[M+Na]^+$ (Calcd for $C_{184}H_{176}O_{32}Na$, 2920.2042).

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Thermal and microwave assisted reactions of 2,5-disubstituted thienosultines with [60]fullerene: non-Kekulé biradicals and self-sensitized oxygenation of the cycloadduct

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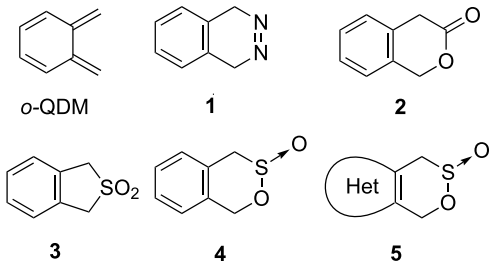
Abstract—Refluxing an *o*-dichlorobenzene solution of 2,5-disubstituted thienosultines **10a–f** with [60]fullerene for 2–24 h gave both 1:1 and 2:1 cycloadducts in 37–79% isolated yields. The reaction was highly accelerated by microwave irradiation giving comparable yields of cycloadducts. Sultines **10a–f** underwent cheletropic extrusion of SO_2 to form the corresponding non-Kekulé biradical intermediates **11a–f**, which were subsequently trapped by [60]fullerene to form corresponding cycloadducts. The activation energy barriers ($\Delta G_c^{\neq}$) determined for the boat-to-boat inversion of these 4′,5′,6′,7′-tetrahydrobenzo[*c*]thieno-[5′,6′:1,2][60]fullerene adducts **12a–f** were found to be in the range of 13.5–14.8 kcal/mol. Unexpectedly, one of the monoadduct **12a** was found to be labile when kept in air under ambient light. Two new products **15** (a sulfine-enone) and **16** (an endione) were isolated from the decomposed **12a** and were found to derive from self-sensitized singlet oxygen reaction on the 2,5-dimethylthieno moiety of **12a**.

1. Introduction

Functionalization of [60]fullerene is fascinating and promising for new ferromagnetic materials and biological application because of its unique spherical structure, photochemistry, and radical quenching properties.[1] The Diels–Alder reaction of [60]fullerene with *ortho*-quinodimethanes (*o*-QDMs)[2] has been developed extensively and represents one of the most powerful methods for synthesizing a large variety of functionalized fullerenes.[1,2] *o*-QDM is usually obtained from thermal or photochemical elimination of a small molecule from various precursors shown in Scheme 1.[2]

The diazene **1** can form *o*-QDM cleanly, but its five-membered ring heterocyclic analogues are usually unstable at room temperature.[3] Isochromanone **2** will undergo thermal decarboxylation only under harsh conditions (such as flash vacuum pyrolysis at 500 °C) unless it is substituted with electron-donating groups on the aromatic moiety.[4] Among the precursors for *o*-QDM, sulfolene[5] **3** and sultine[6] **4** are good choices because they undergo pyrolysis at reasonably low temperatures and yet they are usually stable indefinitely at room temperature.

Despite many reports of using hetero-*o*-QDM to functionalize [60]fullerene,[1,7] relatively little is known about whether the non-Kekulé biradicals[8] such as trimethylenemethane (TMM) or tetramethyleneethane (TME) will add to [60]fullerene efficiently. A pioneering work on the cycloaddition of TMM with C_{60} has been reported by Wudl,[9a] where the TMM biradical was generated from a 7-alkylidene-2,3-diazabicycloheptene, but the cycloadduct of the TMM-C_{60} was not isolated due to its similar polarity with C_{60}.[9a] Palladium-mediated addition of TMM to C_{60} has also been successfully carried out by Luh.[9b] Meanwhile, Ohno et al. reported[9c] the first success in using TME biradical to functionalize C_{60}, where 3,4-fused pyrrolo-3-sulfolenes were used as TME precursors. As our continuous interests in the research of



Scheme 1.

Keywords: Non-Kekulé biradical; TME biradical; Microwave; Cycloaddition; [60]Fullerene; Singlet oxygen reaction.
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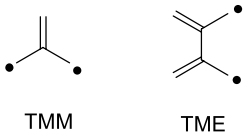
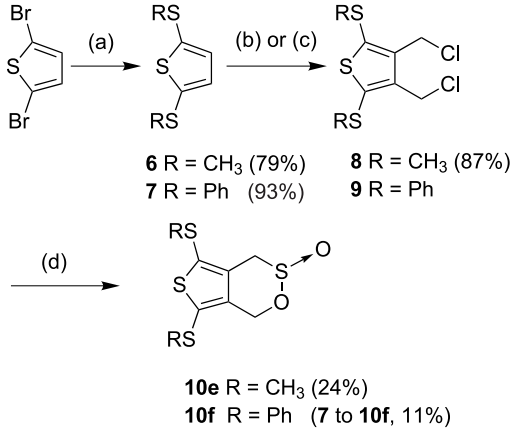
heteroaromatic-fused sultines **5** and their use in the generation of TME biradicals[10a,e] or hetero-*o*-QDMs,[10b–d] we report here the reaction of C_{60} with 2,5-disubstituted-thienosultines **10a–f** and an interesting self-sensitized singlet oxygen reaction of one of the fullerene adducts.



2. Results and discussion

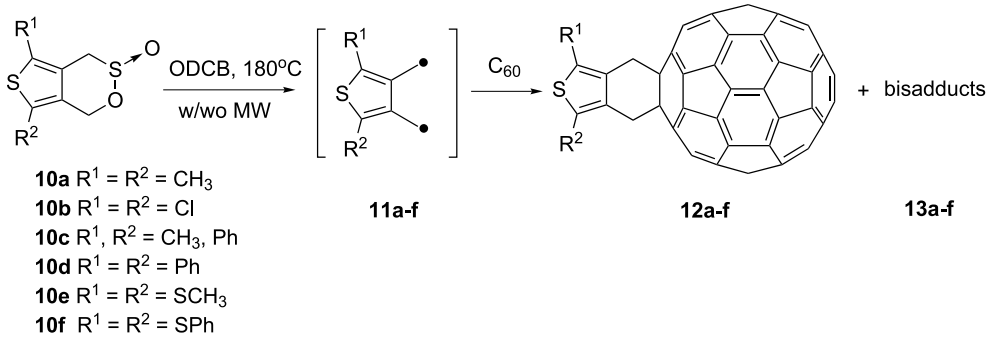
The syntheses of heterocyclic sultines **10a–d** through the reaction of corresponding bis(chloromethyl)thiophenes with Rongalite (sodium formaldehyde sulfoxylate) have been reported elsewhere.[10a,e] Sultines **10e** and **10f** were synthesized from **8** and **9** by a similar method, where the dialkylthio **8** and diarylthio **9** were obtained from lithium exchange of 2,5-dibromothiophene,[11] followed by thiolation, and then chloromethylation[3a,12] (Scheme 2). When refluxed in *o*-dichlorobenzene (ODCB) with C_{60} as a limiting reagent for different duration (2 h for **10a**,**c–f** and 24 h for **10b**), sultines **10a–f** underwent extrusion of SO_2, and the resulting non-Kekulé biradicals **11a–f** were intercepted as a mixture of 1:1 cycloadducts **12a–f** and 2:1 bisadducts **13a–f** in ca. 2–3:1 ratio (Scheme 3 and Table 1). When solutions of sultines **10a–f** with C_{60} were irradiated with microwave (900 W) under 180 °C for only 4 min, comparable yields of cycloadducts were obtained in all cases except **10b**; where sultine **10b** was almost completely converted to sulfolene instead of reacting with the C_{60}, therefore, only trace of adduct **12b** was observed. The isolated yields for these cycloadducts **12** and **13** were in the range of 37–79% (58–96% based on consumed C_{60}, Table 1). It is remarkable that microwave assisted synthesis dramatically shortened the reaction time needed compared to those by conventional heating.[13d] Furthermore, the ratio of monoadduct **12** vs. bisadduct **13** also increased from 2–3:1 to 3.5–6:1 when microwave was applied.



Scheme 2. Reagents and conditions: (a) 2.1 equiv *n*BuLi, THF, −78 °C, 30 min; 2.1 equiv RSSR, −78 °C, 1 h; (b) 37% HCHO, conc. HCl, rt, 8 h (for **8**); (c) $ClCH_2OCH_3$, $ZnCl_2$, $CHCl_3$, rt, 3 h (for **9**); (d) Rongalite, TBAB, DMF, rt, 10–24 h.

All fullerene adducts were separated by column chromatography on silica gel using cyclohexane/toluene as eluents. The low product yield for sultine **10b** was mainly due to its poor reactivity because there was no solubility problem. The bisadducts **13a–f** are mixtures of regioisomers and are usually difficult to be separated; therefore, their characterizations were only done by FAB-MS and ^{1}H NMR spectroscopy. The UV–vis spectra of compounds **12a–f** revealed a typical weak absorption band around 435 nm, which is characteristic of a dihydrofullerene structure for monoadduct.[1] Further support of the monoadducts **12a–f** came from FAB-MS by detecting their molecular ion peaks ($M+H^+$) at following *m*/*z* ratios: 859 for **12a**, 899 for **12b**, 921 for **12c**, 983 for **12d**, 921 for **12e**, and 1047 for **12f**.

^{1}H NMR spectra for **12a** showed that the methylene protons bridging C_{60} and thiophene displayed a singlet (δ 4.43) at 25 °C and the singlet became a well-resolved AB quartet below 5 °C. Variable-temperature NMR experiments revealed that these cycloadducts were in their boat forms and the boat-to-boat inversion rates can be determined. The coalescence temperature T_c of the two methylene doublets and their coupling constants were used to determine the activation energy barriers $\Delta G_c^{\neq}$.[10c,13,14] For **12a**, the two doublets coalesced to a broadened singlet at 291 K (T_c) and an activation energy, $\Delta G_c^{\neq}$, of 14.0±0.2 kcal/mol was calculated (Fig. 1a). Although different T_c values are expected for the two diastereotopic methylenes of **12c** due to molecular asymmetry, they happen to have same T_c values (290 K) and therefore have same activation energy barriers $\Delta G_c^{\neq}$ (Fig. 1b). Furthermore, despite the large variation in 2,5-disubstituents of **12a–f** (such as dimethyl, dichloro, diphenyl, bis(methylthio), and bis(phenylthio) groups), their $\Delta G_c^{\neq}$ are all within 13.5–14.8 kcal/mol



Scheme 3.

Table 1. Results of the cycloaddition reactions of sultines **10a–f** with C_{60} under microwave irradiation or conventional heating

Sultine	Microwave[a], yield (%)			Conventional heating[b], yield (%)		
	Time (min)	Monoadduct **12**	Bisadduct **13**	Time (h)	Monoadduct **12**	Bisadduct **13**
10a	4	47 (64)[c]	11 (15)[c]	2	38 (73)[c]	12 (23)[c]
10b	4	—[d]	—[d]	24	28 (44)[c]	9 (14)[c]
10c	4	39 (64)[c]	—[e]	2	47 (62)[c]	16 (20)[c]
10d	4	53 (81)[c]	9 (14)[c]	2	52 (65)[c]	20 (25)[c]
10e	4	41 (52)[c]	10 (13)[c]	2	52 (62)[c]	27 (32)[c]
10f	4	51 (76)[c]	15 (22)[c]	2	51 (63)[c]	27 (33)[c]

[a] Power 900 W, ODCB, 180 °C.
[b] ODCB, reflux.
[c] Based on consumed C_{60}.
[d] Sultine **10b** was completely converted to sulfolene without reacting with C_{60}.
[e] Trace.

(Table 2 and Figs. S1–S4). Compared to other 4,7-dihydrobenzo[*d*]thiophene-[5,6-*f*]-fullerene adducts such as **14a** and **14b**,[13b] these 4,7-dihydrobenzo[*c*]thiophene-[5,6-*e*]-fullerene adducts **12a–f** have larger $\Delta G_c^{\neq}$ by 2.8 kcal/mol on average.

The activation energy barriers of compounds **12a–f** are close to those of pyrazines[10c] and other carbocyclic fused [60]fullerenes.[14] Factors that may affect the activation energy barriers are dependent on the nature of the heterocyclic systems, such as bond lengths and angles,[7k,13b] tortional and angular constraints,[13b] electronic and steric effects.[10c] Bond order may have played an important role here on the magnitude of $\Delta G_c^{\neq}$, because **12a–f** which contain two *exocyclic* double bonds in the bridged cyclohexene ring have larger values in $\Delta G_c^{\neq}$, whereas compounds **14a**,**b** with an *endo* double bond character in the cyclohexene rings have smaller ones.[7f,13b,c] This observation is consistent with that reported by Illescas et al.[7f] where a correlation was found between the activation energies $\Delta G_c^{\neq}$ and the bond lengths of the cyclohexene double bond across the fullerene junction; that is, as the bond length increases the barrier also increases.

The ^{13}C NMR spectrum of **12a** showed only 20 peaks (with two peaks superimposed) when measured at 70 °C (well above T_c), where rapid ring inversion is expected and the symmetry of the molecule is simplified from C_s to C_{2v}, therefore, an overall of 21 peaks are expected. The ^{13}C NMR spectrum for **12a** showed the characteristic quaternary sp^3-carbon atoms of the 6,6-ring junction on the C_{60} cage at δ 66.9, the α-methyls of thiophene at δ 13.3, and the methylene bridges between thiophene and C_{60} at δ 41.4. There are 17 other peaks of quaternary sp^2 carbons between 134 and 158 ppm for compound **12a**. All spectroscopic features of **12a–f** are consistent with the monoadducts of thienobiradicals **11a–f** that add to C_{60} on its 6,6-ring junction. Complete spectroscopic data of **12a–f** are summarized in Section 3.

Research on the oxygenation[15–19] of fullerene derivatives has attracted considerable attention because it provides an excellent method for ring-opening of the fullerene cage.[1,19] Many oxidizing reagents, such as ozone,[15] iodosobenzene,[16] and *m*-CPBA,[18] have been employed to prepare fullerene oxides. Above all, photo-induced ring opening of [60]fullerene cage by reaction with singlet oxygen ($^1O_2$) seems to have drawn the most attention.[19] We were surprised to find that, short exposure of a non-degassed solution of **12a** in CS_2 to ambient light led to its quick decomposition, where two new products **15** and **16** (in about 1:2 ratio) could be isolated from this solution in 50–73% yields. Compound

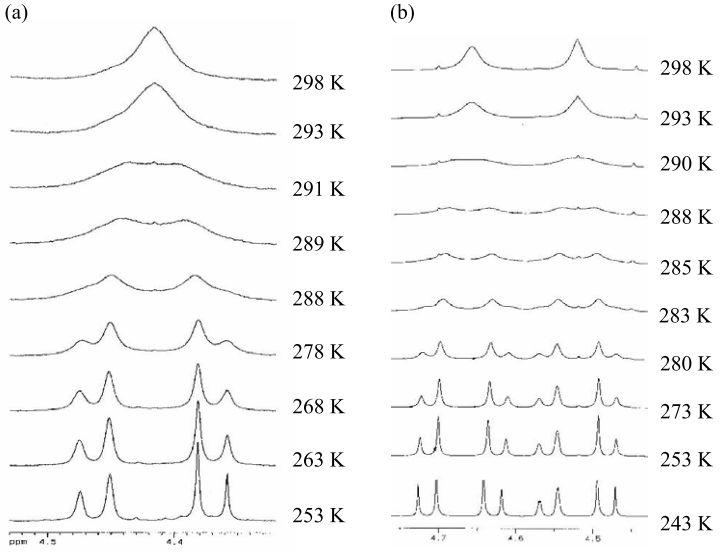
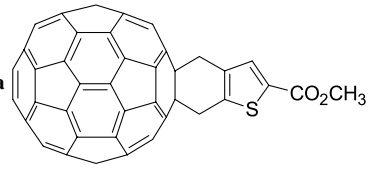
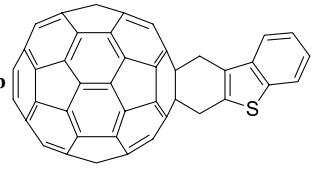


Figure 1. Various temperature ^1H NMR spectra (600 MHz, $CDCl_3/CS_2=1:2$) of cycloadducts: (a) **12a**, for which T_c is 291 K; and (b) **12c**, for which both the two T_c values are 290 K.

Table 2. Activation free energies ($\Delta G_c^{\neq}$) of [60]fullerene adducts **12a–f** from dynamic ^{1}H NMR[a] studies

Thienoadduct (substituents)	T_c (K)	$\Delta\nu$ (Hz)[b]	J_{AB} (Hz)[b]	$\Delta G_c^{\neq}$ (kcal/mol)	Reference
12a[c] (2,5-Dimethyl)	291	53.8	14.0	14.0±0.2	This work
12b[d] (2,5-Dichloro)	286	95.6	14.1	13.5±0.2	This work
12c[c] (2-Methyl-5-phenyl)	290	48.7	14.1	14.2±0.2	This work
	290	42.6	14.0	14.2±0.2	This work
12d[c] (2,5-Diphenyl)	304	59.1	14.1	14.8±0.2	This work
12e[c] (2,5-Bis(methlthio))	298	120.9	14.5	14.6±0.2	This work
12f[c] (2,5-Bis(phenylthio))	298	152.3	14.4	14.0±0.2	This work
14a 	245	26.2	14.7	12.0±0.2	13b
	241	14.8	13.9	11.9±0.2	13b
14b 	223	51.0	15.4	10.7±0.2	13b
	231	86.7	15.4	11.0±0.2	13b

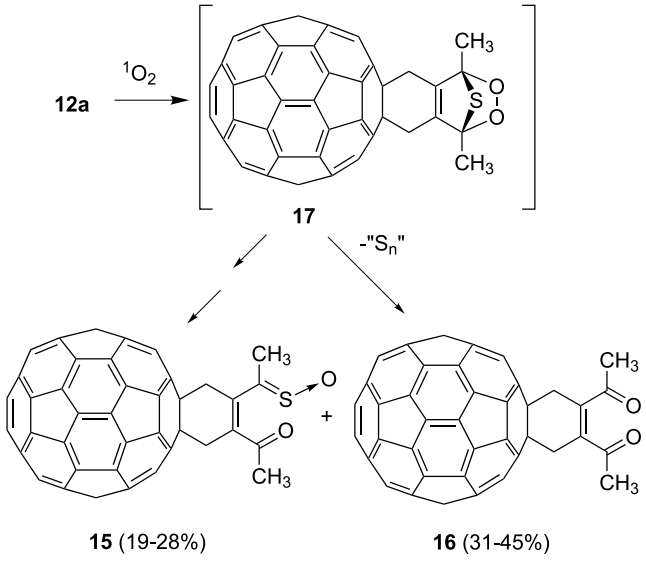
[a] Various temperature measurements were taken in a 600 MHz NMR (**12e** in a 500 MHz NMR). The activation free energies were obtained using equation: $k_c=2.22\ (\Delta\nu_{AB}^2+6J_{AB}^2)^{1/2}$, $\Delta G_c^{\neq}=4.58\ T_c\ (10.32+\log\ (T_c/k_c))\times10^{-3}$ kcal/mol.
[b] Data are reported at the highest temperature that affords well-separated quartet: −10 °C for **12a**, −15 °C for **12b**, 7 °C for **12c**, 20 °C for **12d**, −5 °C for **12e**, and 0 °C for **12f**.
[c] In $CDCl_3/CS_2=1:2$.
[d] In d_4-*ortho*-dichlorobenzene.

12a was found to be stable if either oxygen or light was kept from the system.

The new product **15** shows a molecular ion peak ($M+H^+$) at $m/z=891$, which is 32 units more than the cycloadduct **12a**. Furthermore, FT-IR spectrum of **15** shows medium signals at 1700 and 1529 cm^{-1}. Compound **16** shows strong vibrations at 1685, 1636 and 1617 cm^{-1} (Fig. S5, Supporting Information), but its molecular ion peak is the same with **12a** ($m/z=859$). The ^{13}C NMR of compound **15** shows the characteristic absorption of two carbonyl carbons at 197.7 (C=O) and 193.0 ppm (C=S→O) as well as two quaternary carbons of C_{60} moiety at 65.8 and 65.5 ppm. Compound **16** shows the characteristic absorption of only one carbonyl carbon at 200.6 ppm and one quaternary carbon of C_{60} moiety at 65.3 ppm.

Based on all structural information available for **15** and **16** and literature precedents,[19–21] we speculated that singlet oxygen reaction must have occurred on the thiophene moiety first and forming an endoperoxide **17**. Subsequent rearrangement of the endoperoxide **17** should lead to two fullerene products: one, an asymmetrical sulfine-enone **15**, and the other, a symmetrical endione **16** (see Scheme 4). Similar reactions have been reported in the methylene blue sensitized singlet oxygen reactions of cyclohexenone-fused thiophenes[20b,c] and 2,5-dimethylthiophene.[21] All spectroscopic data for **15** and **16** are consistent with the proposed structures.

It should be noted that other thienoadducts, such as 2,5-dichloro-, diphenyl-, bis(methylthio)-, bis(phenylthio)-, and 2-methyl-5-phenylthienofullerenes **12b–f**, are free from the singlet oxygen induced reaction and can be stored for several months in air with ambient light. There are two possibilities from the experimental results: (a) singlet oxygen was not formed in the solution of **12b–f**; therefore, they are stable in air and ambient light, or (b) singlet oxygen did form, however, the other cycloadducts **12b–f**, with different 2.5-substituents, simply did not react with it. We thus carried out two series of experiments to clarify possible reasons for the big differences in singlet oxygen reactivity towards **12a** and **12b–f**. In the first series of experiments, we found that adding 2,5-dimethylthiophene to the solution of other fullerene derivatives (e.g., **12d**) did result in the photoinduced oxygenation of 2,5-dimethylthiophene (entry



Scheme 4.

3 in Table 3 of Supporting Information). The results suggest that singlet oxygen is formed in all solutions of fullerene adducts **12a–f** and yet it reacts with them in very different rates.[22] In the second series of experiments, we prepared *d*-chloroform solutions of various 2,5-disubstituted thiophenes (**A–F**) with C_{60} (1.5 mol %) as a singlet oxygen sensitizer and irradiated them simultaneously with tungsten lamp to make sure that they were exposed to the same doses of light. The relative reactivity of singlet oxygen towards these 2,5-disubstituted thiophenes are: 2,5-dimethylthiophene **A** (37%), 2,5-bis(methylthio)thiophene **E** (26%), 2-methyl-5-phenylthiophene **C** (<6%) (Table 3, Supporting Information).[21c] The rest of the other 2,5-disubstituted-thiophenes (**B**, **D**, and **F**) did not show any observable reactivity toward singlet oxygen (namely <1% conversion) even after 42 h irradiation by tungsten lamp.

In summary, we report here the syntheses of a series of thieno-fused fullerenes which represents one of the rare examples in the derivatization of [60]fullerene through TME non-Kekulé biradicals.[9] When ODCB solutions of sultines **10a–f** and C_{60} were refluxed for 2–24 h or under microwave irradiation (900 W, <180 °C) for only 4 min, moderate to good yields (37–79%) of cycloadducts **12a–f** were obtained in all cases except **10b**. To our surprise, of the six thieno-[60]fullerene adducts **12a–f**, only **12a** was unstable in the presence of oxygen and ambient light. The decomposed products from **12a** were characterized and found to derive from singlet oxygen reaction on the 2,5-dimethylthiophene moiety of **12a**. Why some of the fullerene derivatives attract oxygen on standing, while others resist oxidation, deserves further photophysical and theoretical calculation study.

3. Experimental

3.1. General

3.1.1. 2,5-Bis(methylthio)thiophene 6. The preparation of **6** followed a literature[11] procedure. To a solution of 2,5-dibromothiophene (5.00 g, 20.7 mmol) in diethyl ether (100 mL) at −78 °C was added *n*-butyllithium (2.5 M in hexane, 43.4 mmol) via syringe under nitrogen. After the solution was stirred for 30 min, dimethyl disulfide (4.28 g, 45.5 mmol) in ether (20 mL) was added dropwise with vigorous stirring. The mixture was stirred at −78 °C for 1 h and then slowly warmed to room temperature. An ice-cold saturated ammonium chloride solution (50 mL) was added. The two layers were separated, and the aqueous layer was extracted with ether (3×30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was subjected to silica gel chromatography using hexane as the eluent to yield 2.89 g (16.4 mmol, 79%) of **6** as a colorless oil: R_f=0.68 (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (2H, s), 2.48 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 139.1 (Cq), 131.0 (CH), 21.9 (CH_3); MS (EI) *m/z* 178/177/176 (M^+, 9/5/95), 161 (M^+-CH_3, 100), 114 ($M^+-CH_3-SCH_3$, 42), 69 (42); HRMS *m/z* calcd for $C_6H_8^{32}S_3$ 175.9789, found 175.9788.

3.1.2. 2,5-Bis(phenylthio)thiophene 7. Follow the same procedures as in the preparation of **6**. 2,5-Dibromothiophene (5.00 g, 20.7 mmol) was allowed to react with *n*-butyllithium (2.5 M in hexane, 43.4 mmol), and then with diphenyl disulfide (9.48 g, 43.4 mmol). The crude product was purified by column chromatography (hexane) to give 5.79 g (19.3 mmol, 93%) of **7** as a colorless solid: mp 42–43 °C (hexane); R_f=0.33 (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (10H, m), 7.16 (2H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.4 (Cq), 136.9 (Cq), 135.5 (CH), 129.1 (CH), 128.1 (CH), 126.7 (CH); MS (EI) *m/z* 303/302/301/300 (M^+, 3/16/24/100), 299 (M^+-1, 23), 190 (78); HRMS *m/z* calcd for $C_{16}H_{12}S_3$ 300.0103, found 300.0096; Anal. Calcd for $C_{16}H_{12}S_3$: C, 63.96; H, 4.03. Found: C, 63.73; H, 4.17.

3.1.3. 3,4-Bis(chloromethyl)-2,5-bis(methyl)thiophene 8.[12] Concentrate hydrochloric acid (12 M, 20 mL) was added to the mixture of **6** (2.00 g, 11.3 mmol) and 37% formaldehyde aqueous solution (1.70 g, 56.7 mmol). The mixture was stirred at room temperature for 8 h, then poured into water (30 mL), and extracted with CH_2Cl_2 (3×20 mL). The organic layers were combined, washed with water (2×30 mL), brine, dried over $MgSO_4$, filtered, and concentrated in vacuum to yield 2.71 g (9.92 mmol, 87%) of **8** as a pale green solid. Product **8** decomposed after chromatography on silica gel; therefore, crude product was used without further purification. Mp 75.5–77 °C (a colorless solid after recrystallization from hexane). (lit.[23] 78–78.5 °C); R_f=0.75 (hexane/ethyl acetate=4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (4H, s), 2.47 (6H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 139.2 (Cq), 138.9 (Cq), 37.2 (CH_2), 21.7 (CH_3); MS (EI) *m/z* 276/275/274/273 (M^+, 7/6/30/15), 272 (M^+-1, 61), 239 (30), 237 (M^+-Cl, 100), 186 (38), 69 (57); HRMS *m/z* calcd for $C_8H_{10}^{35}Cl_2S_3$ 271.9324, found 271.9318.

3.1.4. 5,7-Bis(methylthio)-1,4-dihydro-1*H*−3λ^4-thieno[3,4-*d*][2,3]oxathiin-3-oxide, sultine 10e. A solution of **8** (2.86 g, 10.5 mmol), Rongalite (3.33 g, 20.9 mmol), and TBAB (1.71 g, 5.24 mmol) in DMF (50 mL) was stirred at room temperature for 24 h. The mixture was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography (6:1 hexane/ethyl acetate) to give 0.68 g (2.55 mmol, 24%) of **10e**, as a white solid after recrystallization from a solvent of CH_2Cl_2 and hexane: mp 71–73 °C (CH_2Cl_2/hexane); R_f=0.45 (hexane/ethyl acetate=4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19, 5.10 (2H, ABq, J=14.7 Hz), 3.91, 3.81 (2H, A′B′q, J=15.9 Hz), 2.44 (3H, s), 2.42 (3H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 137.1 (Cq), 132.8 (Cq), 132.0 (Cq), 126.8 (Cq), 58.8 (CH_2), 51.1 (CH_2), 21.3 (CH_3), 21.3 (CH_3); MS (EI) *m/z* 268/267/266 (M^+, 3/5/13), 265 (M^+-1, 22), 202 (M^+-SO_2, 32), 201 (40), 187 (100); HRMS *m/z* calcd for $C_8H_{10}O_2S_4$ 265.9565, found 265.9577; Anal. Calcd for $C_8H_{10}O_2S_4$: C, 36.07; H, 3.78. Found: C, 36.42; H, 4.20.

3.1.5. 3,4-Bis(chloromethyl)-2,5-bis(phenylthio)thiophene 9 and 5,7-bis(phenylthio)-1,4-dihydro-1*H*-3λ^4-thieno[3,4-*d*][2,3]oxathiin-3-oxide, sultine 10f. Adapted from a literature method.[4b] To a stirred solution of **7** (2.00 g, 6.66 mmol) and zinc chloride (1.4 g, 10 mmol) in dry chloroform (20 mL) was added dropwise chloromethyl-methyl ether (1.6 g, 20 mmol) via syringe. The mixture

turned dark green upon addition. The reaction mixture was stirred at room temperature under nitrogen for 3 h, and then poured into ice–water (20 mL), and CH_2Cl_2 (40 mL) was added. After stirring for 10 min, the layers were separated and the organic layer was washed with water (20 mL) and dried over $MgSO_4$. The solvent distilled off in vacuum to yield 2.67 g of crude product as viscous orange oil. Without purification, the crude product was dissolved in DMF (50 mL), and added Rongalite (5.16 g, 33.5 mmol) and TBAB (1.08 g, 3.45 mmol). The reaction mixture was stirred at room temperature for 10 h. The mixture diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography (10:1 hexane/ethyl acetate) to give 0.29 g (0.47 mmol, 11% overall yield from **7** in two steps) of **10f**.

3.1.6. Data of compound 9. a colorless liquid; $R_f=0.3$ (hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.20 (10H, m), 4.85 (4H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.5 (Cq), 136.6 (Cq), 135.7 (Cq), 129.3 (CH), 128.9 (CH), 127.3 (CH), 37.1 (CH_2); MS (EI) *m/z* 398/399/400 (M^+, 87/76/13), 396 (M^+-1, 100), 348 (37), 231 (51), 216 (69), 215 (81), 203 (61), 184 (43), 171 (40), 51 (50), 50 (74), 38 (55); HRMS *m/z* calcd for $C_{18}H_{14}^{35}Cl_2S_3$ 395.9637, found 395.9625.

3.1.7. Data of compound 10f. A white solid after recrystallization from a solvent of CH_2Cl_2 and hexane; mp 71–72 °C (CH_2Cl_2/hexane); $R_f=0.65$ (hexane/ethyl acetate=4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (10H, m), 5.17, 5.10 (2H, ABq, $J=15.0$ Hz), 3.87, 3.81 (2H, A′B′q, $J=16.4$ Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 136.0 (Cq), 135.7 (Cq), 135.5 (Cq), 134.2 (Cq), 130.6 (Cq), 129.5 (CH), 129.4 (CH), 128.0 (CH); MS (EI) *m/z* 390/391 (M^+, 2/14), 326 (M^+-SO_2, 80), 325 (M^+-1-SO_2, 100), 216 (38), 215 (41), 184 (67), 77 (40), 51 (71); HRMS *m/z* for $C_{18}H_{14}O_2S_4$ 389.9878, found 389.9885; Anal. Calcd for $C_{18}H_{14}O_2S_4$: C, 55.36; H, 3.61. Found: C, 55.19; H, 3.73.

3.1.8. Cycloaddition reactions of thienosultines 10a–f with C_{60}. General procedure. A solution of C_{60} (50 mg, 0.069 mmol) and thienosultine (1.5 equiv. for **10a–f**) in ODCB (20 mL) was refluxed under nitrogen or irradiated with microwave (900 W, $\leq$180 °C). The resulting brown reaction mixture was evaporated to dryness under reduced pressure. The residue was subjected to silica gel chromatography with cyclohexane/toluene (4/1) as the eluent. The reaction conditions and yields after purification are shown in Table 1.

3.1.9. 1′,3′-Dimethyl-4′,5′,6′,7′-tetrahydrobenzo[*c*]-thieno-[5′,6′:1,2][60]fullerene (12a). A brown solid; mp>495 °C; $R_f=0.75$ (cyclohexane); ^{1}H NMR (25 °C, 600 MHz, *o*-$C_6D_4Cl_2$) δ 4.43 (4H, s), 2.56 (6H, s); ^{1}H NMR (5 °C, 600 MHz, *o*-$C_6D_4Cl_2$) δ 4.43, 4.38 (4H, ABq, $J=$ 13.5 Hz), (2H, ABq, $J=13.3$ Hz), 2.55 (6H, s); ^{13}C NMR (70 °C, 150 MHz, *o*-$C_6D_4Cl_2$) δ 159.9, 148.5, 147.3, 147.0, 146.6, 146.3, 146.2, 146.1, 145.5, 143.9, 143.4, 143.1, 142.9, 142.4, 141.1, 136.4, 135.8, 134.7, 66.9 (sp^3 C of C_{60}), 41.4 (CH_2), 13.3 (CH_3); FAB-MS (MNB) *m/z* 859 ($M+H^+$, 4), 858 (M^+, 4), 721 (90), 461 (100), 460 (95); UV ($CHCl_3$) λ_{max}, nm (log ε) 434 (3.33), 308 (4.47), 256 (4.97); HRMS (FAB+) calcd for $C_{68}H_{10}S$ 858.0504, found 858.0523.

3.1.10. Adduct 13a. A brown solid; $R_f=0.45$ (cyclohexane); FAB-MS (MNB) *m/z* 997/998 ($M+H^+$, 5/3), 857/858 (4/3), 721 (100); HRMS (FAB+) calcd for $C_{76}H_{20}S_2$ 996.1006, found 996.1751.

3.1.11. 1′,3′-Dichloro-4′,5′,6′,7′-tetrahydrobenzo[*c*]-thieno-[5′,6′:1,2][60]fullerene (12b). A brown solid; mp>495 °C; $R_f=0.75$ (cyclohexane); ^{1}H NMR (25 °C, 600 MHz, *o*-$C_6D_4Cl_2$) δ 4.49 (4H, s); ^{1}H NMR (−15 °C, 600 MHz, *o*-$C_6D_4Cl_2$) δ 4.54, 4.38 (4H, ABq, $J=14.1$ Hz); ^{13}C NMR (70 °C, 150 MHz, *o*-$C_6D_4Cl_2$) δ 156.5, 148.5, 147.3, 147.1, 146.5, 146.3, 146.2, 145.8, 145.4, 143.8, 143.4, 142.9, 142.4, 141.1, 136.2, 135.8, 122.7, 65.8 (sp^3 C of C_{60}), 40.6 (CH_2); FAB-MS (MNB) *m/z* 899 ($M+H^+$, 3), 898 (M^+, 3), 720 (8), 460 (100); UV ($CHCl_3$) λ_{max}, nm (log ε) 434 (3.57), 310 (4.37), 257 (4.89); HRMS (FAB+) calcd for $C_{66}H_4Cl_2S$ 897.9712, found 897.9510.

3.1.12. Adduct 13b. A brown solid; $R_f=0.63$ (cyclohexane); FAB-MS (MNB) *m/z* 1074/1076/1077/1078/1079/1080 ($M+H^+$, 0.7/0.9/0.9/1/1/0.8), 720 (8), 307 (100); HRMS (FAB+) calcd for $C_{72}H_8Cl_4S_2$ 1075.8821, found 1075.8821.

3.1.13. 1′-Methyl-3′-phenyl-4′,5′,6′,7′-tetrahydrobenzo[*c*]thieno-[5′,6′:1,2][60]fullerene (12c). A brown solid; mp>495 °C; $R_f=0.6$ (cyclohexane); ^{1}H NMR (25 °C, 600 MHz, 1:2 $CDCl_3/CS_2$) δ 7.53–7.51 (2H, m), 7.38–7.36 (2H, m), 7.29–7.26 (1H, m), 4.66 (2H, br s), 4.52 (2H, br s), 2.67 (3H, s); ^{1}H NMR (−20 °C, 600 MHz, 1:2 $CDCl_3/CS_2$) δ 7.53–7.52 (2H, m), 7.40–7.38 (2H, m), 7.31–7.28 (1H, m), 4.72, 4.63 (2H, ABq, $J=14.1$ Hz), 4.56, 4.48 (2H, ABq, $J=14.0$ Hz), 2.69 (3H, s); ^{13}C NMR (25 °C, 150 MHz, 1:2 $CDCl_3/CS_2$) δ156.4 (br), 147.4, 146.2, 146.2, 146.0, 145.6, 145.2, 144.7, 144.5, 142.9, 142.4, 141.9, 141.8, 141.4 (br), 140.0, 134.6, 133.6, 133.1, 132.6, 128.8 (CH), 128.6 (CH), 127.4 (CH), 65.5 (sp^3 C of C_{60}), 65.4 (sp^3 C of C_{60}), 40.5 (CH_2), 34.0 (CH_2), 12.8 (CH_3); FAB-MS (MNB) *m/z* 921 ($M+H^+$, 5), 920 (M^+, 5), 720 (100); UV ($CHCl_3$) λ_{max}, nm (log ε) 487 (3.34), 432 (3.64), 257 (5.07); HRMS (FAB+) calcd for $C_{73}H_{12}S$ 920.0661, found 920.0663.

3.1.14. Adduct 13c. A brown solid; $R_f=0.3$ (cyclohexane); FAB-MS (MNB) *m/z* 1121 ($M+H^+$, 8), 721 (18), 392 (100); HRMS (FAB+) calcd for $C_{86}H_{24}S_2$ 1120.1321, found 1120.1461.

3.1.15. 1′,3′-Diphenyl-4′,5′,6′,7′-tetrahydrobenzo[*c*]thieno-[5′,6′:1,2][60]fullerene (12d). A brown solid; mp>495 °C; $R_f=0.54$ (cyclohexane); ^{1}H NMR (25 °C, 600 MHz, 1:2 $CDCl_3/CS_2$) δ 7.59–7.57 (4H, m), 7.42–7.39 (4H, m), 7.33–7.31 (2H, m), 4.76 (2H, br s), 4.69 (2H, br s); ^{1}H NMR (−20 °C, 600 MHz, 1:2 $CDCl_3/CS_2$) δ 7.59–7.58 (4H, m), 7.44–7.41 (4H, m), 7.34–7.32 (2H, m), 4.79, 4.69 (4H, ABq, $J=14.2$ Hz); ^{13}C NMR (−20 °C, 150 MHz, 1:2 $CDCl_3/CS_2$) δ 156.0, 155.9, 147.1, 145.98, 145.96, 145.8, 145.7, 145.32, 145.27, 145.1, 145.1, 144.95, 144.91, 144.88, 144.4, 144.2 (2C), 142.7, 142.6, 142.1, 142.1, 141.7, 141.6, 141.6, 141.5, 141.3, 141.1, 139.78, 139.76, 137.9, 135.7,

134.7, 133.9, 132.9, 128.8 (CH), 128.5 (CH), 127.7 (CH), 65.0 (sp^3 C of C_{60}), 40.1 (CH_2); FAB-MS (MNB) *m/z* 984/983 ($M+H^+$, 2/3), 982 (M^+, 3), 721 (24), 461 (67), 392 (100); UV ($CHCl_3$) λ_{max}, nm (log ε) 432 (3.55), 257 (5.10); HRMS (FAB+) calcd for $C_{78}H_{14}S$ 982.0817, found 982.0905.

3.1.16. Adduct 13d. A brown solid; R_f=0.2 (cyclohexane); FAB-MS (MNB) *m/z* 1246/1245 ($M+H^+$, 4/5), 721 (67), 461 (57), 392 (100); HRMS (FAB+) calcd for $C_{96}H_{28}S_2$ 1244.1634, found 1244.1669.

3.1.17. 1′,3′-Bis(methylthio)-4′,5′,6′,7′-tetrahydrobenzo[*c*]thieno-[5′,6′:1,2][60]fullerene (12e). A brown solid; mp>495 °C; R_f=0.45 (cyclohexane); ^{1}H NMR (25 °C, 500 MHz, 1:2 $CDCl_3/CS_2$) δ 4.62 (4H, br s), 2.46 (6H, s); ^{1}H NMR (−25 °C, 500 MHz, 1:2 $CDCl_3/CS_2$) δ 4.74, 4.49 (4H, ABq, J=14.5 Hz), 2.46 (6H, s); ^{13}C NMR (70 °C, 150 MHz, *o*-$C_6D_4Cl_2$) δ 157.3, 148.5, 147.3, 147.0, 146.5, 146.2, 146.2, 146.0, 145.5, 143.9, 143.4, 142.9, 142.4, 141.1, 136.2, 135.8, 135.0, 66.5 (sp^3 C of C_{60}), 41.8 (CH_2), 23.2 (CH_3); FAB-MS (MNB) *m/z*; 923 ($M+H^+$, 3), 614 (32), 462 (100), 444 (26); UV ($CHCl_3$) λ_{max}, nm (log ε) 435 (3.67), 310 (4.80), 256 (5.31); HRMS (FAB+) calcd for $C_{68}H_{10}S_3$ 921.9946, found 922.0023.

3.1.18. Adduct 13e. A brown solid; R_f=0.41 (cyclohexane: toluene=9:1); FAB-MS (MNB) *m/z* 1124 ($M+H^+$, 3), 1123 (M^+, 3) 720 (18), 442 (25), 308 (100); HRMS (FAB+) calcd for $C_{76}H_{20}S_6$ 1123.9892, found 1123.9897.

3.1.19. 1′,3′-Bis(phenylthio)-4′,5′,6′,7′-tetrahydrobenzo[*c*]thieno-[5′,6′:1,2][60]fullerene (12f). A brown solid; mp> 495 °C; R_f=0.35 (cyclohexane); ^{1}H NMR (40 °C, 600 MHz, 1:2 $CDCl_3/CS_2$) δ 7.32–7.30 (4H, m), 7.17–7.15 (4H, m), 7.10–7.09 (2H, m), 4.66 (4H, br s); ^{1}H NMR (−30 °C, 600 MHz, 1:2 $CDCl_3/CS_2$) δ 7.28–7.24 (4H, m), 7.19–7.16 (4H, m), 7.11–7.10 (2H, m), 4.78, 4.52 (4H, ABq, J=14.4 Hz); ^{13}C NMR (40 °C, 150 MHz, 1:2 $CDCl_3/CS_2$) δ 156.0, 147.5, 146.3, 146.1, 145.6, 145.4, 145.3, 144.9, 144.5, 144.4, 143.0, 142.4, 141.9, 141.9, 141.4, 140.1, 136.8, 135.2, 131.2, 129.0 (CH), 128.3 (CH), 126.7 (CH), 65.0 (sp^3 C of C_{60}), 40.7 (CH_2); FAB-MS (MNB) *m/z* 1047 ($M+H^+$, 5), 1046 (M^+, 5), 766 (5), 720 (20), 613 (40), 460 (100); UV ($CHCl_3$) λ_{max}, nm (log ε) 435 (3.67), 310 (4.80), 256 (5.31); HRMS (FAB+) calcd for $C_{78}H_{14}S_3$ 1046.0259, found 1046.0404.

3.1.20. Adduct 13f. A brown solid; R_f=0.28 (cyclohexane/toluene=9:1); FAB-MS (MNB) *m/z* 1373 ($M+H^+$, 5), 1372 (M^+, 5), 721 (32), 442 (37), 308 (100); HRMS (FAB+) calcd for $C_{96}H_{28}S_6$ 1372.0518, found 1372.0522.

3.1.21. Synthesis of 15 and 16. An air-saturated solution of **12a** (25 mg, 0.029 mmol) in CS_2 (15 mL) was stirred at room temperature under the irradiation of room light and monitored by TLC chromatography until the starting compound disappeared which took about 3 days. After removal of the solvent, the residue was purified by silica gel chromatography (3–1:2 cyclohexane/$CHCl_3$) to give 7.3 mg of **15** (28%) and 11.6 mg of **16** (45%).

3.1.22. Data of 15. A brown solid, mp>495 °C; R_f=0.3 (cyclohexane: $CHCl_3$=1:1); FT-IR (KBr, cm^{-1}) 1700 (C=O), 1529 (C=C); ^{1}H NMR (25 °C, 600 MHz, $CDCl_3$) δ 4.56 (2H, br s), 4.45 (2H, br s), 2.71 (3H, s), 2.53 (3H, s); ^{13}C NMR (25 °C, 150 MHz, $CDCl_3$) δ 197.7 (C=O), 193.0 (C=S→O), 155.5, 155.4, 147.7 (2C), 146.6 (2C), 146.3 (2C), 145.8, 145.6 (3C), 145.5 (2C), 145.2, 144.7 (2C), 143.2, 142.7, 142.6, 142.3, 142.2, 142.1 (2C), 141.7 (2C), 140.2 (2C), 137.9, 135.8, 135.7, 65.8 (sp^3 C of C_{60}), 65.5 (sp^3 C of C_{60}), 49.1 (CH_2), 42.6 (CH_2), 30.9 (CH_3), 30.3 (CH_3); FAB-MS (MNB) *m/z* 891 ($M+H^+$, 2), 890 (M^+, 3), 889 (M^+-1, 2), 721 (100); HRMS (FAB+) calcd for $C_{68}H_{10}O_2S$ 890.0402, found 890.0382.

3.1.23. Data of 16. A brown solid; mp>495 °C; R_f=0.25 (cyclohexane/$CHCl_3$=2:3); FT-IR (KBr, cm^{-1}) 1685 (C=O); ^{1}H NMR (25 °C, 600 MHz, $CDCl_3$) δ 4.31 (4H, s), 2.63 (6H, s); ^{13}C NMR (25 °C, 150 MHz, $CDCl_3$) δ 200.6 (C=O), 155.2, 147.5, 146.6, 146.4, 145.7, 145.7, 145.6, 145.2, 144.9, 144.7, 143.2, 142.7, 142.3, 142.1, 141.7, 140.3, 135.7, 65.3 (sp^3 C of C_{60}), 41.7 (CH_2), 29.2 (CH_3); FAB-MS (NMB) 859 ($M+H^+$, 2), 858 (M^+, 2), 720 (100); HRMS (FAB+) calcd for $C_{68}H_{10}O_2$ 858.0681, found 858.0712.

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Supplementary data

Various temperature ^{1}H NMR spectra of compounds **12b**, **d–f**, ^{1}H NMR spectra of compounds **6**, **8**, **9**, and **10e**, ^{1}H and/or ^{13}C NMR spectra of compounds **12**, **13**, **15** and **16** and FTIR spectra of adducts **15** and **16**.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.09.040

References and notes

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Stable structures of 12-crown-O_3N complexes with Li^+ or Na^+ in aqueous and acetonitrile solutions

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Abstract—Molecular geometries of crown ether derivatives play an important role in capturing and transporting alkali metal ions such as Li^+ and Na^+. As the selectivity of ions is observed in solutions, it is necessary to know their molecular structures in solutions. Recently, we investigated stable conformations of 12-crown-O_3N and its Li^+ complex in aqueous solution by the combination of three programs, the CONFLEX, Gaussian 98, and BOSS programs. In the present study, we applied the same procedure to investigate stable structures of 12-crown-O_3N complexes with an alkali ion in aqueous and acetonitrile solutions. It was confirmed that the stable structures of Li^+ and Na^+ complexes in solutions are highly dependent on the polarity of the solvents.

1. Introduction

Crown ethers have an interesting function in that they capture and transport alkali metal ions selectively. For example, it is known that 15-crown-5 selectively forms a complex with Na^+ and 18-crown-6 with K^+.[1] As a reason for the selectivity, the relation between ion size and cavity size of crown ethers has been considered to be the most important since Pedersen first synthesized the cyclic ethers.[2] However, in polar solvents such as water, alcohol, and so on, 12-crown-4 with the optimal hole for Li^+ shows little selectivity for the small ion. It was experimentally found that the stability of complexes depends greatly on the solvents used.[1] These results show the importance of not only the ion–hole relation but also the solvent effect for the ion selectivity. Later, it was pointed out that the solvent effect rather than spatial factors largely participates in ion selectivity.[3]

Theoretical calculation has been a powerful tool to solve the mechanism of selective capture and transportation of alkali ions by the use of crown ether derivatives.[4] For example, it was observed that an amine side arm is effective for improving the Li^+ selectivity of crown derivatives.[5] That is, the interaction energy between Li^+ and an amine arm is important for the selectivity. The presence of an amine arm increases the interaction energy between Li^+ and the 12-crown-O_3N derivatives so that solvent molecules around Li^+ are removed to form their stable complex.

As crown ethers function in solution, solvent effects should be included in efforts to clarify the mechanism of the ion selectivity. Previous theoretical works, however, estimated the effect partially by including a few solvent molecules in molecular orbital calculations.[6] Furthermore, the crown ether derivatives have a flexible ring and this property is considered to greatly affect the selectivity of ions. In a previous paper,[7] we used three programs, the Conflex,[8] Gaussian 98[9] and BOSS[10] programs, for investigating geometrical and solvent effects on ion selectivity.

The first program can generate stable conformations of 12-crown-O_3N **1** and its alkali ion complex. The second one calculates energies at the B3LYP/6-31G**//RHF/6-31G* level of theory, and the last one calculates differences in free energy of solvation between two conformers by using results of Monte Carlo (MC) simulations. It was confirmed that this combination of programs makes it possible to study stable conformations of the (12-crown-O_3N)Li^+ complex in aqueous solution. The results of the calculations agree well with experimental findings for **1** in alcohol (Drawing 1).

Keywords: Stable conformations in solution; Monte Carlo simulation; Ab initio molecular orbital calculations; 12-Crown-O_3N.
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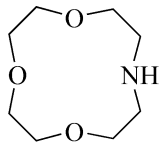


12-crown-O_3N **1**

Drawing 1.

In the present study, we used the same procedure to study the stability of 12-crown-O_3N complexes with alkali ions not only in water but also in acetonitrile. Neither Li^+ nor Na^+ complexes were observed in the former solvent. By means of this procedure we were able to compare their stability in acetonitrile with that in water.

2. Method of calculations

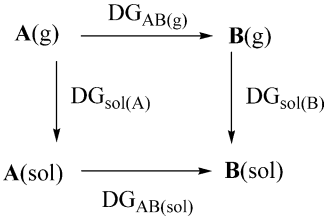
2.1. Quantum mechanical calculations and Monte Carlo simulations

The Gaussian 98 program was used for optimizing a complex of Li^+ or Na^+ with four solvents, the solvated complex, at the RHF/6-31G* level of theory. The electrical charges for Monte Carlo (MC) simulations were calculated by applying the Merz–Singh–Kollman[11] scheme at the same level of theory. MC simulations were performed by using the BOSS Version 3.5 program.[12]

An orthorhombic box for MC calculations contains a solute as well as 500 TIP4P waters or 267 acetonitriles as solvents. These calculations make it possible to calculate the difference in free energy of solvation $\Delta\Delta G_{sol}$. Metropolis sampling and periodic boundary conditions were employed. The range of the movement was chosen to yield an acceptance rate of 30–40% for new configurations. The run for each window involved the equilibration for 10^6 configurations, followed by averaging over an additional 10^6 configurations.

2.2. Calculation of $\Delta\Delta G_{sol(AB)}$ and potential energy profile in solutions

The potential curves for solvated complexes in a vacuum were calculated by the use of energies at the B3LYP/6-31G**//RHF/6-31G*level of theory. The results are listed in Table 1. The statistical perturbation theory (SPT)[13,14] was applied to calculate the difference in free energy of solvation $\Delta\Delta G_{sol(AB)}$ between two structures, A and B, which have the ion in the different positions. MC simulations in aqueous and acetonitrile solutions were used for calculating $\Delta\Delta G_{sol(AB)}$. Thermodynamic cycle for calculating the energy is shown below (Drawing 2).



Drawing 2.

From the thermodynamic cycle, $\Delta G_{AB(sol)}$ (sol = acetonitrile or water), a free energy difference in solution could be expressed to Eq. 1.

$$\Delta G_{AB(sol)} = \Delta G_{AB(g)} + (\Delta G_{sol(B)} - \Delta G_{sol(A)})$$

$$= \Delta G_{AB(g)} + \Delta\Delta G_{sol(AB)} \cong \Delta E_{AB(g)}$$

$$+ \Delta\Delta G_{sol(AB)} \quad (1)$$

$\Delta G_{AB(g)}$, a free energy difference in gas phase is approximated to $\Delta E_{AB(g)}$, an energy difference between two structures, A and B, in the gas phase obtained from ab initio MO or density functional theory (DFT) calculations. $\Delta\Delta G_{sol(AB)}$, the difference in free energy of solvation between two structures, A and B, was from MC simulations. Potential energies in solutions were calculated by adding the $\Delta\Delta G_{sol(AB)}$ to the potential energies for solvated complexes in the a vacuum. As will be shown later, $\Delta E_{AB(g)}$ and $\Delta G_{AB(sol)}$ are plotted along the positions of the alkali ion.

3. Results and discussion

3.1. The most stable geometry of the (12-crown-O_3N)M^+ complex with solvent molecules in the gas phase

It is necessary to calculate potential energies including bulk

Table 1

r	LW	NW	LA	NA
0	0.00 (0.00)	0.00 (0.00)		0.00 (0.00)
0.3	−0.46 (−0.79)	3.73 (0.27)	0.00 (0.00)	3.73 (2.01)
0.6	−1.02 (135)	9.90 (3.58)	1.51 (1.59)	9.27 (9.48)
0.9	4.71 (6.08)	16.79 (7.76)	9.62 (7.20)	11.05 (12.90)
1.2	5.08 (10.41)	25.17 (8.31)	12.46 (10.62)	15.23 (15.88)
1.5	0.50 (15.10)	23.66 (7.24)	16.04 (14.36)	17.40 (18.43)
1.8	−1.38 (13.68)	23.52 (10.08)	24.23 (19.77)	22.38 (20.45)
2.1	−5.04 (11.54)	24.38 (10.55)	25.10 (21.22)	27.56 (21.80)
2.4	−8.28 (9.56)	23.63 (11.35)	25.07 (21.19)	34.09 (22.30)
2.7	−12.72 (8.69)	24.41 (11.64)		
3.0	−13.52 (10.98)	24.97 (14.36)		
3.3	−8.13 (12.12)	30.02 (19.04)		

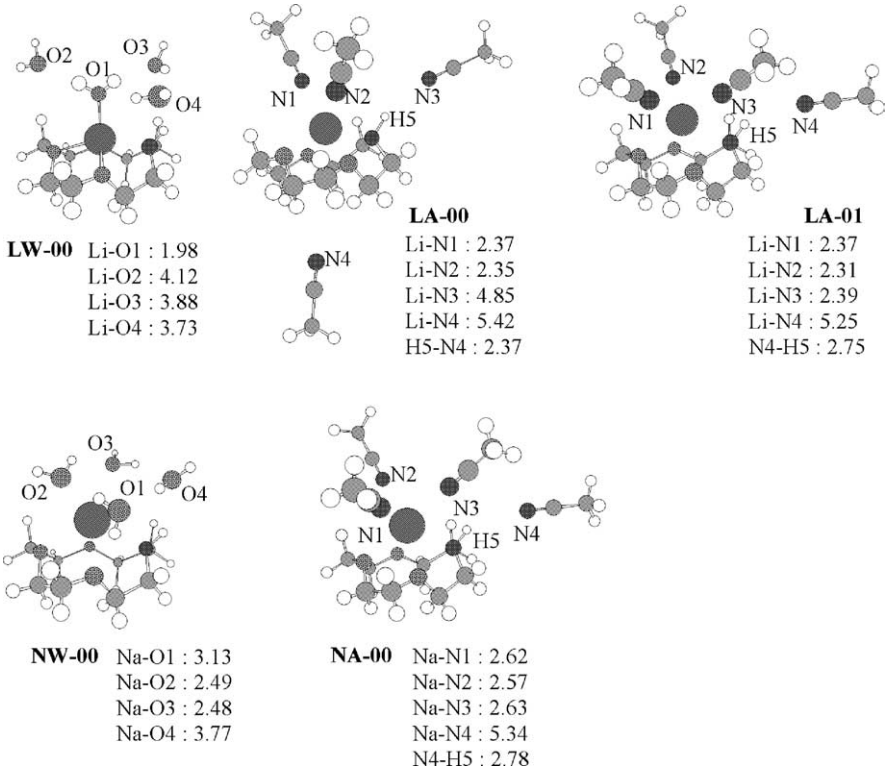


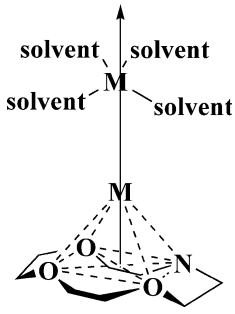
Figure 1.

solvent effects to ascertain whether or not the 12-crown-O_3N complexes with an ion are stable or not in polar solvents. First of all, the geometry of the 12-crown-O_3N complex with Li^+ and four water molecules as coordinated solvents was optimized at the RHF/6-31G* level of theory. Similar optimizations for the Na^+ complex were performed and are shown in Figure 1. These optimized structures represented as MS-R, where M (L = Li^+ or N = Na^+) and S (W = water or A = acetonitrile) show the metal ion and the solvent, respectively. *R* shows the position of the ion as will be discussed later. The most stable structures of the solvated complexes are designated as LW-00 and NW-00.In the former, only one H_2O coordinates to Li^+ and the other three waters make hydrogen bonds with the coordinated water. In contrast, two waters in NW-00 coordinate to Na^+ since the Na–O2 and Na–O3 lengths are ca. 2.5 Å. The other two make hydrogen bonds with the coordinated waters according to atomic distances (Na–O1: 3.13 Å and Na–O4: 3.77 Å). The interaction between the 12-crown-O_3N ring and the ions prevents two waters from coordinating to the ion.

Similar solvated complexes, in which four acetonitriles were included instead of waters, with the alkali ions were optimized at the same level of theory. They are represented as LA-00 and NA-00. In LA-00, two acetonitriles coordinate to Li^+ and one makes a hydrogen bond with the H–N fragment of the ring. It is necessary to emphasize that one acetonitrile of LA-00 locates under the 12-crown-O_3N ring. The ion size of Li^+ is too small to accommodate the fourth solvent on the same side where the ion is located. The NA-00 possesses four solvents over the crown ring. In the structure, three acetonitriles coordinate to Na^+ within 2.7 Å and the other makes a hydrogen bond with the N–H fragment of the crown ring, that is, the N4–H5 is 2.78 Å in length. The geometry difference between the LW-00 and the NW-00 complexes comes from the difference in the ion size.

3.2. The coordination geometry depends on the ion position in the vacuum

To obtain dependence of coordination geometry of solvents on the alkali ion position, we optimized a solvated complex with an ion, changing its position by 0.3 Å from that in the most stable structure along the axis perpendicular to the O_3N plain. As written above, *R* in the MS-R description is the number showing how long the ion locates away from the most stable position 'M' by $\Delta r = 0.3R$ Å (Drawing 3).



Drawing 3.

LA-01 in Figure 1 indicates the acetonitrile complex with Li^+ at the position $\Delta r = 0.3$ Å, and only the geometries of the solvent molecules were optimized at the RHF/6-31G* level of theory. The geometry of the crown ring was fixed at that of the most stable complex. The optimized structures

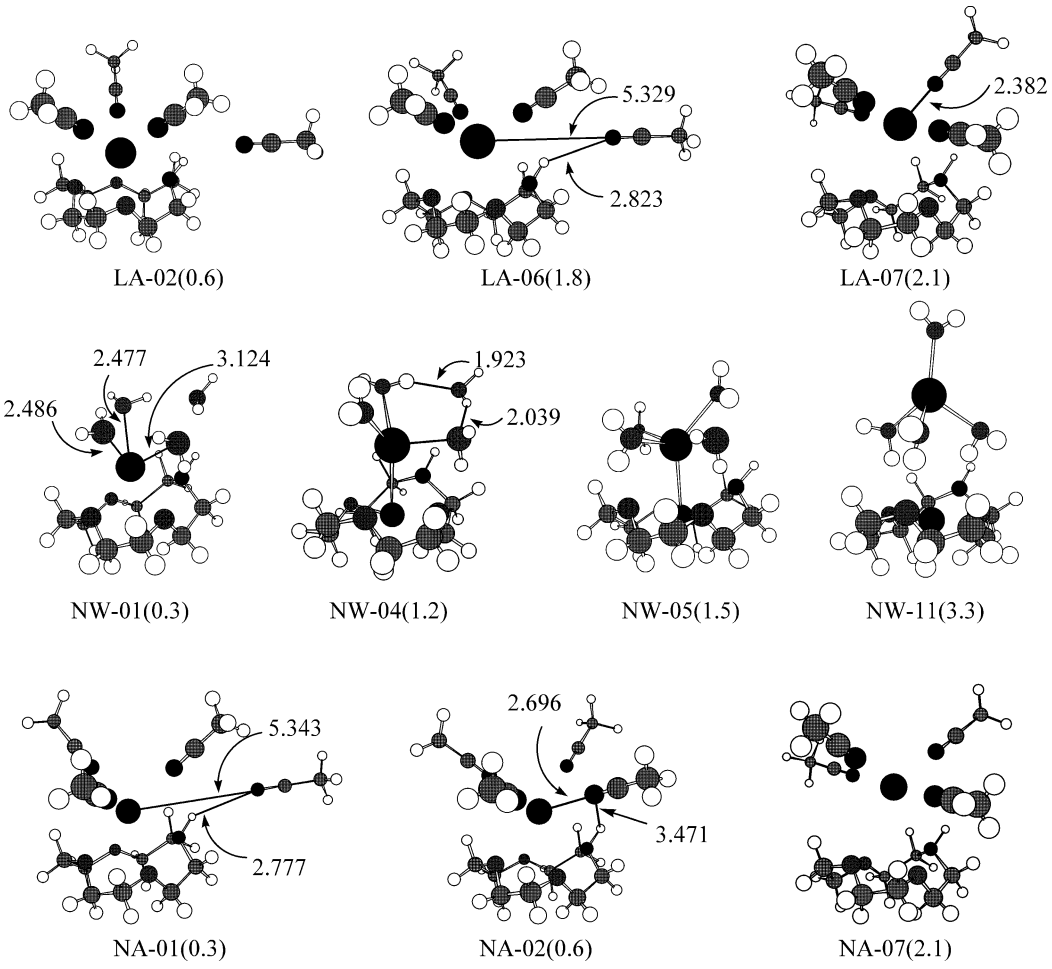


Figure 2.

LA-R, NW-R, and NA-R, depending on the ion position, are shown in Figure 2.

The same coordination number of Na^+ was obtained for the structures from NW-00 to NW-06 (Δr=0.3–1.8 Å). Four waters can interact with Na^+ in the geometry with more than Δr=2.1 Å. In NW-11 (Δr=3.3 Å), the Na^+ has a tetrahedral geometry of waters since there is space enough to accommodate the solvent waters between the crown rings and the ion.

As discussed before, LA-00 has an acetonitrile located under the crown ring. On the other hand, all the acetonitriles locate on the same side of the crown ring in LA-01 as shown in Figure 1. It is impossible to continually change the coordination geometry of solvents from LA-00 to LA-01. The continuous change in geometry is strictly required, however, for calculating the difference in free energy of solvation by using SPT. Therefore, LA-01 is used for the initial geometry for calculating $\Delta G_{AB(sol)}$ along the ion position in acetonitrile. The ion size makes it possible to make a complex of Na^+ coordinated with three acetonitriles in NA-00, whose geometry is similar to that of LA-01. In NA-07 (2.1), four acetonitriles coordinate to Na^+, although the ion does not adopt a tetrahedral geometry. This is due to the size of the organic solvent as well as the space between the ion and 12-crown-O_3N.

3.3. The relative free energy change depends on the position of Li^+

We previously reported that the coordination number of waters, which changes from one to four, depends on the position of Li^+ of LW in the vacuum. While the most stable structure is LW-00, the potential energy curve in the vacuum (Fig. 3) has another minimum around LW-09 (Δr= 2.7). While the latter minimum is less stable by ca. 9 kcal mol^{-1} than LW-00, the latter geometry in aqueous solution (closed circles) is more stable by ca. 15 kcal mol^{-1} than the former. The potential curve shows that no stable

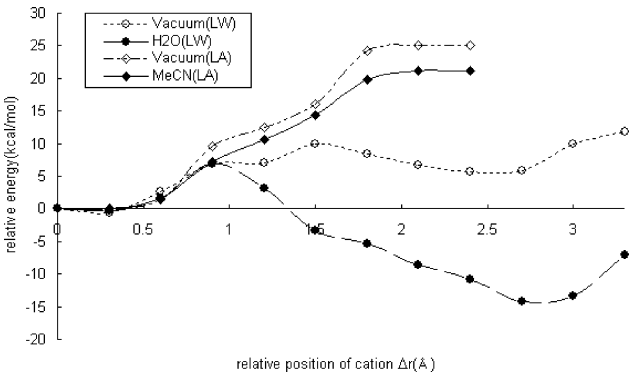


Figure 3.

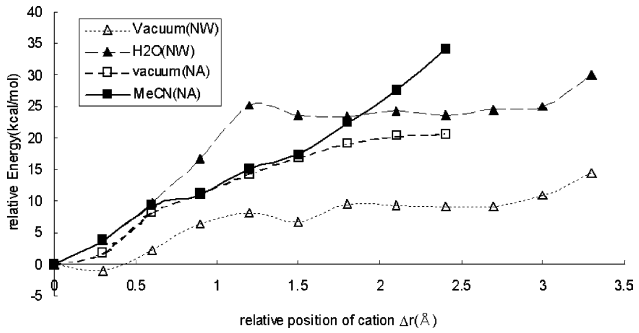


Figure 4.

complex of 12-crown-O_3N with Li^+ forms in aqueous solution. This is consistent with the experimental results as mentioned above.

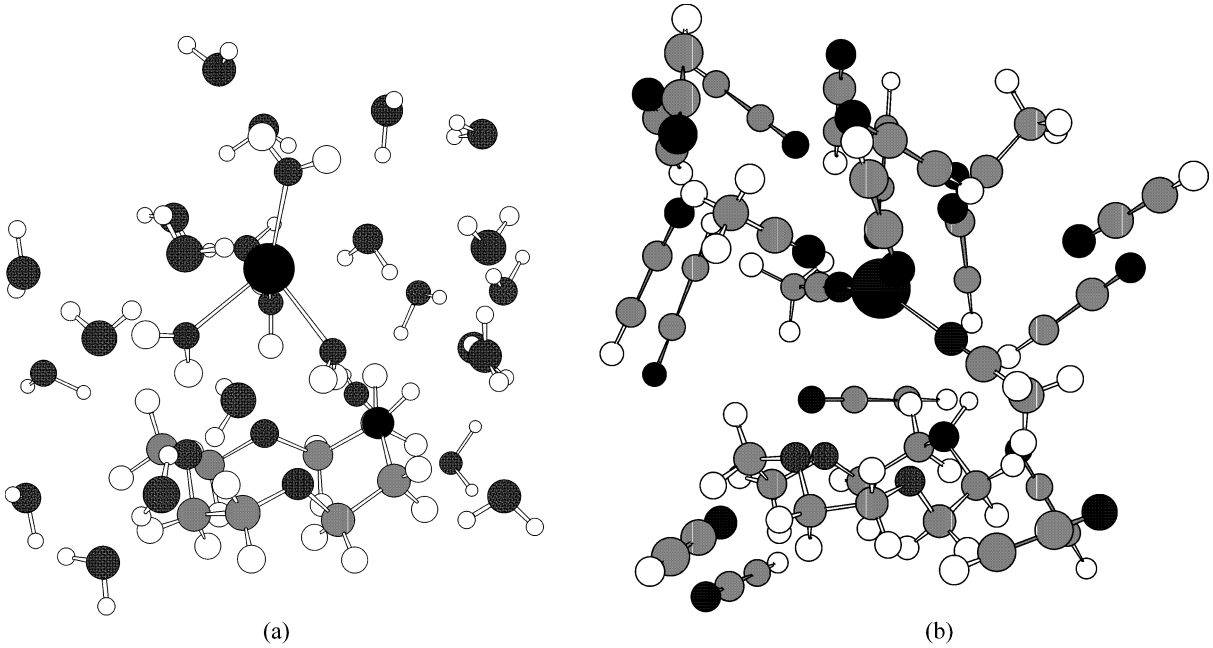
The curves of LA are different from those for LW. The potential curve in the vacuum (open square) goes up from $\Delta r=0.0$–1.8 Å by ca. 25 kcal mol^{-1} and is almost the same in the region with more than $\Delta r=1.8$ Å, as shown in Figure 3. The coordination number of Li^+ changes from three such as with LA-02 ($\Delta r=0.6$ Å) to four as for LA-07. While one acetonitrile still interacts with the NH fragment in LA-06, all the solvents coordinate to Li^+ according to their Li–O distances. This change happens between LA-06 and LA-07. However, the coordination geometry of acetonitriles around Li^+ is not tetrahedral even in LA-07, since the solvent molecules cannot enter the space between the 12-crown-O_3N and Li^+. The potential curve for LA in acetonitrile (closed square) almost overlaps with that in the vacuum. This result means that 12-crown-O_3N tends to form a complex with Li^+ in acetonitrile. This change accompanying the difference of the solvent polarity is very important for understanding the solvent effect on the ion selectivity.

3.4. The relative free energy change depends on the position of Na^+

The potential curves for the Na^+ complex in aqueous and acetonitrile solutions are shown in Figure 4. The curve for NW in the vacuum (open triangles) becomes unstable by 10 kcal mol^{-1} with the increase of Δr from 0.0 to 1.2 Å. In the region of more than 1.2 Å, the potential is almost constant. The number of the water molecules coordinating to Na^+ change from 3 to 4 around $\Delta r=1.2$–1.5 Å, as shown in Figure 2. This change is related to the shape of the potential curve. In aqueous solution (closed triangles), the maximum of ca. 25 kcal mol^{-1} is seen around $\Delta r=1.2$ Å. For the longer distances, the $\Delta G_{AB(sol)}$ value of ca. 24 kcal mol^{-1} keeps almost constant. The most stable structure was also calculated to be NW-00 in water. The snapshot of NW-11 ($\Delta r=3.3$ Å) is shown in Figure 5a. In this structure, $Na(OH_2)_4^+$ interacts with 12-crown-O_3N and the solvent waters surrounding these two fragments.

Near the point of $\Delta r=1.2$ Å, the coordination number of Na^+ changes from three to four between NA-06 and NA-07, as shown in Figure 2. The snap shot of the MC simulation for NA-11 is displayed in Figure 5b. Acetonitriles as solvents surround the (12-crown-O_3N)$Na^+(NCCH_3)_4$, in which the Na^+ ion still interacts with the crown ring. The potential curve for acetonitrile (open squares) goes up monotonically until $\Delta r=2.4$ Å by ca. 20 kcal mol^{-1} in the vacuum. That in acetonitrile (closed squares) showed almost the same tendency, until $\Delta r<1.5$ Å, as that in the vacuum. The most stable structure in the organic solvent was calculated to be NA-00, which is also the most stable in aqueous solution.

The $\Delta G_{AB(sol)}$ between NA-00 and NA-08 ($\Delta r=2.4$ Å) was calculated to be ca. 34 kcal mol^{-1} (Table 1). This value is larger by 9 kcal mol^{-1} than that in water. Therefore, it is



(a) (b)

Figure 5.

considered that the complex in acetonitrile is more stable than that in water. These results of calculations indicate that Na^+ is likely to interact with the 12-crown-O_3N ring. That is, their interaction energy is larger than that of the ion with solvents. It is, therefore, considered that the azaethers tend to make sandwich complexes with Na^+ in acetonitrile and, probably, in aqueous solutions.[15] This expectation is consistent with our experimental results.

4. Concluding remarks

In the present study, the stable structures of alkali ion complexes of the cyclic azaether not only in the aqueous but also in acetonitrile solution were investigated by using the method mentioned in the previous paper.[7] Even in the organic solvent, the present procedure is applicable for examining whether or not the stable complex with an alkali ion and crown ether derivatives structures forms.

For the Li^+ complex, it was confirmed that LW-10, the uncomplexed structure, is the most stable in aqueous solution; that is, 12-crown-O_3N makes no stable complex with Li^+. On the other hand, LA-01, the complexed structure, is the most stable in acetonitrile. NA-00 is the most stable in acetonitrile and the same tendency was obtained for an aqueous solution. It is considered that Na^+ can complex with the crown ring in both solutions.

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Photoinduced ene-reaction of 9-methylene-9,10-dihydrophenanthrene with alkenes

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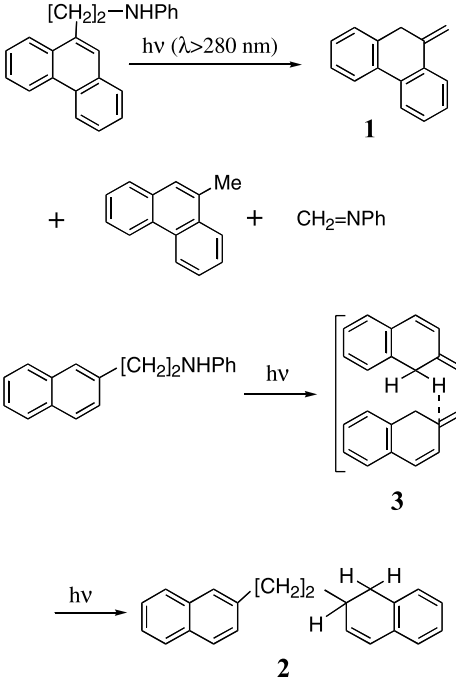
Abstract—Irradiation of 9-methylene-9,10-dihydrophenanthrene (**1**) in the presence of 1,1-diphenylethene or styrene in benzene afforded ene-reaction adduct in good yield. In the absence of arylalkenes, the dimerized product of **1**, 9-[2-(9-phenanthryl)ethyl]-9,10-dihydrophenanthrene, and 9-methylphenanthrene were obtained as major products.

1. Introduction

Previously, we have reported the chemical properties of 9-methylene-9,10-dihydrophenanthrene (**1**) which was prepared by the photolysis of 9-(2-anilinoethyl)phenanthrene[1,2] (Eq. 1). Similarly, 1-methylene-1,2-dihydronaphthalene and 2-methylene-2,3-dihydrobenzo[*b*]thiophene were also prepared from the corresponding 2-anilinoethyl derivatives and their chemical properties were reported.[2] In the photolysis of 2-(2-anilinoethyl)naphthalene, however, 2-[2-(2-naphthyl)ethyl]-1,2-dihydronaphthalene (**2**) as an ene-adduct of the corresponding *exo*-methylene compound (**3**) with another **3** (Eq. 2), was exclusively obtained and neither **3** nor 2-methylnaphthalene was obtained.[3] Lots of ene-reactions have been reported so far and their mechanisms have been discussed in relation to the Diels–Alder reaction.[4–8] However, photoinduced ene-reactions are less known,[9–12] because [2+2]photocycloaddition proceeds predominantly.[13] The chemical properties of 5-methylene-1,3-cyclohexadiene and its benzologues[14–23] have also been attracted considerable attention from the synthetic and mechanistic viewpoints, but photochemistry of them was rarely noted. We now report the photoinduced ene-reaction of **1** to clarify the photochemical reactivity of **1**.[3]



(1)

(2)

2. Results and discussion

A degassed benzene solution of **1** in a sealed Pyrex-tube was irradiated with a 300 W high-pressure mercury lamp. The reaction products obtained were 9-[2-(9-phenanthryl)ethyl]-9,10-dihydrophenanthrene (**4**) and 9-methylphenanthrene (**5**) (Eq. 3) and no other product was detected by ^{1}H NMR

Keywords: Photoreaction; Ene reaction; Isomerization; Aromatization.
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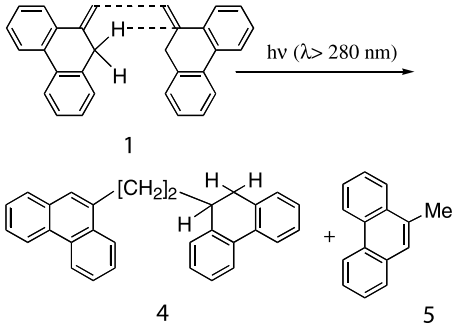
Table 1. Solvent effect on the photoreaction[a] of **1**

Solvent	Yield/%		Recovery/%
	4	**5**	**1**
C_6H_6	34	21	45
C_6H_{12}	37	31	32
CH_3CN	31	69	0
CH_3OH	37	63	Trace

[a] The values were estimated from the intensities of ^{1}H NMR spectra ($CDCl_3$) of the irradiated mixture after 8 h irradiation.

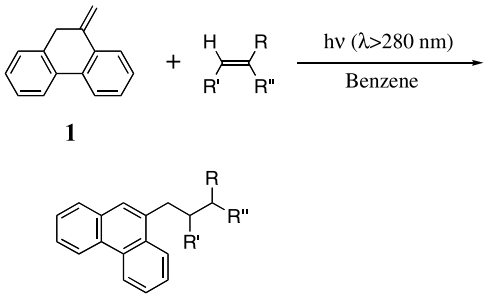
spectrum. The formation of **4** and **5** can be readily interpreted by the ene-reaction and 1,3-hydrogen shift reaction, respectively. The former is a photochemically forbidden reaction and the latter is an allowed one if the reactions proceed by a concerted mechanism.[24] From the mechanistic viewpoint, irradiation was carried out in several solvents as shown in Table 1. In all cases, the products were the same as those in benzene. The photoreaction proceeded almost completely in polar solvents, and **5** was obtained as major product, although the yield of **4** did not depend on the solvent polarity. It was suggested that the formation of **5** might involve a polar intermediate.



(3)

Based on these results, the photoinduced ene-reaction of **1** in the presence of arylalkenes as enophiles were investigated. Irradiation of a degassed benzene solution of **1** containing a large excess (20-fold excess) of 1,1-diphenylethene afforded 9-(3,3-diphenylpropyl)phenanthrene **6** in a 69% isolated yield. Similar irradiation of **1** in the presence of styrene, 1-phenylpropene, and 1,3-pentadiene gave the corresponding ene-adducts **7**–**9**. However, the photoreaction of **1** with 1-hexene and butyl vinyl ether did not afford ene-products, but **4** and **5**. In the cases of stilbene and cinnamaldehyde, **1** was almost recovered. The results are summarized in Table 2. The ene-adducts **6**–**8** were identified by comparing their spectroscopic data with those of authentic compounds, which were prepared by the other methods without irradiation. The photoproduct **9** was converted into the hydrogenated derivative, 9-hexylphenanthrene, and identified.

The incident light (Pyrex filtered light: >280 nm) is competitively absorbed by **1** ($\lambda_{max}=278$ nm) and the added alkenes, although the amounts of alkenes are large excess.[1] 1,1-Diphenylethene, styrene, and 1-phenylpropene reacted with the excited singlet of **1** regioselectively to give substituted propane derivatives **6**, **7**, and **8**, respectively. These ene-adducts bear phenanthrylmethyl group regioselectively to the sterically less-hindered carbon atom of the alkenes. However, irradiation of **1** in the presence of (*E*)-stilbene gave only (*Z*)-stilbene and unchanged **1** was recovered, presumably due to most of the light absorption by (*E*)-stilbene. Phenylacetylene reacted with **1** upon irradiation to give a complex mixture.



(4)

6 : R' = H, R = R" = Ph

7 : R' = R = H, R" = Ph

8 : R' = Me, R" = Ph, R = H

9 : R' = R = H, R" = CH=CHMe

The photoreaction of **1** in the presence of a large amount of 1,3-pentadiene (120-fold) also afforded an ene-adduct in 15%. However, the less amount of 1,3-pentadiene (20-fold) did not give the ene-adduct, but **5** was obtained in 96% yield. In this case, the excited singlet state of **1** may rearrange to **5** before being trapped by 1,3-pentadiene.

Mono-olefins such as 1-hexene and butyl vinyl ether gave no ene-adduct. These results suggested that the reactive

Table 2. Photoreaction of **1** with alkenes in benzene[a,b]

Alkene[c]	Yield/%			Recovery/%
	Ene-adduct	**4**	**5**	**1**
$Ph_2C{=}CH_2$	**6** (69)	nd	nd	nd
$PhCH{=}CH_2$	**7** (62)	nd	(4)	(4)
PhCH=CHMe	**8** (21)	nd	(7)	(19)
(*E*)-PhCH=CHPh	(0)	(0)	(0)	(100)
$CH_2{=}CHCH{=}CHMe$	**9** (0)	(0)	96	nd
$CH_2{=}CHCH{=}CHMe$[d]	**9** (15)	(10)	nd	nd
$CH_2{=}CH(CH_2)_3Me$	(0)	(18)	(16)	(44)
Bu-O-CH=CH_2	(0)	(20)	(12)	(35)
PhCH=CHCHO	(0)	(0)	(0)	(75)

[a] Isolated yields and recoveries were obtained based on **1** used.
[b] nd: not determined.
[c] 20 equiv of an alkene based on **1** used.
[d] 120 equiv of 1,3-pentadiene based on **1** used.

alkene has to be conjugated with a phenyl group or with a C=C double bond. Carbonyl compounds such as 2-propenal, β-ionone, and cinnamaldehyde gave no ene-adduct in detectable amount under similar reaction conditions and unchanged **1** was recovered on irradiation, suggesting that an abstraction of hydrogen atom by carbonyl group did not take place under the reaction conditions.

Compound **1** reacted with typical electron-acceptors such as tetracyanoethene and dimethyl acetylenedicarboxylate in the dark at room temperature to give ene-adducts, respectively. But it did not react with styrene, maleic anhydride, and fumaronitrile.[2] 1,1-Diphenylethene did not react with **1** even in refluxing benzene. On the basis of these observations, the present photoreaction is regarded as a photoinduced ene-reaction, although it has been stated that photo-initiated ene-reactions do not occur at less polar conditions.[13]

As mentioned before,[3] irradiation of 2-(2-anilinoethyl)-naphthalene affords the ene-adduct **2** without formation of the *exo*-methylene compound **3**, while that of 9-(2-anilinoethyl)phenanthrene affords the *exo*-methylene compound **1** without formation of the ene-adduct **4**. These observation may be explained by the difference in their absorption spectra. Thus, the compounds **3** and **1** show an absorption maximum at 297 and 278 nm ($\log \varepsilon = 4.14$), respectively.[25] On the other hand, the absorption maximum of 2-(2-anilinoethyl)naphthalene was observed at 276 nm ($\log \varepsilon = 3.83$) and that of 9-(2-anilinoethyl)phenanthrene was at 298 nm ($\log \varepsilon = 4.00$).[2] Namely, in the case of naphthalene derivative, most of the incident light should be absorbed by the photo-product **3** which may change into the ene-adduct **2**. In the case of **1**, the starting amine should absorb the incident light preferentially and therefore after the consumption of starting amine, the photo-induced ene-reaction of **1** might take place.

3. Experimental

Mp's were determined with a Yanaco micromelting point apparatus (MP-500) and are uncorrected. Spectra were obtained with a Hitachi infrared spectrophotometer (type-215), an NMR spectrometer (JNM-GX-270) (270 MHz) using tetramethylsilane as internal standard, a gas chromatograph-mass spectrometer (Shimadzu-LKB 9000) (mass), and a Shimadzu UV spectrophotometer (UV-160A).

3.1. Materials

9-Methylene-9,10-dihydrophenanthrene **1** was prepared by the method described previously.[1,2] As **1** gradually changed into the methyl isomer, photoreactions were performed without separation of the two isomers (the starting material **1** was contaminated with 5–10% of **5**). The yields in Tables 1 and 2 are based on the amount of **1** at the start of the irradiation.

3.2. Photoreactions

3.2.1. Preparative irradiation. A general procedure is shown for the irradiation of **1** with 1,1-diphenylethene: a solution of **1** [58 mg, purity 91% contained **1** (0.27 mmol)] and 1,1-diphenylethene (973 mg, 5.4 mmol) in benzene (20 mL) in a Pyrex tube was degassed by three freeze-pump-thaw cycles under argon, and the tube was sealed under reduced pressure. The solution was irradiated externally with 300 W high-pressure mercury lamp (Eikosha PIH-300) for 8 h at room temperature. After irradiation, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel with hexane–benzene (5:1, v/v) to give 3-(9-phenanthryl)-1,1-diphenylpropane **6** as a colorless solid (70 mg, 69%), mp 129.5–130.5 °C (from hexane); δ ($CDCl_3$) 2.53–2.62 (2H, m, CH_2), 3.05–3.10 (2H, t, CH_2), 4.05–4.10 (1H, t, CH), and 7.14–7.92 (17H, m) and 8.63–8.74 (2H, m) (together 19H ArH); *m/z* 372 (M+, 46%), 205 (22), 192 (100), and 191 (29). Found: C, 93.39; H, 6.19. Calcd for $C_{29}H_{24}$: C, 93.51; H, 6.49%.

The spectral data of the other photo ene-adducts, **7**, **8**, and **9** isolated from the irradiation mixtures by chromatography were compared with those of the corresponding authentic compounds are identified after hydrogenation.

3.2.2. Preparation of 9-[2-(9-phenanthryl)ethyl]-9,10-dihydrophenanthrene 4. A solution of **1** [61 mg, purity 90% contained **1** (0.286 mmol)] in acetonitrile (20 mL) was irradiated. Chromatography of the irradiated mixture on silica gel with benzene–hexane (1:3, v/v) gave **4** from the third eluent (12 mg, 22%), mp 153–154 °C (from chloroform–ethanol); ν_{max} (KBr)/cm^{-1} 3060, 3030, 3010, 2920, 1500, 1485, 1455, 1440, 880, 740, and 720; λ_{max} (hexane)/nm 212, 254, and 298 ($\log \varepsilon$ 4.79, 4.79, and 4.14); δ ($CDCl_3$) 1.86–1.95 (2H, m, CH_2), 2.94–3.28 (5H, m, two CH_2 and CH), and 7.21–7.82 (15H, m) and 8.59–8.69 (2H, m) (together 17H ArH); δ ($CDCl_3$) 31.31, 33.90, 34.08, 38.83, 122.40, 123.13, 123.55, 124.14, 124.26, 125.82, 125.88, 126.04, 126.44, 126.54, 127.05, 127.17, 127.47, 127.61, 127.96, 128.32, 129.01, 129.60, 130.67, 131.13, 131.86, 133.66, 134.12, 135.24, 136.41, 140.82; *m/z* 384 (M+, 33%), 193 (22), 192 (100), 191 (19), 179 (26), and 178 (27). Found: C, 93.46; H, 6.02. Calcd for $C_{30}H_{24}$: C, 93.71; H, 6.29%.

3.2.3. Preparation of authentic compounds. 1,1-Diphenyl-3-(9-phenanthryl)propane **6** (ene-adduct with 1,1-diphenylethene) was obtained by the hydrogenation of 3-(9-phenanthryl)-1,1-diphenylpropene (mp 141–141.5 °C) which was prepared by the reaction of methyl 3-(9-phenanthryl)propanoate with phenylmagnesium bromide followed by the dehydration and 5% Pd–C catalyzed hydrogenation, mp 128.5–129.5 °C; λ_{max} (hexane)/nm 210, 253, 277, 286, and 298 ($\log \varepsilon$ 4.65, 4.74, 4.12, 4.01, and 4.08); δ ($CDCl_3$) 2.57 (2H, q, J=7.7 Hz, CH_2), 3.07 (2H, t, J=7.7 Hz, CH_2), 4.07 (1H, t, J=7.7 Hz, CH), 7.17–7.21 (2H, m, ArH), 7.28–7.36 (10H, m, ArH), 7.51–7.65 (5H, m, ArH), 7.79 (1H, dd, J=1.5, 7.3 Hz, ArH), 7.90 (1H, d, J=8.0 Hz, ArH), 8.64 (1H, d, J=7.9 Hz, ArH), 8.72 (1H, d, J=8.2 Hz, ArH); δ ($CDCl_3$) 32.00, 36.37, 51.52, 122.50, 123.27, 124.42, 126.02, 126.18, 126.22, 126.34, 126.55, 126.65, 128.00, 128.06, 128.60, 129.70, 130.75, 131.18, 131.90, 136.34, 144.82.

3.2.4. 3-Phenyl-1-(9-phenanthryl)propane 7. Ene-adduct

with styrene. This compound was prepared by the hydrogenation of 3-(9-phenanthryl)-1-phenylpropene (mp 105–107.5 °C) which was obtained by 3 steps from 9-phenanthrylethenyl phenyl ketone (mp 136.5–138 °C), mp 84–85 °C (from pentane); λ_{max} (hexane)/nm 211, 253, 277, 286, and 298 (log ε 4.57, 4.77, 4.13, 4.02, and 4.07); δ ($CDCl_3$) 2.15 (2H, quintet, J=7.7 Hz, CH_2), 2.79 (2H, t, J=7.7 Hz, CH_2), 3.13 (2H, t, J=7.7 Hz, CH_2), 7.15–7.36 (2H, m, ArH), 7.50–7.68 (5H, m, ArH), 7.51–7.65 (5H, m, ArH), 7.81 (1H, d, J=7.5 Hz, ArH), 8.01 (1H, d, J=7.9 Hz, ArH), 8.63 (1H, d, J=8.2 Hz, ArH), 8.72 (1H, d, J=8.2 Hz, ArH); δ ($CDCl_3$) 31.89, 33.10, 36.12, 122.48, 123.25. 124.42, 125.88, 125.96, 126.11, 126.15, 126.52, 126.62, 128.05, 128.40, 128.56, 129.67, 130.73, 131.26, 131.91, 136.40, 142.17; *m/z* 296 (M+, 44%), 192 (100), and 191 (42). Found: C, 93.15; H, 6.8. Calcd for $C_{23}H_{20}$: C, 93.2; H, 6.8%.

3.2.5. 1-(9-Phenanthryl)-2-benzylpropane 8. Ene-adduct with 1-phenylpropene. This compound was prepared by the following route: propiophenone to 1-(9-phenanthryl)-2-benzoylpropane (mp 140–140.5 °C) and from this to **8**, mp 112–115 °C (from pentane); λ_{max} (hexane)/nm 211, 253, 277, 286, and 298 (log ε 4.56, 4.75, 4.12, 4.03 and 4.12); δ ($CDCl_3$) 0.93 (3H, d, J=7.6 Hz, CH_3), 2.27 (1H, m, CH), 2.61 (1H, dd, J=7.7, 13.7 Hz, CH_2), 2.78 (2H, dd, J=8.8, 13.8 Hz, CH_2), 3.25 (1H, dd, J=5.2, 13.7 Hz, CH_2), 7.17–7.34 (5H, m, ArH), 7.50–7.66 (5H, m, ArH), 7.78–7.84 (2H, m, ArH), 8.64 (1H, d, J=8.2 Hz, ArH), 8.71 (1H, d, J=8.2 Hz, ArH); δ ($CDCl_3$) 20.15, 36.11, 41.01, 44.26, 122.49, 123.22, 124.73, 125.95, 125.96, 126.07, 126.42, 126.62, 127.52, 128.07, 128.26, 129.36, 129.75, 130.80, 131.45, 131.75, 135.41, 141.19; *m/z* 310 (M+, 45%), 192 (100), and 191 (73). Found: C, 92.53; H, 6.94. Calcd for $C_{24}H_{22}$: C, 92.86; H, 7.14%.

3.2.6. 9-Hexylphenanthrene.[26] The hydrogenated product of **9**, which corresponds to the ene-adduct with 1,3-pentadiene. This was prepared from 9-phenanthrenecarbaldehyde by the reaction with pentylmagnesium bromide followed by dehydration and hydrogenation, mp 78–79 °C (from pentane); λ_{max} (hexane)/nm 253, 277, 285, and 298 (log ε 4.76, 4.13, 4.00 and 4.06); δ ($CDCl_3$) 0.90 (3H, t, J=7.1 Hz, CH_3), 1.25–1.41 (4H, m, CH_2CH_2), 1.43–1.54 (2H, m, CH_2), 1.81 (2H, quintet, J=7.7 Hz, CH_2), 3.11 (2H, t, J=7.8 Hz, CH_2), and 7.52–7.71 (5H, m, ArH), 7.78–7.84 (1H, m, ArH), 8.03–8.14 (1H, m, ArH), 8.65 (1H, d, J=8.4 Hz, ArH), and 8.61–8.76 (1H, m, ArH); δ ($CDCl_3$) 14.40, 22.94, 29.81, 30.49, 32.03, 33.73, 122.48, 123.25, 124.54, 125.86, 125.96, 126.09, 126.48, 126.59, 128.04, 129.63, 130.73, 131.39, 132.00, 137.05; *m/z* 262 (M+, 60%), 191 (100), and 179 (28). Found: C, 91.51; H, 8.66. Calcd for $C_{20}H_{22}$: C, 91.55; H, 8.45%.

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Photoreactions of β-aziridinylacrylonitriles and acrylates with alkenes: formation of head-to-head adducts and application to the preparation of pyrrolizidine alkaloid

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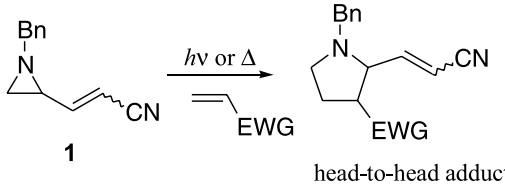
Abstract—The photochemical C,C-bond cleavage of *N*-benzyl β-aziridinylacrylonitrile **1** and acrylate **2** and the subsequent [3+2] cycloaddition with electron-deficient alkenes afforded head-to-head adducts selectively and efficiently. Irradiation of *N*-phenyl aziridine **3** with acrylonitrile gave adducts, but photoreaction of *N*-benzoyl aziridine **4** and thermal reactions of **3** and **4** with alkenes yielded C(γ),N-cleaved products instead of cycloadducts. *N*-trityl aziridine **5** also reacted with electron-deficient alkenes, affording 2,3-*cis*-pyrrolidine derivatives exclusively. A formal synthesis of a pyrrolizidine alkaloid, isoretronecanol (**27**), starting from **5** was achieved in a convenient manner.

1. Introduction

The 1,3-dipolar cycloaddition of azomethine ylides with alkenes is an important and useful strategy for the construction of nitrogen-containing five-membered heterocycles.[1] One of the method for the generation of azomethine ylide is the heating or irradiation of aziridines, most of which bear an adjacent electron-withdrawing or phenyl group.[2] However, mild and efficient methods for the C,C-bond cleavage of aziridines have not been widely studied.

We have investigated photochemical reactions of α,β-unsaturated γ,δ-epoxy nitriles systematically.[3] These studies have revealed that carbonyl ylides photochemically generated from epoxy nitriles undergo 1,3-diporlar cycloaddition with electron-rich alkenes to afford tetrahydrofurans.[3d] On the basis of these studies, we became interested in extending the photochemistry of epoxy nitriles to that of β-aziridinylacrylonitrile.

As part of these studies, we reported in a previous letter that direct irradiation or heating of β-aziridinylacrylonitrile **1** with electron-deficient alkenes causes the ring-opening of **1** and subsequent cycloaddition reactions, leading to head-to-head adducts selectively and efficiently (Scheme 1).[4] In this paper, we describe the details of the reactions of nitrile **1**, the photochemical behavior of β-aziridinylacrylate **2**, and the effects of N-substituents in the aziridine ring [*N*-phenyl, *N*-benzoyl and *N*-trityl aziridines **3**–**5** (Fig. 1)] on the cycloaddition with alkenes. Furthermore, we describe that using the cycloadducts **5**, the formal preparation of a pyrrolizidine alkaloid, isoretronecanol (**27**),[5] was achieved conveniently.



Scheme 1.

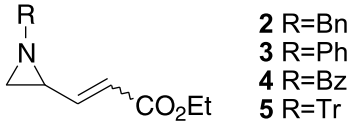


Figure 1.

Keywords: Aziridine; Photolysis; [3+2] Cycloaddition; Pyrrolidine; Pyrrolizidine.
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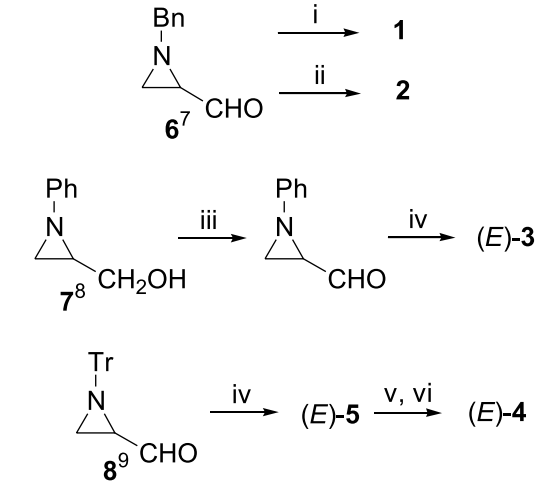
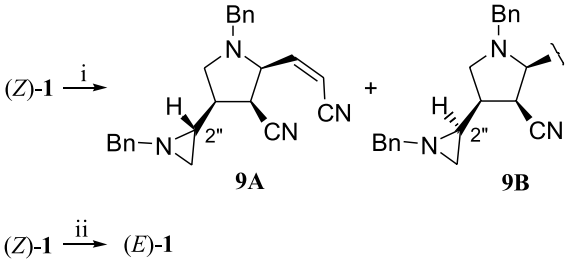
2. Results and discussion

The *N*-benzylnitrile **1** and ester **2** were prepared from aldehyde **6**[6] with diethyl cyanomethylphosphonate and diethyl ethoxycarbonylmethylphosphonate in 75% yield (*E*/*Z*=44:31) and 75% yield (*E*/*Z*=68:7), respectively. *N*-phenyl ester (*E*)-**3** and *N*-trityl ester (*E*)-**5** were synthesized from the corresponding alcohol **7**[7] and aldehyde **8**,[8] respectively, as shown in Scheme 2. *N*-Benzoyl ester (*E*)-**4** was prepared in 58% yield by the detritylation and benzoylation of (*E*)-**5** (Scheme 2).



Scheme 2. Reagents and conditions: (i) $(EtO)_2P(O)CH_2CN$, NaH, THF, 0 °C; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; (iii) oxalyl chloride, DMSO, CH_2Cl_2, −78 °C; (iv) $(EtO)_2P(O)CH_2CO_2Et$, NaH, CH_2Cl_2, 0 °C; (v) TFA, MeOH, $CHCl_3$; (vi) $(PhCO)_2O$, NEt_3, $CHCl_3$.



Scheme 3. Reagents and conditions: (i) $\lambda=254$ nm, acetonitrile, rt; (ii) $\lambda>280$ nm, acetone, rt.

Direct irradiation of a solution of (*Z*)-**1** in acetonitrile with a low-pressure mercury lamp in a quartz test tube at rt (conversion 83%) afforded dimers **9A** (32%[9]) and **9B** (14%) (Scheme 3). On triplet sensitization, the nitrile (*Z*)-**1** in acetone with a high-pressure mercury lamp in a Pyrex test tube at rt (conversion 58%) selectively underwent (*E*/*Z*)-isomerization of the side chain leading to (*E*)-**1** (64%[9]) (Scheme 3).

Since the photolysis of nitrile **1** had given cycloadducts **9** in moderate yield, the reactions of **1** and electron-deficient alkenes or an alkyne were studied. The results are summarized in Table 1 and Figure 2. No significant differences in reactivity between (*E*)- and (*Z*)-**1** were observed (entries 1–4).

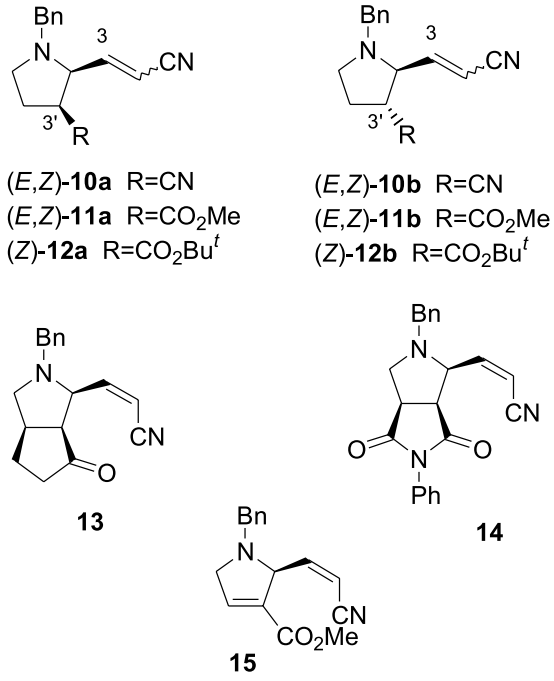


Figure 2.

Table 1. Photochemical and thermal reactions of aziridine **1** with alkenes or an alkyne[a]

Entry	(*E*)/(*Z*)-**1**	Alkene or alkyne	Reaction time (h)	Conversion (%)	Products and yields (%)[9,b]
1	(*E*)	Acrylonitrile	6	100	(*E*)-**10a** (52) and (*E*)-**10b** (26)
2	(*Z*)	Acrylonitrile	7	100	(*Z*)-**10a** (52) and (*Z*)-**10b** (15)
3	(*E*)	Methyl acrylate	2	87	(*E*)-**11a** (37) and (*E*)-**11b** (25)
4	(*Z*)	Methyl acrylate	4	98	(*Z*)-**11a** (38) and (*Z*)-**11b** (48)
5	(*Z*)	*tert*-Butyl acrylate	2 [3][c]	90 [86]	**12a** (23) [21] and **12b** (49) [13]
6	(*Z*)	2-Cyclopentenone	2.5	91	**13** (39)
7	(*Z*)	*N*-Phenylmaleimide	2 [2]	84 [81]	**14** (39) [42]
8	(*Z*)	Methyl propiolate	0.75	66	**15** (49)

[a] A 0.060 mol L^{-1} solution of **1** in acetonitrile with 10 equiv of alkene or alkyne was irradiated at rt.
[b] Isolated yield.
[c] Values in square brackets are yields of thermal reactions of **1** with 10 equiv of alkene in refluxing xylene.

The reactions **1** and mono-substituted alkenes selectively afforded 3-substituted pyrrolidines in moderate yields (62–86%[9]) (entries 1–5). The photoreactions of nitrile **1** and dimethyl fumarate or dimethyl acetylenedicarboxylate gave only dimethyl maleate and a complex mixture, respectively.

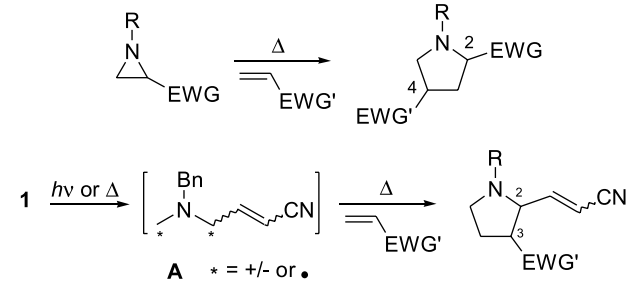


Figure 3.

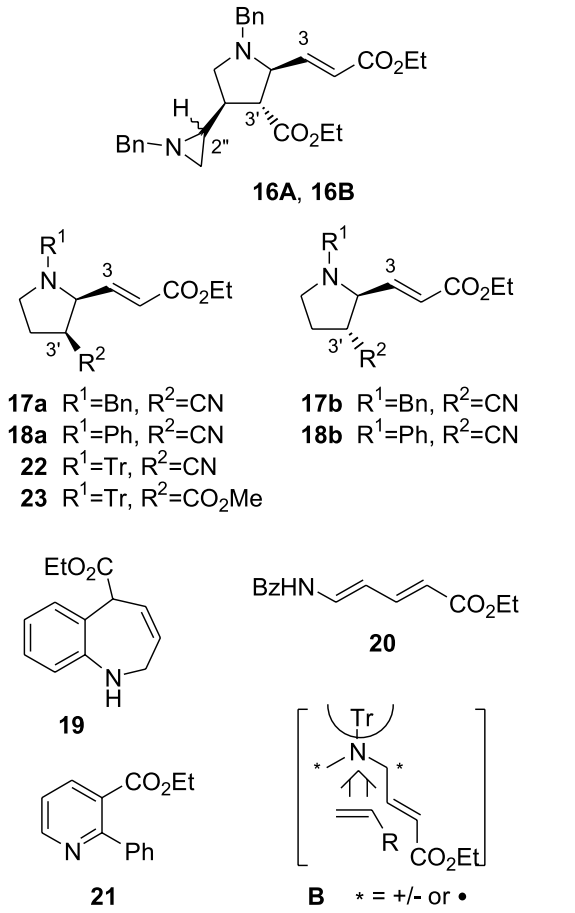


Figure 4.

On the other hand, the reactions of **1** and non-activated (bicyclo[2.2.1]hept-2-ene and cyclohexene) or electron-rich alkenes (ethyl vinyl ether) gave only dimers **9** instead of the adducts with alkenes.

The thermal 1,3-dipolar cycloaddition of an azomethine ylide derived from an aziridine bearing an ester function and electron-deficient alkenes normally affords products possessing the electron-withdrawing group (EWG) at the C(4) position in the pyrrolidine (Fig. 3).[2b] However, the position of the EWG in our cycloadducts was at C(3). In order to investigate the mechanism of the cycloaddition step between electron-deficient alkenes and ring-cleaved intermediate **A** (Fig. 3), thermal reactions of **1** and alkenes were performed. A solution of (*Z*)-**1** with *tert*-butyl acrylate or *N*-phenylmaleimide was heated in refluxing xylene and gave the same adducts **12** (**a** 21% and **b** 13%[9]) and **14** (42%[9]) as yielded by the photoreactions, respectively. The results may suggest that the C,C-bond cleavage of aziridine **1** proceeds photochemically or thermally and the cycloaddition occurs thermally.

We next investigated ethyl β-aziridinylacrylate **2** possessing an ester group, which is easily transformed to other functional groups. Direct irradiation of a solution of (*E*)-**2** in acetonitrile with a low-pressure mercury lamp in a quartz test tube at rt (conversion 98%) afforded dimers **16A** (19%[9]) and **16B** (7%[9]) (Fig. 4).

On triplet sensitization, ester (*E*)-**2** in acetone with a high-pressure mercury lamp in a Pyrex test tube at rt (conversion 84%) selectively underwent (*E*/*Z*)-isomerization of the side chain leading to (*Z*)-**2** (25%[9]).

Since the photochemical behavior of ester **2** was similar to that of nitrile **1**, the reactions of **2** and acrylonitrile were studied (Table 2, Fig. 4).

The structures of the cycloadducts **9**–**15** were deduced mainly on the basis of their spectral data and were discussed in the previous communication.[4] Particularly, in the ^{1}H NMR spectra of the *N*-benzyl pyrrolidines **9**–**12**, the signals due to H-(3′) for 2,3-*cis*-pyrrolidines appear in a lower field (δ 3.18–3.46) than those of 2,3-*trans*-pyrrolidines (δ 2.74–2.85) (Table 3).

The molecular ion peak in the mass spectrum (MS) of **17** indicates the 1:1 adducts of **2** and acrylonitrile. The regio- and stereochemistries of **17a** and **17b** were determined by the H–H and C–H COSY spectra. In particular, the configurations at the 2′,3′-positions of **17a** and **17b** were deduced from a comparison of the chemical shifts

Table 2. Photochemical reactions of aziridines **2**–**5** with alkenes[a]

Entry	Aziridine	Alkene	Reaction time (h)	Conversion (%)	Products and yields (%)[9,b]
1	(*E*)-**2**	Acrylonitrile	3	100	**17a** (42) and **17b** (21)
2	(*E*)-**3**	Acrylonitrile	2	52	**18a** (10) and **18b** (6)
3	(*E*)-**4**	Acrylonitrile	5	74	**20** (30)
4	(*E*)-**5**	Acrylonitrile	1.3	40	**22** (43)
5	(*E*)-**5**	Methyl acrylate	4	57	**23** (61)

[a] A 0.060 mol L^{-1} solution of **2**–**5** in acetonitrile with 10 equiv of alkene was irradiated at rt.
[b] Isolated yield.

Table 3. The chemical shift of H–C(3′) in the ^{1}H NMR spectra for **9–12**, **16** and **17**

cis-Adduct	δ	*trans*-Adduct	δ
(*E*)-**10a**	3.18–3.25 m	(*E*)-**10b**	2.82 ddd
(*Z*)-**10a**[a]	3.29 ddd	(*Z*)-**10b**[a]	2.85 ddd
(*E*)-**11a**[a]	3.20–3.28 m	(*E*)-**11b**	2.81 ddd
(*Z*)-**11a**[a]	3.29–3.37 m	(*Z*)-**11b**	2.83 ddd
12a[a]	3.18–3.24 m	**12b**[a]	2.74 ddd
17a	3.16–3.21 m	**17b**	2.84 ddd
9A[a]	3.46 dd	**16A**[a]	2.49 dd
9B[a]	3.36 dd	**16B**	2.62 dd

[a] The stereochemistry was also determined by phase-sensitive NOESY spectrum.

(δ 3.16–3.21 for **17a** and δ 2.84 for **17b**) with those of the compounds described in Table 3.

The molecular ion peak in the mass spectrum (MS) of **16A** and **16B** shows that they are the dimers of **2**. The regio- and stereochemistries of **16A** and **16B** were determined from the H–H and C–H COSY spectra and from a comparison of the spectral data with those of **9A** and **9B**. In particular, in the ^{1}H NMR spectrum, the 2′,3′-*trans* configuration in the pyrrolidine ring was deduced from a comparison of the chemical shifts at the 3′-position of **16A** (δ 2.49) and **16B** (δ 2.62) with the data described in Table 3. Furthermore, in the NOESY spectrum of **16A**, the cross-peaks showed 2′,3′-*trans* and 3′,4′-*trans* configurations in the pyrrolidine ring (Fig. 5). However, the stereochemistries at C(2″) for **16A** and **16B** could not be determined.

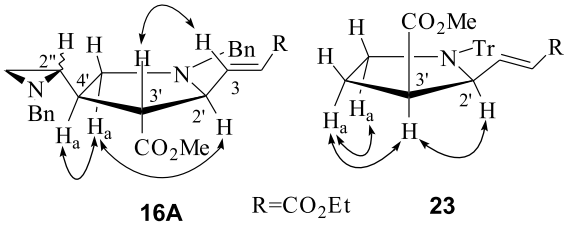


Figure 5. Phase-sensitive NOESY for **16A** and **23**.

As the photochemical reactions of *N*-benzyl aziridines **1** and **2** with electron-deficient alkenes afforded the cycloadducts in moderate yields, the effects of other N-substituents in the aziridine ring on the cycloaddition were studied. Aziridines substituted with phenyl or benzoyl groups, which possess stronger electron-withdrawing characteristics than the benzyl group, were supposed to react with electron-rich or non-activated alkenes.[2b]

Irradiation of a solution of (*E*)-**3** and acrylonitrile in acetonitrile with a low-pressure mercury lamp in a quartz test tube afforded the adducts **18a** and **18b** (Table 2, Fig. 4). The yields of adducts from **3** were reduced in comparison with those from the *N*-benzyl aziridine **2**. Aziridine (*E*)-**3** also did not react with electron-rich alkene (ethyl vinyl ether) photochemically giving a complex mixture. On the other hand, the thermal reaction of (*E*)-**3** and 3,4-dihydro-2*H*-pyran in refluxing xylene yielded no adducts but underwent an electrocyclic reaction leading to benzazepine **19** (Fig. 4). This type of rearrangement is also observed by thermal reaction[10] or treatment with silica gel[11] of 1-phenyl-2-vinylaziridines.

The structures of **18a** and **18b** were deduced from the chemical shifts for H–(C3′) in the ^{1}H NMR spectra in comparison with those of the adducts shown in Table 3; the signal (δ 3.28) for **18a** appears in a lower field than that for **18b** (δ 3.06–3.11). Furthermore, in the phase-sensitive NOESY spectrum of **18a** the crosspeak between H-2′ and H-3′ was observed. The structure of **19** was determined on the basis of its spectral data. In particular, the molecular ion peak in MS indicates that **19** is an isomer of **3**, and the ^{1}H NMR spectrum shows the signals due to four aromatic protons, two isolated alkenic protons and amino moiety (see Section 4).

An acetonitrile solution of **4** and acrylonitrile was irradiated with a low-pressure mercury lamp in a quartz test tube affording the C(γ),N-bond-cleaved product **20** (Table 2, Fig. 4). The thermal reaction of (*E*)-**4** and *tert*-butyl acrylate in refluxing xylene yielded no adducts but a mixture of C(γ),N-bond-cleaved compounds (mainly isomers of **20**) and pyridine derivative **21** (4%[9]) (Fig. 4).[12]

The structure of **20** was deduced from the spectral data (see Section 4). The structure of **21** was determined by a comparison of the spectral data with those of reference 12. The *N*-benzoyl substituent indicated a tendency to cleave the C(γ),N-bond on thermal and photochemical reactions.

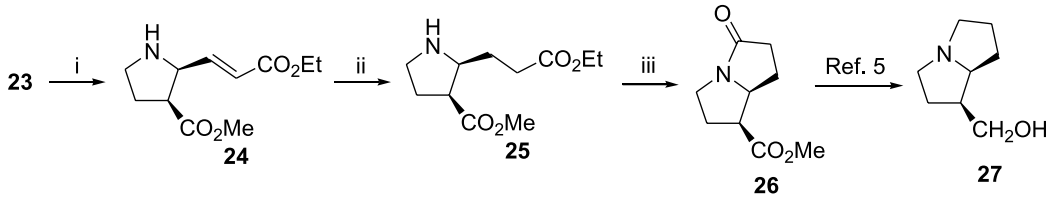
In order to improve the stereoselectivity at the 2,3-position of the pyrrolidine ring on the cycloaddition, we chose trityl group, which is more bulky than benzyl group, as the N-substituent of aziridine. Acetonitrile solutions of *N*-trityl aziridine **5** with acrylonitrile and methyl acrylate were irradiated with a low-pressure mercury lamp in quartz test tubes affording the adducts **22** and **23**, respectively (Table 2, Fig. 4).

The regio- and stereochemistries of **22** and **23** were determined by the H–H COSY and the phase-sensitive NOESY spectra. In particular, the crosspeaks between H-2′ and H-3′, between H-3′ and H_a-4′ and between H_a-4′ and H_a-5′ are observed in the NOESY spectra of **23** (Fig. 5).

In the case of the reaction of *N*-trityl aziridine **5**, the relative configuration between C(2′) and C(3′) in the isolated adducts was absolutely *cis*. In the transition state **B** for the formation of **22** and **23**, both the acrylate moiety of the aziridine-ring-cleaved intermediate and the substituent R of alkenes were presumably orientated on the opposite side of the trityl group because of the steric hindrance (Fig. 4).

Since the photolysis of *N*-trityl aziridine **5** and methyl acrylate gave 2,3-*cis*-pyrrolidine **23** in moderate yield, we were interested in the synthesis of a pyrrolizidine alkaloid, isoretronecanol (**27**), using the stereochemistry of **23**. Hydrogenolysis of the side chain in **23** over Pd/C gave no reduced product. After detritylation of **23** with trifluoroacetic acid, reduction of the double bond in **24** over Pd/C proceeded successfully, affording propionate **25** (64%). Cyclization of **25** in toluene gave pyrrolizidine **26**[5] in 87% yield, which can be transformed by authentic methods[5] into **27** (Scheme 4).

To clarify the chemical behavior and the utility of



Scheme 4. Reagents and conditions: (i) TFA, rt; (ii) 10% Pd/C, H_2 (1 bar), AcOEt; (iii) toluene, 110 °C.

β-aziridinylacrylates, further work with 2,3-disubstituted aziridines and the synthetic application of the cycloadducts is currently in progress.

3. Summary

In conclusion, the photoreactions of *N*-benzyl β-aziridinylacrylonitrile **1** and acrylate **2** with electron-deficient alkenes afforded novel head-to-head adducts selectively and efficiently. Aziridines **3** and **4**, possessing the N-conjugated substituent had a tendency to cleave the C(γ),N-bond. *N*-trityl aziridine **5** also reacted with electron-deficient alkenes, yielding 2,3-*cis*-pyrrolidine derivatives selectively. A formal synthesis of a pyrrolizidine alkaloid, isoretronecanol (**27**), starting from the pyrrolidine **23** was achieved in a convenient manner.

4. Experimental

4.1. General

Melting points and boiling points are uncorrected. Melting points were measured with a Yanaco MP-3 apparatus and boiling points were measured with a Büchi Kugel Rohr GKR-50 apparatus. UV spectra were recorded on a Hitachi 124 spectrometer and IR spectra on a Hitachi 215 spectrometer. NMR spectra were obtained with a JEOL JNM-AL300 (300 MHz; AL3), a JEOL JNM-AL400 (400 MHz; AL4) or JEOL JNM-LA500 (500 MHz; LA) spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution MS (HRMS) were taken on a JEOL JMS-700 spectrometer. Column chromatography was performed with Merck silica gel 60 (230–400 mesh) and Chromatorex NH (Fuji Silysia Chemical LTD.), and preparative TLC with Wakogel B-5F.

An Eikosha 60 W low-pressure mercury lamp and a Riko 400 W high-pressure mercury lamp were used for irradiation. The photolysis solutions were purged with argon both before and during irradiation.

4.2. Preparations of aziridines

4.2.1. (*E*)-3-(1-Benzylaziridin-2-yl)acrylonitrile (*E*)-1 and (*Z*)-3-(1-benzylaziridin-2-yl)acrylonitrile (*Z*)-1. To a suspension of NaH [1.48 g, 61.8 mmol; prepared from a NaH dispersion (60%, 2.47 g) by washing it twice with hexane (30 mL)] in dry THF (125 mL) was added dropwise a solution of diethyl cyanomethylphosphonate (10.9 g, 61.8 mmol) in dry THF (125 mL) at 0 °C. After the mixture had been stirred for 10 min at 0 °C, a solution of *N*-benzylaziridinecarbaldehyde **6**[6] (6.64 g, 41.2 mmol) in dry THF (40 mL) was added dropwise, and stirring was continued for 1.5 h at 0 °C. Ice/water was added to the mixture, and the organic phase was extracted with diethyl ether. The ethereal extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving a residue that was subjected to flash column chromatography [hexane–ethyl acetate (9:1)] to afford (*E*)-**1** (3.30 g, 44%) and (*Z*)-**1** (2.34 g, 31%).

Compound (*E*)-**1**. Bp 130 °C at 0.35 mm Hg; IR (film): 2300 cm^{-1} (C≡N); ^1H NMR (AL4): δ 1.84 (d, 1H, J=6.4 Hz, H-3′), 1.92 (d, 1H, J=3.2 Hz, H-3′), 2.09–2.14 (m, 1H, H-2′), 3.47, 3.58 (each d, 2H, J=13.6 Hz, CH_2Ph), 5.59 (dd, 1H, J=16.4, 0.8 Hz, H-2), 6.55 (dd, 1H, J=16.4, 6.8 Hz, H-3), 7.26–7.42 (m, 5H, Ph); ^{13}C NMR (AL4): δ 37.7 (t, C-3′), 39.0 (d, C-2′), 64.0 (t, *C*H_2Ph), 99.8 (d, C-2), 117.1 (s, C-1), 127.2, 127.6 128.3 (3d, 5 C in Ph), 137.9 (s, C in Ph), 153.9 (d, C-3); EI-MS *m*/*z* 184 (M^+, 19%), 104 (4), 91 (100), 77 (3), 65 (10), 51 (3), 39 (7). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20%. Found: C, 78.01; H, 6.72; N, 14.85%.

Compound (*Z*)-**1**. An oil; IR ($CHCl_3$): 2220 cm^{-1} (C≡N); ^1H NMR (AL4): δ 1.94 (d, 1H, J=6.4 Hz, H-3′), 2.02 (d, 1H, J=3.6 Hz, H-3′), 2.56–2.62 (m, 1H, 2′-H), 3.46, 3.66 (each d, 2H, J=13.2 Hz, CH_2Ph), 5.39 (dd, 1H, J=10.8, 0.8 Hz, H-2), 6.10 (dd, 1H, J=16.4, 9.3 Hz, H-3), 7.26–7.42 (m, 5H, Ph); ^{13}C NMR (AL4): δ 36.1 (t, C-3′), 39.0 (d, C-2′), 64.1 (t, *C*H_2Ph), 99.7 (d, C-2), 115.6 (s, C-1), 127.2, 127.8, 128.3 (3d, 5C in Ph), 137.8 (s, C in Ph), 154.2 (d, C-3); EI-MS *m*/*z* 184 (M^+, 15%), 104 (4), 91 (100), 77 (3), 65 (9), 51 (3), 39 (6); HRMS calcd for $C_{12}H_{12}N_2$: 184.1000. Found: 184.1004.

4.2.2. Ethyl (*E*)-3-(1-benzylaziridin-2-yl)acrylate (*E*)-2 and ethyl (*Z*)-3-(1-benzylaziridin-2-yl)acrylate (*Z*)-2. By analogy with the synthesis of **1**, aldehyde **6** (6.79 g, 42.1 mmol) was treated with NaH (1.52 g, 63.2 mmol) and diethyl ethoxycarbonylmethylphosphonate (14.2 g, 63.2 mmol) in dry THF at 0 °C, and the resulting mixture was stirred for 1 h at 0 °C. Flash column chromatography [hexane–ethyl acetate (9:1)] of the reaction mixture afforded esters (*E*)-**2** (6.61 g, 68%) and (*Z*)-**2** (680 mg, 7%).

Compound (*E*)-**2**. An oil; IR (film): 1710 cm^{-1} (C=O); ^1H NMR (AL4): δ 1.27 (t, 3H, J=6.9 Hz, CH_3), 1.84 (d, 1H, J=6.6 Hz, H-3′), 1.95 (d, 1H, J=3.0 Hz, H-3′), 2.09–2.17 (m, 1H, H-2′), 3.51, 3.54 (each d, 2H, J=13.5 Hz, CH_2Ph), 4.18 (q, 2H, J=6.9 Hz, OCH_2), 6.05 (d, 1H, J=15.8 Hz, H-2), 6.69 (dd, 1H, J=15.8, 7.9 Hz, H-3), 7.24–7.34 (m, 5H, Ph); ^{13}C NMR (AL4): δ 14.3 (q, CH_3), 36.8 (t, C-3′), 39.3 (d, C-2′), 60.3, 64.3 (2t, O*C*H_2, *C*H_2Ph), 121.8 (d, C-2), 127.0, 127.6, 128.2 (3d, 5C in Ph), 138.3 (s, C in Ph), 147.8 (d, C-3), 165.8 (s, C-1); EI-MS *m*/*z* 231 (M^+, 2%), 186 (9),

158 (98), 140 (36), 112 (47), 96 (19), 91 (100), 83 (27); HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1259.

Compound (*Z*)-**2**. An oil; IR (film): 1705 cm^{-1} (C═O); ^1H NMR (AL4): δ 1.30 (t, 3H, J=7.1 Hz, CH_3), 1.87 (d, 1H, J=6.6 Hz, H-3′), 1.92 (d, 1H, J=3.2 Hz, H-3′), 3.43, 3.65 (each d, 2H, J=13.4 Hz, CH_2Ph), 3.43–3.48 (m, 1H, H-2′), 4.20 (q, 2H, J=7.1 Hz, OCH_2), 5.80 (dd, 1H, J=11.5, 8.5 Hz, H-3), 5.86 (d, 1H, J=11.5 Hz, H-2), 7.24–7.34 (m, 5H, Ph); ^{13}C NMR (AL4): δ 14.4 (q, CH_3), 36.1 (t, C-3′), 37.4 (d, C-2′), 60.7, 64.2 (2t, OCH_2, CH_2Ph), 120.9 (d, C-2), 126.9, 127.8, 128.2 (3d, 5C in Ph), 138.5 (s, C in Ph), 149.7 (d, C-3), 166.2 (s, C-1); EI-MS *m*/*z* 231 (M^+, 3%), 186 (6), 158 (90), 140 (31), 112 (38), 96 (18), 91 (100), 83 (28); HRMS calcd for $C_{14}H_{17}NO_2$: 231.1259. Found: 231.1250.

4.2.3. Ethyl (*E*)-3-(1-phenylaziridin-2-yl)acrylate 3. To a solution of oxalyl chloride (410 mg, 3.2 mmol) in dry CH_2Cl_2 (7.0 mL) was added dropwise a solution of DMSO (440 mg, 5.6 mmol) in dry CH_2Cl_2 (7.0 mL) at −70 °C. After the mixture had been stirred for 20 min at −70 °C, a solution of alcohol **7**[7] (404 mg, 2.8 mmol) in dry CH_2Cl_2 (5.0 mL) was added dropwise, and stirring was continued for 15 min at −70 °C. Triethylamine (1.9 mL, 14 mmol) was added slowly to the reaction mixture, which was stirred for 10 min at −70 °C, warmed to 0 °C and further stirred for 2 h. Water was added to the mixture, and the organic phase was extracted with CH_2Cl_2. The organic extract was washed with brine, dried with $MgSO_4$, and concentrated in vacuo, giving a aldehyde that was used for the next step without further purification. By analogy with the synthesis of **1**, the aldehyde (1.03 g, 7.0 mmol) was treated with NaH (202 mg, 8.4 mmol) and diethyl ethoxycarbonylmethylphosphonate (1.88 g, 8.4 mmol) in dry CH_2Cl_2 at 0 °C, and the resulting mixture was stirred for 10 min at 0 °C. Flash column chromatography [hexane–ethyl acetate (3:1)] of the reaction mixture afforded ester (*E*)-**3** (679 mg, 45%). An oil; IR (film): 1710 cm^{-1} (C═O); ^1H NMR (AL3): δ 1.29 (t, 3H, J=7.2 Hz, CH_3), 2.35 (d, 1H, J=3.3 Hz, H-3′), 2.42 (d, 1H, J=6.3 Hz, H-3′), 2.70–2.77 (m, 1H, H-2′), 4.21 (q, 2H, J=7.2 Hz, OCH_2), 6.19 (d, 1H, J=15.6 Hz, H-2), 6.78 (dd, 1H, J=15.6 Hz, 7.8, H-3), 6.95–7.05, 7.21–7.29 (m, 5H, Ph); ^{13}C NMR (AL4): δ 14.3 (q, CH_3), 35.9 (t, C-3′), 39.6 (d, C-2′), 60.4 (t, OCH_2), 120.3, 122.7, 128.8 (3d, 5C in Ph), 122.5 (d, C-2), 146.7 (d, C-3), 152.9 (s, C in Ph), 165.6 (s, C-1); EI-MS *m*/*z* 217 (M^+, 16%), 172 (6), 144 (100), 112 (13), 104 (13), 91 (6), 84 (14), 77 (20), 51 (5); HRMS calcd for $C_{15}H_{15}NO_2$: 217.1103. Found: 217.1104.

4.2.4. Ethyl (*E*)-3-(1-tritylaziridin-2-yl)acrylate (*E*)-5. By analogy with the synthesis of **1**, aldehyde **8**[8] (4.0 g, 12.8 mmol) was treated with NaH (460 mg, 19 mmol) and diethyl ethoxycarbonylmethylphosphonate (4.3 g, 19 mmol) in dry CH_2Cl_2 at 0 °C, and the resulting mixture was stirred for 10 min at 0 °C. Flash column chromatography [hexane–ethyl acetate (9:1)] of the reaction mixture afforded ester (*E*)-**5** (4.26 g, 87%). Colorless crystals; mp 82–83 °C (hexane–ethyl acetate); IR ($CHCl_3$): 1710 cm^{-1} (C═O); ^1H NMR (AL4): δ 1.29 (t, 3H, J=7.3 Hz, CH_3), 1.48 (d, 1H, J=6.4 Hz, H-3′), 1.80–1.85 (m, 1H, H-2′), 1.92 (d, 1H, J=2.4 Hz, H-3′), 4.20 (q, 2H, J=7.3 Hz, OCH_2), 6.04 (d, 1H, J=15.6 Hz, H-2), 6.94 (dd, 1H, J=15.6, 8.0 Hz, H-3), 7.18–7.45 (m, 9H, Ph), 7.47 (d, 6H, J=1.2 Hz, Ph); ^{13}C NMR (AL4): δ 14.4 (q, CH_3), 30.8 (t, C-3′), 33.2 (d, C-2′), 60.3 (t, OCH_2), 74.4 (s, CPh_3) 121.9 (d, C-2), 127.2, 127.4, 129.0 (3d, 15C in Ph), 143.8 (s, 3C in Ph), 149.0 (d, C-3), 166.0 (s, C-1); EI-MS *m*/*z* 383 (M^+, 0.1%), 257 (4), 243 (100), 228 (8), 215 (4), 180 (3), 165 (52), 154 (2), 115 (2), 91 (3), 77 (4). Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65%. Found: C, 81.30; H, 6.50; N, 3.59%.

4.2.5. Ethyl (*E*)-3-(1-benzoylaziridin-2-yl)acrylate (*E*)-4. To a solution of **5** (897 mg, 2.34 mmol) in $CHCl_3$ (2.3 mL) and MeOH (1.8 mL) was added dropwise trifluoroacetic acid (3.5 mL) at 0 °C. After the mixture had been stirred for 30 min at 0 °C, water was added to the mixture, and the organic phase was extracted with $CHCl_3$. The organic extract was washed with sat. aqueous $NaHCO_3$ solution and brine, dried with Na_2SO_4, and concentrated in vacuo. To a solution of the residue (236 mg) in $CHCl_3$ (3 mL) was added triethylamine (0.47 mL) and then benzoic anhydride (378 mg, 1.67 mmol) at 0 °C. After the mixture had been stirred for 2 h at 0 °C, water was added to the mixture, the organic phase was extracted with $CHCl_3$. The extract was subjected to the same workup as used for the synthesis of **1**. The residue was subjected to flash column chromatography [hexane–ethyl acetate (3:1)] to yield ester (*E*)-**4** (334 mg, 58% from **5**). A colorless oil; IR (film): 1710 cm^{-1} (C═O); ^1H NMR (AL4): δ 1.31 (t, 3H, J=7.2 Hz, CH_3), 2.43 (d, 1H, J=3.2 Hz, H-3′), 2.85 (d, 1H, J=5.6 Hz, H-3′), 3.11–3.17 (m, 1H, H-2′), 4.22 (q, 2H, J=7.2 Hz, OCH_2), 6.21 (d, 1H, J=16.0 Hz, H-2), 6.74 (dd, 1H, J=16.0, 8.0 Hz, H-3) 7.45 (t, 2H, J=7.6 Hz, Ph), 7.54–7.59 (m, 1H, Ph), 7.99 (d, 2H, J=7.6 Hz, Ph); ^{13}C NMR (AL4): δ 14.3 (q, CH_3), 33.6 (t, C-3′), 38.0 (d, C-2′), 60.7 (t, OCH_2), 124.4 (d, C-2), 128.4, 129.0, 132.9 (3d, 5C in Ph), 132.3 (s, C in Ph), 144.0 (d, C-3), 165.3 (s, C-1), 177.9 (s, NC═O); EI-MS *m*/*z* 245 (M^+, 7%), 200 (2), 140 (3), 117 (20), 105 (100), 95 (2), 77 (22), 51 (3); HRMS calcd for $C_{14}H_{15}NO_3$: 245.1052. Found: 245.1053.

4.3. Irradiation of acrylonitrile 1

4.3.1. (2*Z*,2′*RS*,3′*RS*,4′*SR*,2″*SR*)-3-[1-Benzyl-4-(1-benzylaziridin-2-yl)-3-cyanopyrrolidin-2-yl]acrylonitrile 9A and (2*Z*,2′*RS*,3′*RS*,4′*SR*,2″*RS*)-3-[1-Benzyl-4-(1-benzylaziridin-2-yl)-3-cyanopyrrolidin-2-yl]acrylonitrile 9B. A solution of (*Z*)-**1** (733 mg, 3.98 mmol) in acetonitrile (66 mL) was irradiated with a low-pressure mercury lamp in a quartz test tube (conversion 83%) for 6.5 h at rt. After removal of the solvent, flash column chromatography [hexane–ethyl acetate (7:3)] of the residue afforded dimers **9A** (197 mg, 32%) and **9B** (83.8 mg, 14%).[9]

Compound **9A**. Colorless crystals, mp 113–114 °C (hexane/ethyl acetate); IR ($CHCl_3$): 2240, 2230 cm^{-1} (C≡N); ^1H NMR (LA): δ 1.65 (d, 1H, J=6.1 Hz, H-3″), 1.75 (d, 1H, J=3.4 Hz, H-3″), 1.84–1.89 (m, 1H, H-2″), 1.96–2.02 (m, 1H, H-4′), 2.45 (dd, 1H, J=10.1, 7.9 Hz, H-5′), 2.73 (dd, 1H, J=10.1, 4.3 Hz, H-5′), 3.31, 3.50 (each d, 2H, J=12.8 Hz, 1″-CH_2Ph), 3.36 (dd, 1H, J=8.5, 7.0 Hz, H-3′), 3.40, 3.69 (each d, 2H, J=13.4 Hz, 1′-CH_2Ph), 3.72 (dd, 1H, J=9, 7.0 Hz, H-2′), 5.53 (dd, 1H, J=11.0, 0.6 Hz, H-2), 6.59 (dd, 1H, J=11.0, 9.2 Hz, H-3), 7.16–7.33 (m, 10H, Ph); ^{13}C NMR (LA): δ 33.9 (t, C-3″), 37.5 (d, C-3′),

40.5 (d, C-2″), 42.5 (d, C-4′), 56.0 (t, C-5′), 57.1 (t, 1′-*C*H$_2$Ph), 64.5 (t, 1″-*C*H$_2$Ph), 65.0 (d, C-2′), 103.6 (d, C-2), 114.9, 116.9 (2s, C-1, CN), 127.3, 127.4, 128.29, 128.31, 128.4, 128.5 (6d, 10C in Ph), 137.4, 138.6 (2s, 2C in Ph), 151.9 (d, C-3); EI-MS *m/z* 368 (M^+, 0.9%), 277 (4), 261 (12), 210 (23), 158 (8), 120 (27), 91 (100), 65 (5). Anal. Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.57; N, 15.20%. Found: C, 78.17; H, 6.63; N, 15.10%.

Compound **9B**. Colorless crystals, mp 58–60 °C (hexane/ethyl acetate); IR ($CHCl_3$): 2260, 2240 cm^{-1} (C≡N); ^1H NMR (LA): δ 1.48 (d, 1H, *J*=6.1 Hz, H-3″), 1.68 (d, 1H, *J*=3.4 Hz, H-3″), 1.85–1.89 (m, 1H, H-2″), 2.11–2.18 (m, 1H, H-4′), 2.49 (dd, 1H, *J*=10, 9.2 Hz, H-5′), 2.98 (ddd, 1H, *J*=10, 5.2, 4.9 Hz, H-5′), 3.07, 4.03 (each d, 2H, *J*=13.4 Hz, 1″-C*H*$_2$Ph), 3.40, 3.83 (each d, 2H, *J*=13.4 Hz, 1′-C*H*$_2$Ph), 3.46 (dd, 1H, *J*=8, 6.1 Hz, H-3′), 3.75 (dd, 1H, *J*=9.2, 6.1 Hz, H-2′), 5.59 (dd, 1H, *J*=11.0, 0.6 Hz, H-2), 6.65 (dd, 1H, *J*=11.0, 9.2 Hz, H-3), 7.25–7.33 (m, 10H, Ph); ^{13}C NMR (LA): δ 33.4 (t, C-3″), 38.8 (d, C-3′), 40.0 (d, C-2″), 43.1 (d, C-4′), 54.4 (t, C-5′), 57.3 (t, 1′-*C*H$_2$Ph), 64.2 (t, 1″-*C*H$_2$Ph), 65.3 (d, C-2′), 104.0 (d, C-2), 114.8, 117.4 (2s, C-1, CN), 127.1, 127.5, 128.1, 128.38, 128.43, 128.44 (6d, 10C in Ph), 137.5, 138.6 (2s, 2C in Ph), 151.9 (d, C-3); EI-MS *m/z* 368 (M^+, 0.8%), 277 (4), 261 (15), 210 (31), 158 (6), 120 (31), 91 (100), 65 (5); HRMS calcd for $C_{24}H_{24}N_4$: 368.2001. Found: 368.2007.

4.3.2. Triplet sensitization of 1. A solution of (*Z*)-**1** (794 mg, 4.31 mmol) in acetone (80 mL) was irradiated with a high-pressure mercury lamp in a Pyrex test tube (conversion 58%) for 20 h at rt. After removal of the solvent, flash column chromatography [hexane–ethyl acetate (7:3)] of the residue afforded (*E*)-**1** (295 mg, 64%[9]).

4.4. General procedure for the irradiation of acrylonitrile 1 with various alkenes

A 0.060 mol L^{-1} solution of (*E*)- or (*Z*)-**1** in dry acetonitrile with 10 equiv of alkene was irradiated with a low-pressure mercury lamp in a quartz test tube at 0 °C. After removal of the solvent, flash column chromatography afforded the adducts. The results are summarized in Table 1.

4.4.1. (2*E*,2′*RS*,3′*RS*)-3-(1-Benzyl-3-cyanopyrrolidin-2-yl)acrylonitrile (*E*)-10a. An oil; IR ($CHCl_3$): 2240 cm^{-1} (C≡N); ^1H NMR (AL4): δ 2.04–2.20, 2.21–2.30 (each m, 2H, H_2-4′), 2.37–2.43 (m with td character, 1H, *J*=9.5, 7 Hz, H-5′), 3.13 (ddd, 1H, *J*=9.5, 7.0, 2.9 Hz, H-5′), 3.18–3.25 (m, 1H, H-3′), 3.34–3.39 (m, 1H, overlapped with d at δ 3.36, H-2′), 3.36, 3.86 (each d, 2H, *J*=13.6 Hz, 1′-C*H*$_2$Ph), 5.77 (dd, 1H, *J*=16.1, 1.1 Hz, H-2), 6.78 (dd, 1H, *J*=16.1, 7.3 Hz, H-3), 7.24–7.38 (m, 5H, Ph); ^{13}C NMR (AL4): δ 28.5 (t, C-4′), 33.4 (d, C-3′), 51.6 (t, C-5′), 57.5 (t, 1′-*C*H$_2$Ph), 65.5 (d, C-2′), 103.7 (d, C-2), 116.2, 118.8 (2s, C-1, CN), 127.2, 128.17, 128.20 (3d, 5C in Ph), 137.1 (s, C in Ph), 151.1 (d, C-3); EI-MS *m/z* 237 (M^+, 30%), 197 (6), 184 (17), 160 (5), 146 (8), 91 (100), 65 (9); HRMS calcd for $C_{15}H_{15}N_3$: 237.1266. Found: 237.1271.

4.4.2. (2*E*,2′*RS*,3′*SR*)-3-(1-Benzyl-3-cyanopyrrolidin-2-yl)acrylonitrile (*E*)-10b. An oil; IR ($CHCl_3$): 2220 cm^{-1} (C≡N); ^1H NMR (AL4): δ 2.07–2.16, 2.20–2.30 (each m, 2H, H_2-4′), 2.47–2.55 (m with q character, 1H, *J*=9 Hz, H-5′), 2.82 (ddd, 1H, *J*=10.3, 7.7, 5.9 Hz, H-3′), 3.08 (ddd, 1H, *J*=9.5, 8, 2.9 Hz, H-5′), 3.32 (t, 1H, *J*=7.7 Hz, H-2′), 3.37, 3.86 (each d, 2H, *J*=12.8 Hz, 1′-C*H*$_2$Ph), 5.77 (dd, 1H, *J*=16.1, 0.7 Hz, H-2), 6.58 (dd, 1H, *J*=16.1, 7.7 Hz, H-3), 7.23–7.38 (m, 5H, Ph); ^{13}C NMR (AL4): δ 27.8 (t, C-4′), 34.0 (d, C-3′), 52.0 (t, C-5′), 57.9 (t, 1′-*C*H$_2$Ph), 69.6 (d, C-2′), 103.5 (d, C-2), 116.0, 119.8 (2s, C-1, CN), 127.5, 128.3, 128.4 (3d, 5C in Ph), 137.0 (s, C in Ph), 151.9 (d, C-3); EI-MS *m/z* 237 (M^+, 27%), 197 (6), 184 (16), 160 (6), 146 (10), 91 (100), 65 (9); HRMS calcd for $C_{15}H_{15}N_3$: 237.1266. Found: 237.1270.

4.4.3. (2*Z*,2′*RS*,3′*RS*)-3-(1-Benzyl-3-cyanopyrrolidin-2-yl)acrylonitrile (*Z*)-10a. Colorless crystals; mp 105–106 °C (hexane–ethyl acetate); IR ($CHCl_3$): 2230, 2210 cm^{-1} (C≡N); ^1H NMR (LA): δ 2.16–2.24, 2.25–2.30 (each m, 2H, H_2-4′), 2.31–2.36, 3.12–3.16 (each m, 2H, H_2-5′), 3.29 (ddd, 1H, *J*=8.8, 7.3, 5.5 Hz, H-3′), 3.43, 3.83 (each d, 2H, *J*=13.4 Hz, 1′-C*H*$_2$Ph), 3.68 (dd, 1H, *J*=9.2, 7.3 Hz, H-2′), 5.59 (dd, 1H, *J*=11.0, 0.6 Hz, H-2), 6.61 (dd, 1H, *J*=11.0, 9.2 Hz, H-3), 7.24–7.36 (5H, m, Ph); ^{13}C NMR (LA): δ 28.5 (t, C-4′), 33.3 (d, C-3′), 51.8 (t, C-5′), 57.4 (t, 1′-*C*H$_2$Ph), 64.9 (d, C-2′), 103.8 (d, C-2), 114.9, 119.3 (2s, C-1, CN), 127.5, 128.4, 128.6 (3d, 5C in Ph), 137.5 (s, C in Ph), 151.9 (d, C-3); EI-MS *m/z* 237 (M^+, 35%), 197 (5), 184 (20), 160 (7), 146 (10), 91 (100), 65 (9). Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71%. Found: C, 75.71; H, 6.48; N, 17.61%.

4.4.4. (2*Z*,2′*RS*,3′*SR*)-3-(1-Benzyl-3-cyanopyrrolidin-2-yl)acrylonitrile (*Z*)-10b. A colorless oil; IR ($CHCl_3$): 2260, 2240 cm^{-1} (C≡N); ^1H NMR (LA): δ 2.12–2.19, 2.26–2.35 (each m, 2H, H_2-4′), 2.48–2.55 (m with q character, 1H, *J*=9 Hz, H-5′), 2.85 (ddd, 1H, *J*=10.1, 8.9, 6.7 Hz, H-3′), 3.05–3.10 (m with td character, 1H, *J*=9, 3 Hz, H-5′), 3.44, 3.83 (each d, 2H, *J*=12.8 Hz, 1′-C*H*$_2$Ph), 3.75 (dd, 1H, *J*=9.5, 8.9 Hz, H-2′), 5.56 (d, 1H, *J*=11.0 Hz, H-2), 6.28 (dd, 1H, *J*=11.0, 9.5 Hz, H-3), 7.25–7.33 (m, 5H, Ph); ^{13}C NMR (LA): δ 27.8 (t, C-4′), 33.6 (d, C-3′), 52.1 (t, C-5′), 57.8 (t, 1′-*C*H$_2$Ph), 68.3 (d, C-2′), 104.2 (d, C-2), 114.7, 119.5 (2s, C-1, CN), 127.6, 128.4, 128.7 (3d, 5C in Ph), 137.5 (s, C in Ph), 151.2 (d, C-3); EI-MS *m/z* 237 (M^+, 35%), 197 (7), 184 (17), 160 (8), 146 (14), 91 (100), 65 (10); HRMS calcd for $C_{15}H_{15}N_3$: 237.1266. Found: 237.1270.

4.4.5. Methyl (2*RS*,3*RS*)-1-benzyl-2-[(*E*)-2-cyanovinyl]-pyrrolidine-3-carboxylate (*E*)-11a. An oil; IR ($CHCl_3$): 2210 (C≡N), 1725 cm^{-1} (C=O); ^1H NMR (AL4): δ 1.95–2.14, 2.15–2.26 (each m, 2H, H_2-4), 2.40–2.47 (m with td character, 1H, *J*=9.5, 6 Hz, H-5), 3.04–3.10 (m with ddd character, 1H, *J*=9, 7.5, 2 Hz, H-5), 3.20–3.28 (m with q character, 1H, *J*=9 Hz, H-3), 3.41, 3.80 (each d, 2H, *J*=13.2 Hz, 1-C*H*$_2$Ph), 3.51 (ddd, 1H, *J*=9.2, 7.0, 1.1 Hz, H-2), 3.68 (s, 3H, OCH_3), 5.53 (dd, 1H, *J*=16.1, 1.1 Hz, H-2′), 6.78 (dd, 1H, *J*=16.1, 7.0 Hz, H-1′), 7.24–7.35 (m, 5H, Ph); ^{13}C NMR (AL3): δ 26.7 (t, C-4), 48.1 (d, C-3), 52.0 (q, OCH_3), 52.4 (t, C-5), 58.1 (t, 1-*C*H$_2$Ph), 66.0 (d, C-2), 101.6 (d, C-2′), 116.9 (s, CN), 127.2, 128.3, 128.4 (3d, 5C in Ph), 137.9 (s, C in Ph), 152.8 (d, C-1′), 171.8 (s, CO_2); EI-MS *m/z* 270 (M^+, 18%), 230 (15), 211 (22), 179 (51), 91

(100), 65 (11); HRMS calcd for $C_{16}H_{18}N_2O_2$: 270.1368. Found: 270.1371.

4.4.6. Methyl (2*RS*,3*SR*)-1-benzyl-2-[(*E*)-2-cyanovinyl]-pyrrolidine-3-carboxylate (*E*)-11b. An oil; IR ($CHCl_3$): 2210 (C≡N), 1725 cm^{-1} (C=O); ^1H NMR (AL4): δ 2.01–2.14 (m, 2H, H_2-4), 2.34–2.42 (m with q character, 1H, J=9 Hz, H-5), 2.81 (ddd, 1H, J=9.9, 7.7, 5.5 Hz, H-3), 2.98–3.03 (m with ddd character, 1H, J=9.5, 7.3, 2.9 Hz, H-5), 3.30, 3.85 (each d, 2H, J=12.8 Hz, 1-CH_2Ph), 3.34–3.39 (m with t character, 1H, J=7 Hz, 2-H), 3.72 (s, 3H, OCH_3), 5.69 (dd, 1H, J=16.3, 1.1 Hz, H-2′), 6.70 (dd, 1H, J=16.3, 7.2 Hz, H-1′), 7.24–7.35 (m, 5H, Ph); ^{13}C NMR (AL4): δ 27.2 (t, C-4), 49.2 (d, C-3), 52.2 (q, OCH_3), 52.7 (t, C-5), 58.5 (t, 1-CH_2Ph), 68.6 (d, C-2), 101.3 (d, C-2′), 116.9 (s, CN), 127.2, 128.3, 128.5 (3d, 5C in Ph), 138.1 (s, C in Ph), 155.0 (d, C-1′), 173.5 (s, CO_2); EI-MS *m*/*z* 270 (M^+, 17%), 230 (27), 211 (26), 179 (75), 91 (100), 65 (11); HRMS calcd for $C_{16}H_{18}N_2O_2$: 270.1368. Found: 270.1364.

4.4.7. Methyl (2*RS*,3*RS*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]-pyrrolidine-3-carboxylate (*Z*)-11a. An oil; bp 160 °C at 0.40 mm Hg; IR ($CHCl_3$): 2220 (C≡N) and 1730 cm^{-1} (C=O); ^1H NMR (AL4): δ 2.01–2.09, 2.23–2.89 (each m, 2H, H_2-4), 2.45 (dt, 1H, J=9.5, 7.0 Hz, H-5), 3.04–3.09 (m, 1H, H-5), 3.29–3.37 (m with q character, 1H, J=9 Hz, H-3), 3.54, 3.76 (each d, 2H, J=13.2 Hz, 1-CH_2Ph), 3.66 (s, 3H, OCH_3), 3.86–3.91 (m with dd character, 1H, J=9.5, 9.2 Hz, H-2), 5.35 (dd, 1H, J=11.0, 0.7 Hz, H-2′), 6.42 (dd, 1H, J=11.0, 9.5 Hz, H-1′), 7.29–7.31 (5H, m, Ph); ^{13}C NMR (AL3): δ 27.1 (t, C-4), 47.7 (d, C-3), 51.8 (q, OCH_3), 52.4 (t, C-5), 57.7 (t, 1-CH_2Ph), 65.2 (d, C-2), 101.0 (d, C-2′), 115.3 (s, CN), 127.2, 128.2, 128.7 (3d, 5C in Ph), 138.1 (s, C in Ph), 153.3 (d, C-1′), 172.6 (s, CO_2); EI-MS *m*/*z* 270 (M^+, 33%), 230 (16), 211 (24), 184 (15), 179 (62), 91 (100), 65 (8). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36%. Found: C, 70.94; H, 6.70; N, 10.30%.

4.4.8. Methyl (2*RS*,3*SR*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]-pyrrolidine-3-carboxylate (*Z*)-11b. Colorless crystals; mp 45–48 °C; IR ($CHCl_3$): 2220 (C≡N), 1730 cm^{-1} (C=O); ^1H NMR (AL4): δ 2.05–2.23 (m, 2H, H_2-4), 2.37–2.45 (m, 1H, H-5), 2.83 (ddd, 1H, J=10.6, 8.4, 5.5 Hz, H-3), 3.00–3.05 (m with ddd character, 1H, J=9.5, 8.1, 2 Hz, H-5), 3.40, 3.80 (each d, 2H, J=13.2 Hz, 1-CH_2Ph), 3.61–3.67 (m with t character, 1H, J=9 Hz, H-2), 3.75 (s, 3H, OCH_3), 5.42 (dd, 1H, J=11.0, 0.7 Hz, H-2′), 6.38 (dd, 1H, J=11.0, 9.2 Hz, H-1′), 7.25–7.32 (m, 5H, Ph); ^{13}C NMR (AL4): δ 26.8 (t, C-4), 49.0 (d, C-3), 52.3 (q, OCH_3), 53.1 (t, C-5), 58.4 (t, 1-CH_2Ph), 68.3 (d, C-2), 101.8 (d, C-2′), 115.2 (s, CN), 127.1, 128.1, 128.6 (3d, 5C in Ph), 138.2 (s, C in Ph), 154.3 (d, C-1′), 173.0 (s, CO_2); EI-MS *m*/*z* 270 (M^+, 23%), 230 (34), 211 (29), 179 (100), 91 (82), 65 (9); HRMS calcd for $C_{16}H_{28}N_2O_2$: 270.1368. Found: 270.1367.

4.4.9. *tert*-Butyl (2*RS*,3*RS*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]pyrrolidine-3-carboxylate 12a. Colorless crystals; mp 54–55 °C; IR ($CHCl_3$): 2230 (C≡N), 1725 cm^{-1} (C=O); ^1H NMR (LA): δ 1.42 (s, 9H, CMe_3), 1.96–2.03, 2.16–2.26 (each m, 2H, H_2-4), 2.46 (dt, 1H, J=9.2, 7.0 Hz, H-5), 3.02 (ddd, 1H, J=9.2, 8, 2 Hz, H-5), 3.18–3.24 (m with q character, 1H, J=9 Hz, H-3), 3.55, 3.75 (each d, 2H, J=13.4 Hz, 1-CH_2Ph), 3.88–3.92 (m with t character, 1H, J=9.5 Hz, 2-H), 5.34 (dd, 1H, J=11.0, 0.9 Hz, H-2′), 6.45 (dd, 1H, J=11.0, 10 Hz, H-1′), 7.22–7.31 (m, 5H, Ph); ^{13}C NMR (LA): δ 27.0 (t, C-4), 28.1 (q, CMe_3), 48.5 (d, C-3), 52.4 (t, C-5), 57.7 (t, 1-CH_2Ph), 65.2 (d, C-2), 81.1 (s, CMe_3), 100.7 (d, C-2′), 115.5 (s, CN), 127.2, 128.3, 128.7 (3d, 5C in Ph), 138.4 (s, C in Ph), 153.7 (d, C-1′), 171.2 (s, CO_2); EI-MS *m*/*z* 312 (M^+, 11%), 255 (21), 239 (17), 221 (19), 211 (11), 184 (9), 165 (37), 133 (14), 91 (100), 41 (9); HRMS calcd for $C_{19}H_{24}N_2O_2$: 312.1838. Found: 312.1834.

4.4.10. *tert*-Butyl (2*RS*,3*SR*)-1-benzyl-2-[(*Z*)-2-cyanovinyl]pyrrolidine-3-carboxylate 12b. Colorless needles; mp 78–79 °C (hexane/ethyl acetate); IR ($CHCl_3$): 2230 (C≡N), 1725 cm^{-1} (C=O); ^1H NMR (LA): δ 1.48 (s, 9H, CMe_3), 1.99–2.08, 2.12–2.18 (each m, 2H, H_2-4), 2.37–2.43 (m with q character, 1H, J=9 Hz, H-5), 2.74 (ddd, 1H, J=10.3, 8, 5 Hz, H-3), 2.97–3.02 (m with ddd character, 1H, J=9, 8, 2 Hz, H-5), 3.38, 3.82 (each d, 2H, J=13.1 Hz, 1-CH_2Ph), 3.57–3.61 (m with dd character, 1H, J=9, 8 Hz, H-2), 5.40 (dd, 1H, J=11.0, 0.6 Hz, H-2′), 6.37 (dd, 1H, J=11.0, 9.5 Hz, H-1′), 7.21–7.31 (m, 5H, Ph); ^{13}C NMR (LA): δ 26.6 (t, C-4), 27.9 (q, CMe_3), 50.2 (d, C-3), 53.2 (t, C-5), 58.3 (t, 1-CH_2Ph), 68.3 (d, C-2), 81.4 (s, CMe_3), 101.6 (d, C-2′), 115.6 (s, CN), 127.2, 128.2, 128.7 (3d, 5C in Ph), 138.5 (s, C in Ph), 154.9 (d, C-1′), 172.0 (s, CO_2); EI-MS *m*/*z* 312 (M^+, 4%), 255 (39), 239 (15), 216 (10), 165 (48), 91 (100), 41 (6). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97%. Found: C, 73.14; H, 7.81; N, 8.92%.

4.4.11. (2*Z*,1′*RS*,2′*RS*,5′*SR*)-3-(3-Benzyl-8-oxo-3-azabicyclo[3.3.0]oct-2-yl)acrylonitrile 13. Colorless crystals; mp 91–92 °C (hexane/ethyl acetate); IR ($CHCl_3$): 2220 (C≡N), 1730 cm^{-1} (C=O); ^1H NMR (AL4): δ 1.80–1.89, 2.03–2.14 (each m, 2H, H_2-6′), 2.21–2.30 (m with dddd character, 1H, J=18, 8, 5, 1 Hz, H-7′), 2.35–2.46 (m, 1H, H-7′), 2.54 (dd, 1H, J=9.8, 8 Hz, H-4′), 2.78–2.83 (m with t character, 1H, J=8 Hz, H-1′), 2.89 (dd, 1H, J=9.8, 1.4 Hz, H-4′), 2.90–2.98 (m, 1H, H-5′), 3.17, 3.79 (each d, 2H, J=13.8 Hz, 3′-CH_2Ph), 3.68 (dd, 1H, J=9.8, 7.3 Hz, H-2′), 5.51 (dd, 1H, J=11.0, 0.7 Hz, H-2), 6.46 (dd, 1H, J=11.0, 9.8 Hz, H-3), 7.22–7.32 (5H, m, Ph); ^{13}C NMR (AL3): δ 28.3 (t, C-6′), 38.0 (d, C-5′), 39.4 (t, C-7′), 55.2 (d, C-1′), 57.9, 61.0 (2t, C-4′, 1-CH_2Ph), 68.3 (d, C-2′), 102.1 (d, C-2), 115.3 (s, C-1), 127.0, 128.1, 128.2 (3d, 5C in Ph), 138.2 (s, C in Ph), 153.0 (d, C-3), 217.9 (s, C-8′); EI-MS *m*/*z* 266 (M^+, 33%), 226 (5), 210 (20), 184 (13), 175 (16), 91 (100), 65 (9). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52%. Found: C, 76.71; H, 6.86; N, 10.46%.

4.4.12. (2*Z*,1′*RS*,2′*RS*,5′*SR*)-3-(3-Benzyl-6,8-dioxo-7-phenyl-3,7-diazabicyclo[3.3.0]oct-2-yl)acrylonitrile 14. Colorless crystals; mp 49–51 °C; IR ($CHCl_3$): 2230 (C≡N), 1720 cm^{-1} (C=O); ^1H NMR (LA): δ 2.56 (dd, 1H, J=10.1, 7.9 Hz, H-4′), 3.33, 3.83 (each d, 2H, J=13.4 Hz, 3′-CH_2Ph), 3.36 (td, 1H, J=7.9, 0.6 Hz, H-5′), 3.47 (d, 1H, J=10.1 Hz, H-4′), 3.54 (t, 1H, J=7.9 Hz, H-1′), 3.79 (dd, 1H, J=9.8, 7.9 Hz, H-2′), 5.59 (dd, 1H, J=11.0, 0.6 Hz, H-2), 6.45 (dd, 1H, J=11.0, 9.8 Hz, H-3), 7.20–7.23, 7.24–7.32, 7.39–7.43, 7.47–7.51 (4m, 10H, Ph); ^{13}C NMR (LA): δ 43.4 (d, C-5′), 48.8 (d, C-1′), 55.9 (t, C-4′), 56.8 (t, 3′-CH_2Ph), 66.4 (d, C-2′), 103.5 (d, C-2), 115.2 (s, C-1), 126.3, 127.6, 128.4, 128.5, 128.8, 129.2 (6d, 10C in Ph), 131.7, 136.8 (2s, 2C in Ph), 151.1 (d, C-3),

174.4, 177.4 (2s, C-6′, C-8′); EI-MS *m/z* 357 (M^+, 55%), 317 (21), 266 (21), 184 (19), 119 (8), 91 (100), 65 (8); HRMS calcd for $C_{22}H_{19}N_3O_2$: 357.1477. Found: 357.1479.

4.4.13. Methyl (*Z*)-1-benzyl-2-(2-cyanovinyl)-3-pyrroline-3-carboxylate 15. An oil; bp 160 °C at 0.20 mm Hg; IR ($CHCl_3$): 2230 (C≡N), 1720 cm^{-1} (C=O); ^1H NMR (LA): δ 3.50 (ddd, 1H, *J*=17, 5, 2 Hz, H-5), 3.74 (s, 3H, OCH_3), 3.74, 3.97 (each d, 2H, *J*=13.4 Hz, 1-CH_2Ph), 3.87 (ddd, 1H, *J*=17, 5.5, 2 Hz, H-5), 4.82–4.87 (m, 1H, 2-H), 5.39 (dd, 1H, *J*=10.7, 0.6 Hz, H-2′), 6.37 (dd, 1H, *J*=10.7, 9.2 Hz, H-1′), 6.89 (q, 1H, *J*=2.1 Hz, H-4), 7.23–7.33 (m, 5H, Ph); ^{13}C NMR (LA): δ 51.7 (q, OCH_3), 57.5 (t, 1-*C*H_2Ph), 59.0 (t, C-5), 68.8 (d, C-2), 100.7 (d, C-2′), 115.7 (s, CN), 127.3, 128.4, 128.6 (3d, 5C in Ph), 133.5 (s, C-3), 138.3 (s, C in Ph), 141.8 (d, C-4), 153.2 (d, C-1′), 163.0 (s, CO_2); EI-MS *m/z* 268 (M^+, 8%), 216 (17), 177 (15), 91 (100), 65 (14); HRMS calcd for $C_{16}H_{16}N_2O_2$: 268.1212. Found: 268.1218.

4.5. Thermal reactions of nitrile 1 with alkenes

By analogy with the photoreactions of (*Z*)-**1**, a 0.060 mol L^{-1} solution of (*Z*)-**1** in xylene with 10 equiv of *tert*-butyl acrylate or *N*-phenylmaleimide was heated under reflux. Flash column chromatography afforded the adducts. The results are summarized in Table 1.

4.6. Irradiation of ethyl acrylate 2

4.6.1. Ethyl (2*E*,2′*RS*,3′*SR*,4′*SR*)-3-[1-benzyl-4-(1-benzylaziridin-2-yl)-3-ethoxycarbonylpyrrolidin-2-yl]acrylate 16A and ethyl (2*E*,2′*RS*,3′*SR*,4′*SR*)-3-[1-benzyl-4-(1-benzylaziridin-2-yl)-3-ethoxycarbonylpyrrolidin-2-yl]acrylate 16B. By analogy with the photolysis of **1**, a solution of (*E*)-**2** (51.8 mg, 0.223 mmol) in acetonitrile was irradiated (conversion 98%) for 2 h at rt. Preparative TLC [hexane–ethyl acetate–diethylamine (9:1:0.5)] of the reaction mixture afforded dimers **16A** (9.8 mg, 19%[9]) and **16B** (3.3 mg, 7%[9]).

Compound **16A**. An oil; IR ($CHCl_3$): 1720 cm^{-1} (C=O); ^1H NMR (LA): δ 1.22, 1.31 (2t, 6H, *J*=7.0 Hz, 2CH_3), 1.36 (d, 1H, *J*=6.1 Hz, H-3″), 1.63–1.67 (m, 2H, H-2″, H-3″), 2.16–2.22 (m, 1H, H-4′), 2.38 (dd, 1H, *J*=9.7, 8 Hz, H-5′), 2.49 (dd, 1H, *J*=8.2, 5.2 Hz, H-3′), 2.77 (dd, 1H, *J*=9.7, 2.4 Hz, H-5′), 3.14, 3.88 (each d, 2H, *J*=13.1 Hz, 1″-CH_2Ph), 3.23, 3.56 (each d, 2H, *J*=12.8 Hz, 1′-CH_2Ph), 3.25 (m, 1H, H-2′), 4.21, 4.22 (2q, 4H, *J*=7.0 Hz, 2OCH_2), 6.00 (dd, 1H, *J*=15.6, 0.6 Hz, H-2), 6.80 (dd, 1H, *J*=15.6, 7.9 Hz, H-3), 7.22–7.33 (m, 10H, 2Ph); ^{13}C NMR (LA): δ 14.2, 14.3 (2q, 2CH_3), 33.2 (t, C-3″), 42.8 (d, C-2″), 43.5 (d, C-4′), 54.2 (d, C-3′), 55.6 (t, C-5′), 58.0 (t, 1″-*C*H_2Ph), 60.4, 60.8 (2t, 2OCH_2), 64.7 (t, 1′-*C*H_2Ph), 69.0 (d, C-2′), 123.2 (d, C-2), 127.0, 127.1, 128.26, 128.34, 128.5 (5d, 10C in Ph), 138.7, 139.2 (2s, 2C in Ph), 148.2 (d, C-3), 166.2, 173.3 (2s, C-1, 3′-CO_2); EI-MS *m/z* 462 (M^+, 2%), 417 (6), 342 (41), 282 (17), 233 (17), 120 (7), 91 (100); HRMS calcd for $C_{28}H_{34}N_2O_4$: 462.2518. Found: 462.2527.

Compound **16B**. An oil; IR ($CHCl_3$): 1730 cm^{-1} (C=O); ^1H NMR (LA): δ 1.22, 1.30 (2t, 6H, *J*=7.0 Hz, 2CH_3), 1.44 (d, 1H, *J*=6.4 Hz, H-3″), 1.68–1.73 (m, 2H, H-2″, H-3″), 1.99–2.05 (m, 1H, H-4′), 2.40 (dd, 1H, *J*=9.8, 7.9 Hz, H-5′), 2.62 (dd, 1H, *J*=8.5, 5.8 Hz, H-3′), 2.73 (dd, 1H, *J*=9.8, 2.7 Hz, H-5′), 3.16, 3.86 (each d, 2H, *J*=13.4 Hz, 1″-CH_2Ph), 3.19, 3.50 (each d, 2H, *J*=12.8 Hz, 1′-CH_2Ph), 3.34 (m with t character, 1H, *J*=8 Hz, H-2′), 4.11, 4.20 (2q, 4H, *J*=7.0 Hz, 2OCH_2), 6.05 (dd, 1H, *J*=15.6, 0.6 Hz, H-2), 6.87 (dd, 1H, *J*=15.6, 7.9 Hz, H-3), 7.15–7.31 (m, 10H, 2Ph); ^{13}C NMR (LA): δ 14.17, 14.23 (2q, 2CH_3), 33.0 (t, C-3″), 43.5 (d, C-2″), 44.5 (d, C-4′), 53.5 (d, C-3′), 57.0 (t, C-5′), 57.8 (t, 1″-*C*H_2Ph), 60.4, 60.8 (2t, 2OCH_2), 64.7 (t, 1′-*C*H_2Ph), 68.5 (d, C-2′), 123.5 (d, C-2), 127.0, 127.1, 128.2, 128.3, 128.5 (5d, 10C in Ph), 138.6, 138.9 (2s, 2C in Ph), 148.2 (d, C-3), 166.2, 172.9 (2s, C-1, 3′-CO_2); EI-MS *m/z* 462 (M^+, 2%), 417 (12), 342 (100), 282 (20), 233 (23), 120 (6), 91 (77); HRMS calcd for $C_{28}H_{34}N_2O_4$: 462.2518. Found: 462.2516.

4.6.2. Triplet sensitization of 2. By analogy with the photolysis of **1**, a solution of (*E*)-**2** (424 mg, 1.83 mmol) in acetone (31 mL) was irradiated with a high-pressure mercury lamp in a Pyrex test tube (conversion 84%) for 11.5 h at rt. After removal of the solvent, flash column chromatography [hexane–ethyl acetate (3:2)] of the residue afforded (*Z*)-**2** (67 mg, 25%[9]).

4.6.3. Ethyl (2*E*,2′*RS*,3′*RS*)-3-(1-benzyl-3-cyanopyrrolidin-2-yl)acrylate 17a and ethyl (2*E*,2′*RS*,3′*SR*)-3-(1-benzyl-3-cyanopyrrolidin-2-yl)acrylate 17b. By analogy with the photoreactions of **1**, a 0.060 mol L^{-1} solution of (*E*)-**2** in dry acetonitrile with 10 equiv of acrylonitrile was irradiated. Preparative TLC [hexane–ethyl acetate (3:1)] afforded the adducts. The results are summarized in Table 2.

Compound **17a**. An oil; bp 180 °C at 0.20 mm Hg (decomp.); IR ($CHCl_3$): 2250 (C≡N), 1715 cm^{-1} (C=O); ^1H NMR (LA): δ 1.31 (t, 3H, *J*=7.0 Hz, CH_3), 2.13–2.27 (m, 2H, H_2-4′), 2.28–2.34 (m with dt character, 1H, *J*=9, 8 Hz, H-5′), 3.07–3.12 (m with ddd character, 1H, *J*=9, 8, 3 Hz, H-5′), 3.16–3.21 (m with ddd character, 1H, *J*=8.5, 7, 6.1 Hz, H-3′), 3.27, 3.92 (each d, 2H, *J*=13.1 Hz, 1′-CH_2Ph), 3.27–3.31 (m, 1H, H-2′), 4.22 (q, 2H, *J*=7.0 Hz, OCH_2), 6.14 (dd, 1H, *J*=15.6, 0.9 Hz, H-2), 6.98 (dd, 1H, *J*=15.6, 8.2 Hz, H-3), 7.22–7.33 (m, 5H, Ph); ^{13}C NMR (LA): δ 14.2 (q, CH_3), 28.4 (t, C-4′), 33.7 (d, C-3′), 51.3 (t, C-5′), 57.1 (t, 1′-*C*H_2Ph), 60.7 (t, OCH_2), 65.8 (d, C-2′), 119.6 (s, CN), 126.2 (d, C-2), 127.3, 128.3, 128.5 (3d, 5C in Ph), 137.9 (s, C in Ph), 144.0 (d, C-3), 165.3 (s, C-1); EI-MS *m/z* 284 (M^+, 10%), 255 (11), 239 (10), 211 (35), 193 (68), 158 (38), 140 (14), 112 (19), 91 (100); HRMS calcd for $C_{17}H_{20}N_2O_2$: 284.1525. Found: 284.1529.

Compound **17b**. An oil; IR ($CHCl_3$): 2240 (C≡N), 1715 cm^{-1} (C=O); ^1H NMR (LA): δ 1.31 (t, 3H, *J*=7.0 Hz, CH_3), 2.05–2.12, 2.26–2.30 (2m, 2H, H_2-4′), 2.38–2.44 (m with q character, 1H, *J*=9 Hz, H-5′), 2.84 (ddd, 1H, *J*=10.7, 8.2, 6.4 Hz, H-3′), 3.03 (ddd, 1H, *J*=9.5, 8.2, 2.7 Hz, H-5′), 3.25, 3.93 (each d, 2H, *J*=12.8 Hz, 1′-CH_2Ph), 3.27 (t, 1H, *J*=8.2 Hz, 2′-H), 4.22 (q, 2H, *J*=7.0 Hz, OCH_2), 6.20 (dd, 1H, *J*=15.9, 0.6 Hz, H-2), 6.79 (dd, 1H, *J*=15.9, 8.2 Hz, H-3), 7.23–7.33 (m, 5H, Ph); ^{13}C NMR (LA): δ 14.2 (q, CH_3), 27.7 (t, C-4′), 33.8 (d, C-3′), 51.8 (t, C-5′), 57.6 (t, 1′-*C*H_2Ph), 60.7 (t, OCH_2), 69.5 (d, C-2′), 120.5 (s, CN), 125.6 (d, C-2), 127.4, 128.4, 128.6 (3d,

5C in Ph), 137.7 (s, C in Ph), 145.1 (d, C-3), 165.5 (s, C-1); EI-MS *m/z* 284 (M^+, 5%), 255 (11), 239 (15), 211 (25), 193 (67), 158 (27), 140 (12), 112 (15), 91 (100); HRMS calcd for $C_{17}H_{20}N_2O_2$: 284.1525. Found: 284.1523.

4.7. Reaction of *N*-phenylaziridine (*E*)-3

4.7.1. Ethyl (2*E*,2′*RS*,3′*RS*)-3-(3-cyano-1-phenylpyrrolidin-2-yl)acrylate 18a and ethyl (2*E*,2′*RS*,3′*SR*)-3-(3-cyano-1-phenylpyrrolidin-2-yl)acrylate 18b. By analogy with the photoreactions of (*Z*)-**1**, a 0.060 mol L^{-1} solution of (*E*)-**3** in dry acetonitrile with 10 equiv of acrylonitrile was irradiated. Preparative TLC [SiO_2; hexane–ethyl acetate (3:1)] afforded the adducts. The results are summarized in Table 2.

Compound **18a**. An oil; IR ($CHCl_3$): 2240 (C≡N), 1720 cm^{-1} (C=O); ^1H NMR (AL3): δ 1.28 (t, 3H, J=7.2 Hz, CH_3), 2.26–2.41, 2.44–2.53 (2m, 2H, H_2-4′), 3.28 (ddd, 1H, J=12.0, 7.8, 6.3 Hz, H-3′), 3.34–3.43 (m with td character, 1H, J=9, 7 Hz, H-5′), 3.60–3.67 (m with td character, 1H, J=9, 2 Hz, H-5′), 4.19 (q, 2H, J=7.2 Hz, OCH_2), 4.55–4.60 (m, 1H, H-2′), 6.00 (dd, 1H, J=15.6, 1.5 Hz, H-2), 6.51–6.54 (m with d character, 2H, J=7.9 Hz, H-2″, H-6″), 6.75–6.80 (m with t character, 1H, J=7.3 Hz, H-4″), 7.04 (dd, 1H, J=15.6, 4.8 Hz, H-3), 7.21–7.26 (m, 2H, H-3″, H-5″); ^{13}C NMR (AL4): δ 14.3 (q, CH_3), 27.9 (t, C-4′), 33.1 (d, C-3′), 47.0 (t, C-5′), 59.9 (d, C-2′), 60.8 (t, OCH_2), 112.1 (d, C-2″, C-6″), 117.5 (s, CN), 117.7 (d, C-4″), 125.3 (d, C-2), 129.2 (d, C-3″, C-5″), 142.4 (d, C-3), 145.4 (s, C-1″), 165.1 (s, C-1); EI-MS *m/z* 270 (M^+, 68%), 241 (70), 225 (34), 197 (50), 171 (18), 144 (100), 112 (16), 104 (11), 84 (13), 77 (24); HRMS calcd for $C_{17}H_{20}N_2O_2$: 270.1368. Found: 270.1371.

Compound **18b**. An oil; IR ($CHCl_3$): 2240 (C≡N), 1720 cm^{-1} (C=O); ^1H NMR (AL3): δ 1.27 (t, 3H, J=7.2 Hz, CH_3), 2.32–2.39 (m, 2H, H_2-4′), 3.06–3.11 (m, 1H, H-3′), 3.57–3.72 (m, 2H, H_2-5′), 4.18 (q, 2H, J=7.2 Hz, OCH_2), 4.58–4.62 (m, 1H, H-2′), 5.99 (dd, 1H, J=15.3, 1.7 Hz, H-2), 6.54–6.58 (m with d character, 2H, J=9 Hz, H-2″, H-6″), 6.76–6.82 (m with t character, 1H, J=7.3 Hz, H-4″), 6.86 (dd, 1H, J=15.3, 4.8 Hz, H-3), 7.20–7.28 (m, 2H, H-3″, H-5″); ^{13}C NMR (AL4): δ 14.3 (q, CH_3), 27.8 (t, C-4′), 34.7 (d, C-3′), 47.2 (t, C-5′), 60.9 (t, OCH_2), 63.3 (d, C-2′), 112.6 (d, C-2″, C-6″), 117.8 (d, C-4″), 119.7 (s, CN), 124.0 (d, C-2), 129.2 (d, C-3″, C-5″), 144.3 (d, C-3), 145.6 (s, C-1″), 165.4 (s, C-1); EI-MS *m/z* 270 (M^+, 67%), 241 (72), 225 (32), 197 (53), 171 (24), 144 (100), 112 (15), 104 (12), 84 (13), 77 (28); HRMS calcd for $C_{17}H_{20}N_2O_2$: 270.1368. Found: 270.1365.

4.7.2. Ethyl 2,5-dihydro-1*H*-1-benzazepine-5-carboxylate 19. A solution of (*E*)-**3** (100 mg, 0.46 mmol) in xylene (7.6 mL) with 10 equiv of 3,4-dihydro-2*H*-pyrane (386 mg, 4.6 mmol) was heated under reflux for 1.5 h (conversion 98%). After removal of the solvent, preparative TLC [hexane–ethyl acetate (3:1)] of the residue afforded benzazepine **19** (41.2 mg, 42%[9]). An oil; IR ($CHCl_3$): 3340 (N–H), 1720 cm^{-1} (C=O); ^1H NMR (AL4): δ 1.22 (t, 3H, J=7.2 Hz, CH_3), 3.30 (br s, 1H, NH), 3.66–3.73 (m with ddd character, 1H, J=17.2, 4.8, 2.8 Hz, H-2), 3.75–3.82 (m with d character, 1H, J=17.2 Hz, H-2), 4.19 (q, 2H, J=7.2 Hz, OCH_2), 4.42–4.44 (m with d character, 1H, J=7.2 Hz, H-5), 5.61–5.66 (m, 1H, H-3), 5.97–6.04 (m, 1H, H-4), 6.87 (dd, 1H, J=7.6, 1 Hz, H-9), 6.96 (td, 1H, J=7.6, 1.2 Hz, H-7), 7.04 (dd, 1H, J=7.6, 1.6 Hz, H-6), 7.16 (td, 2H, J=7.6, 1.6 Hz, H-8); ^{13}C NMR (AL4): δ 14.3 (q, CH_3), 48.4 (t, C-2), 49.2 (d, C-5), 61.0 (t, OCH_2), 121.8 (d, C-9), 122.5 (d, C-7), 124.3 (d, C-4), 128.1 (d, C-8), 128.6 (d, C-6), 129.1 (d, C-3), 134.3 (s, C-5a), 147.9 (s, C-9a), 172.5 (s, 5-CO); EI-MS *m/z* 217 (M^+, 28%), 188 (3), 172 (5), 144 (100), 127 (4), 115 (7), 72 (2); HRMS calcd for $C_{13}H_{15}NO_2$: 217.1103. Found: 217.1099.

4.8. Reaction of *N*-benzoylaziridine (*E*)-4

4.8.1. Ethyl (2*E*,4*E*)-5-benzamido-2,4-pentadienoate 20. By analogy with the photoreactions of **1**, a solution of (*E*)-**4** (124 mg, 0.51 mmol) in dry acetonitrile (8.5 mL) with 10 equiv of acrylonitrile (270 mg, 5.1 mmol) was irradiated for 5 h at rt (conversion 74%). After removal of the solvent, preparative TLC [hexane–ethyl acetate (3:1)] of the residue afforded dienoate **20** (27.9 mg, 30%[9]). Colorless plates; mp 124–127 °C (hexane/ethyl acetate); IR ($CHCl_3$): 1690 cm^{-1} (C=O); ^1H NMR (AL4): δ 1.27 (t, 3H, J=7.2 Hz, CH_3), 4.19 (q, 2H, J=7.2 Hz, OCH_2), 5.74 (d, 1H, J=15.2 Hz, H-2), 6.09 (dd, 1H, J=14.0, 11.6 Hz, H-4), 7.31 (dd, 1H, J=15.2, 11.6 Hz, H-3), 7.45 (t, 2H, J=7.2 Hz, H-3′, H-5), 7.49–7.54 (m with d character, 1H, J=14.0 Hz, H-2), 7.56 (t, 1H, J=7.2 Hz, H-4′), 7.86 (d, 2H, J=7.2 Hz, H-2′, H-6′), 8.78 (br d, 1H, J=11 Hz, NH); ^{13}C NMR (AL4): δ 14.3 (q, CH_3), 60.2 (t, OCH_2), 111.3, 111.8 (2d, C-2, C-4), 127.3, 128.5 (2d, 4C in Ph), 132.5, 133.2 (2d, C-5, C in Ph), 132.8 (s, C in Ph), 143.4 (d, C-3), 164.7, 167.2 (2s, C-1, CONH); EI-MS *m/z* 245 (M^+, 19%), 200 (4), 140 (7), 105 (100), 77 (26), 51 (4); HRMS calcd for $C_{14}H_{15}NO_3$: 245.1052. Found: 245.1046.

4.8.2. Thermal reactions of (*E*)-4. A solution of (*E*)-**4** (300 mg, 1.22 mmol) in xylene (20 mL) with 10 equiv of *tert*-butyl acrylate (1.54 g, 12 mmol) was heated under reflux for 3.5 h (conversion 83%). After removal of the solvent, flash column chromatography [hexane–ethyl acetate (6:1)] of the residue afforded pyridine **21**[12] (9.1 mg, 4%[9]) and a mixture of isomers of dienoate **20** (134 mg).

4.9. Reaction of *N*-trityl aziridine (*E*)-5

4.9.1. Ethyl (2*E*,2′*RS*,3′*RS*)-3-(3-cyano-1-tritylpyrrolidin-2-yl)acrylate 22. By analogy with the photoreactions of (*Z*)-**1**, a 0.060 mol L^{-1} solution of (*E*)-**5** in dry acetonitrile with 10 equiv of acrylonitrile was irradiated. Preparative TLC [hexane–ethyl acetate (5:1)] afforded the adduct **22**. The results are summarized in Table 2. An oil; IR ($CHCl_3$): 2240 (C≡N), 1710 cm^{-1} (C=O); ^1H NMR (AL4): δ 1.27–1.34 (m, 1H, H-3′) 1.36 (t, 3H, J=7.2 Hz, CH_3), 1.62–1.70, 1.75–1.87 (2m, 2H, H_2-4′), 3.07 (td, 1H, J=13, 8.4 Hz, H-5′), 3.48 (ddd, 1H, J=13, 10.0, 4.0 Hz, H-5′), 4.19 (t, 1H, J=6.4 Hz, H-2′) 4.28 (q, 2H, J=7.2 Hz, OCH_2), 6.34 (d, 1H, J=15.6 Hz, H-2), 7.09 (dd, 1H, J=15.6, 6.4 Hz, H-3), 7.18–7.57 (m, 15H, Tr); ^{13}C NMR (AL4): δ 14.4 (q, CH_3), 29.1 (t, C-4′), 31.3 (d, C-3′), 48.3 (t, C-5′), 60.8 (t, OCH_2), 63.0 (d, C-2′), 78.0 (s, *C*Ph_3), 118.9 (s, CN), 123.7 (d, C-2), 126.6 (d, 3C in Ph), 127.9 (d, 6C in Ph), 128.8 (d, 6C in Ph), 143.8 (s, 3C in Ph), 144.8 (d, C-3),

165.8 (s, C-1); EI-MS *m/z* 436 (M^+, 0.4%), 359 (1), 243 (100), 165 (2); HRMS calcd for $C_{29}H_{28}N_2O_2$: 436.2151. Found: 436.2150.

4.9.2. Ethyl (2*E*,2′*RS*,3′*RS*)-3-(3-methoxycarbonyl-1-tritylpyrrolidin-2-yl)acrylate 23. By analogy with the photoreactions of (*Z*)-**1**, a solution of (*E*)-**5** in dry acetonitrile with 10 equiv of methyl acrylate was irradiated. Preparative TLC [hexane–ethyl acetate (7:1)] afforded the adduct **23**. The results are summarized in Table 2. Colorless crystals; mp 134–135 °C (hexane/ethyl acetate); IR ($CHCl_3$): 1720 (C═O), 1710 cm^{-1} (C═O); ^1H NMR (AL4): δ 1.33 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.34–1.40, 1.86–1.97 (2m, 2H, H_2-4′), 1.59 (dt, 1H, J=10.5, 8.3 Hz, H-3′), 2.97–3.06, 3.41–3.49 (m, 2H, H_2-5′), 3.49 (s, 3H, OCH_3), 4.19–4.23 (m, 1H, overlapping with q at δ 4.23, H-2′) 4.23 (q, 2H, J=7.1 Hz, OCH_2), 6.14 (d, 1H, J=15.6 Hz, H-2), 6.86 (dd, 1H, J=15.6, 6.4 Hz, H-3), 7.12–7.29 (m, 9H, Tr), 7.56 (d, 6H, J=7.6 Hz, Tr); ^{13}C NMR (AL4): δ 14.3 (q, OCH_2CH_3), 26.6 (t, C-4′), 47.6 (d, C-3′), 48.3 (t, C-5′), 51.5 (q, OCH_3), 60.4 (t, OCH_2), 63.4 (d, C-2′), 78.0 (s, CPh_3), 122.1 (d, C-2), 126.3 (d, 3C in Ph), 127.7 (d, 6C in Ph), 129.0 (d, 6C in Ph), 144.2 (s, 3C in Ph), 146.6 (d, C-3), 166.2 (s, C-1), 171.6 (s, CO_2CH_3); EI-MS *m/z* 469 (M^+, 1%), 392 (3), 243 (100), 228 (4), 198 (2), 165 (23), 154 (2), 91 (2); HRMS calcd for $C_{30}H_{31}NO_4$: 469.2253. Found: 469.2252.

4.10. Application to the synthesis of (±)-isoretronecanol 27

4.10.1. Ethyl (2*E*,2′*RS*,3′*RS*)-3-(3-methoxycarbonylpyrrolidin-2-yl)acrylate 24. To a solution of **23** (430 mg, 0.86 mmol) in chloroform (0.7 mL) and methanol (0.7 mL) was trifluoroacetic acid (1.3 mL) at rt. After being stirred for 1 h at rt, the reaction mixture was extracted with water (2× 3 mL). The aqueous phase was neutralized with aqueous saturated $NaHCO_3$ and extracted with chloroform (3× 5 mL). The organic phase was washed with brine, dried with $MgSO_4$, and concentrated in vacuo to yield **24** (168 mg, 83%).

An oil; IR ($CHCl_3$): 3510 (N–H), 1710 cm^{-1} (C═O); ^1H NMR (AL4): δ 1.28 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.77 (brs, 1H, NH), 2.01–2.20 (m, 2H, H_2-4′), 2.91–2.99 (m with ddd-character, 1H, J=11, 8.3, 7.8 Hz, H-5′), 3.11–3.17 (m, 1H, H-3′), 3.29 (ddd, 1H, J=11.2, 8.6, 4.4 Hz, H-5′), 3.64 (s, 3H, OCH_3), 3.87–3.92 (m, 1H, H-2′) 4.19 (q, 2H, J=7.2 Hz, OCH_2), 5.99 (dd, 1H, J=15.6, 1.5 Hz, H-2), 6.89 (dd, 1H, J=15.6, 6.3 Hz, H-3); ^{13}C NMR (AL4): δ 14.3 (q, OCH_2CH_3), 29.3 (t, C-4′), 46.3 (t, C-5′), 48.5 (d, C-3′), 51.7 (q, OCH_3), 60.4 (t, OCH_2), 62.8 (d, C-2′), 122.3 (d, C-2), 144.5 (d, C-3), 165.7 (s, C-1), 173.4 (s, CO_2CH_3); EI-MS *m/z* 227 (M^+, 21%), 198 (100), 181 (40), 154 (41), 128 (38), 116 (80), 100 (48), 56 (42); HRMS calcd for $C_{11}H_{17}NO_4$: 227.1158. Found: 227.1160.

4.10.2. Ethyl (2′*RS*,3′*RS*)-3-(3-methoxycarbonylpyrrolidin-2-yl)propanate 25. A solution of **24** (18.1 mg, 0.08 mmol) in ethyl acetate (0.5 mL) with 10% Pd/C (5.2 mg) under hydrogen was stirred for 21 h at rt. The reaction mixture was filtered with celite, and the filtrate was concentrated in vacuo, giving a residue that was subjected to NH-silica gel column chromatography [hexane–ethyl acetate (1:5)] to afford **25** (11.7 mg, 64%).

An oil; IR ($CHCl_3$): 3410 (N–H), 1720 cm^{-1} (C═O); ^1H NMR (AL4): δ 1.25 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.62–1.85 (m, 3H, NH and H_2-3), 1.93–2.10 (m, 2H, H_2-4′), 2.44–2.50 (m, 2H, H_2-2), 2.79–2.87 (m, 1H, H-5′), 2.92–2.97 (m, 1H, H-3′), 3.04–3.11 (m, 1H, H-2′), 3.18–3.25 (m, 1H, H-5′), 3.68 (s, 3H, OCH_3), 4.13 (q, 2H, J=7.2 Hz, OCH_2); ^{13}C NMR (AL4): δ 14.4 (q, OCH_2CH_3), 26.4 (t, C-3), 30.3 (t, C-4′), 32.5 (t, C-2), 46.4 (t, C-5′), 47.6 (d, C-3′), 51.5 (q, OCH_3), 60.4 (t, OCH_2), 63.0 (d, C-2′), 173.0, 174.9 (2s, C-1, CO_2CH_3); EI-MS *m/z* 229 (M^+, 4%), 183 (34), 155 (29), 152 (24), 128 (100), 97 (76), 69 (26); HRMS calcd for $C_{11}H_{19}NO_4$: 229.1314. Found: 229.1314.

4.10.3. Methyl (4*RS*,5*RS*)-8-oxo-1-azabicyclo[3.3.0]oct-4-ylcarboxylate 26. A solution of **25** (14.6 mg, 0.065 mmol) in toluene (1.0 mL) was refluxed for 15.5 h. The reaction mixture was concentrated in vacuo, giving a residue that was subjected to flush column chromatography [ethyl acetate] to afford **26**[5] (10.3 mg, 87%).

An oil; IR ($CHCl_3$): 1730 (C═O), 1695 cm^{-1} (C═O); ^1H NMR (AL4): δ 1.69–1.78 (m, 1H, H-6), 2.16–2.43 (m, 4H, H_2-3, H-6, H-7), 2.61–2.70 (m, 1H, H-7), 3.02 (td, 1H, J=7.1, 3.4 Hz, H-4), 3.04–3.11 (m, 1H, H-2), 3.70 (s, 3H, OCH_3), 3.82 (td, 1H, J=11.2, 7.6 Hz, H-2), 4.16 (q, 1H, J=7 Hz, H-5); ^{13}C NMR (AL4): δ 22.6 (t, C-6), 30.4 (t, C-3), 34.0 (t, C-7), 41.3 (t, C-2), 45.5 (d, C-4), 51.9 (q, OCH_3), 63.2 (d, C-5), 172.6, 175.2 (2s, C-8, CO_2CH_3); EI-MS *m/z* 183 (M^+, 37%), 183 (34), 155 (45), 152 (26), 97 (100), 69 (44); HRMS calcd for $C_9H_{13}NO_3$: 183.0895. Found: 183.0892.

Compound **26**.[5b] ^1H NMR (250 MHz): δ 1.5–1.75 (m, 1H), 2.0–2.4 (m, 4H), 2.45–2.7 (m, 1H), 2.85–3.1 (m, 2H), 3.6 (s, 3H), 3.5–3.8 (m, 1H), 4.08 (q, 1H, J=7 Hz); ^{13}C NMR (62.5 MHz): δ 22.3, 30.2, 33.6, 41.0, 45.2, 51.8, 63.1, 172.9, 175.4.

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Density functional study of the lithiation of cyclic vinyl ethers in solution

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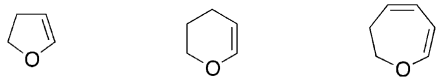
Abstract—Lithiation of three cyclic vinyl ethers—2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran, and 2,3-dihydrooxepin in ethereal solution are investigated at the density functional theory level of B3LYP/6-31++G(d,p). Several solvation models were used, including the microsolvation model, the continuum models such as the Onsager model, the polarized continuum models, and the isodensity polarized continuum model, and the mixed discrete-continuum model. Both the microsolvation and the mixed discrete-continuum model gave results consistent with experiments. Theoretical calculations also indicate that lithiation of 2,3-dihydrooxepin undergoes allylic lithiation concomitant with ring opening.

1. Introduction

The synthetic application of α-lithiated cyclic vinyl ethers in organic chemistry has been of interest since at least 1951. These lithiated compounds have been mainly used as acyl anion synthons and as precursors of α-alkoxyalkenylcuprates in Kocienski's metallate rearrangement.[1] Lithiation of mid-sized cyclic vinyl ethers at vinylic versus allylic positions has been an active project in our group. Computational investigations of the lithiation of cyclic vinyl ethers in the gas phase at Hartree–Fock (geometry optimization) and second-order Møller–Plesset perturbation theory (single point) levels have suggested that in most cases, the vinylic positions are energetically favored.[2] However, using exchange-correlation functionals of B3LYP in combination with the mid-sized basis set, 6-31++G(d,p), we have shown that allylic lithiation is favored in the case of oxete, the 4-membered ring system, which is in contrast with previous studies.[3] The density functional theory (DFT) method-B3LYP has been widely used in most of the recent computational organolithium studies and has proved to be significantly more efficient than some of the post-HF methods (such as MP2 level) of comparable accuracy.[4] It has also been successfully used in investigations of ether solvent effects involving lithium enolates, the results of which agree well with more expensive MP4 level calculations.[5] The inclusion of electron correlation within the geometry optimization increases the accuracy of the optimized structures and therefore the relative energy preferences. Herein we wish to summarize our theoretical work of the ether solvated lithiation of 2,3-dihydrofuran (DHF)—the 5-membered ring system,[6] 3,4-dihydro-2*H*-pyran (DHP)—the 6-membered ring system,[7] and 2,3-dihydrooxepin (DHOP)—the 7-membered ring system with two conjugated double bonds (Fig. 1).



DHF DHP DHOP

Figure 1. Cyclic vinyl ethers included in this study.

The solvation models used here are microsolvation, in which short-range solvent interaction is examined, and the continuum reaction field models, including the Onsager model, the polarized continuum model (PCM, including the newer CPCM–PCM model using the polarizable conductor calculation model and IEFPCM–PCM model using the integral equation formalism model), and the isodensity polarized continuum model (IPCM), where the long-range solvation is considered. We then combined both short-range and long-range solvation into the mixed discrete-continuum solvation model (mixed solvation model). In the current study, both the microsolvation model and the mixed discrete-continuum model seem better in reproducing the experimental results. It is well-known that vinylic lithiation is preferred experimentally for DHF and DHP,[8] and it is

Keywords: Density functional theory; Microsolvation; Continuum solvation; Mixed discrete-continuum solvation; Transition states.
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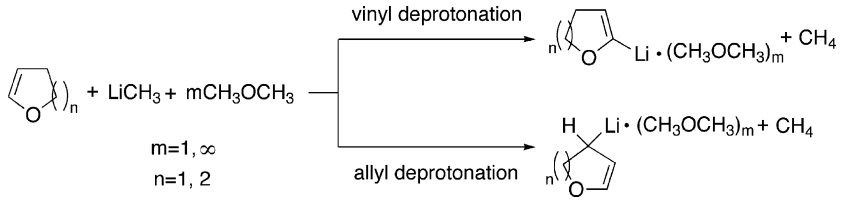


Scheme 1.

generally believed that both the electronegative vinyl ether oxygen and precomplexation affect lithiation regioselectivity. Our DFT-B3LYP calculations incorporated with different solvation models reproduce the vinylic lithiation for DHF in all cases. For DHP, all of the continuum models give allylic lithiation in contrast with experiment, but the microsolvation model predicts vinylic lithiation with a small relative energy preference of only 0.17 kcal/mol. However, when combining the discrete microsolvation and the continuum solvation we obtained more reasonable results, indicating long-range solvation also affects the outcome of the lithiation. We have also shown previously in experiments that lithiation of DHOP with 6-lithiated-3,4-dihydro-2*H*-pyran in THF leads to ring-opening to give a trienolate product,[9] but the detailed mechanism of this reaction was unclear. Our computational work described herein with all solvation models, except for the continuum IPCM model, suggests allylic lithiation with a direct ring-opening mechanism for DHOP.

2. Methods of calculations

The DFT method we used here, B3LYP, includes a combination of Becke's three-parameter nonlocal exchange functional[10] with the correlation functional of Lee–Yang–Parr.[11] The solvent used in the SCRF calculations is diethylether which is available in the Gaussian 98w program package.[12] In the previous DFT studies of the oxete system, the use of water as the 'microsolvent' resulted in unnecessary hydrogen bonding.[3] Limited by computational efficiency and cost, one molecule of dimethyl ether seems to

Table 1. Relative energies (kcal/mol) obtained for DHF, DHP and DHOP in the gas phase and in solution with different solvation models ($\Delta E = E_{\text{vinylic}} - E_{\text{allylic}}$)

Molecule	Models	Reactant[a]	Vinylic transition state	Allylic transition state	Vinylic product	Allylic product	ΔE (TS)	ΔE (products)
DHF	Gas phase	0.00	20.22	22.32	−3.28	1.86	−2.10	−5.14
	Onsager model[b]	0.00	25.12	28.14	0.56	7.16	−3.01	−6.60
	PCM model[b]	0.00	25.62	29.04	−2.38	3.22	−3.42	−5.60
	CPCM model	0.00	25.79	29.30	−2.03	3.39	−3.51	−5.43
	IEFPCM model	0.00	26.01	29.36	−1.91	3.76	−3.35	−5.68
	IPCM model[b]	0.00	15.66	26.24	−1.33	−0.22	−10.58	−1.11
	Microsolvation[c]	0.00	15.28	19.06	−7.41	−4.11	−3.78	−3.30
	PCM (mixed)	0.00	19.81	24.84	−7.61	−1.72	−5.02	−5.89
	CPCM (mixed)	0.00	19.88	24.72	−7.61	−1.65	−4.84	−5.95
	IEFPCM (mixed)	0.00	19.86	24.67	−7.38	−1.60	−4.81	−5.78
	IPCM (mixed)	0.00	19.49	26.01	−8.16	−0.51	−6.52	−7.64
DHP	Gas phase	0.00	22.94	20.39	0.02	−1.64	2.54	1.66
	Onsager model[b]	0.00	28.52	26.90	4.97	4.78	1.62	0.19
	PCM model[b]	0.00	27.97	27.49	1.17	0.60	0.47	0.57
	CPCM model	0.00	28.12	27.78	1.42	0.84	0.34	0.58
	IEFPCM model	0.00	28.43	27.75	1.58	0.96	0.68	0.62
	IPCM model[b]	0.00	27.35	26.06	−2.53	−4.19	1.29	1.66
	Microsolvation[c]	0.00	17.82	17.99	−4.14	−7.71	−0.17	3.57
	PCM (mixed)	0.00	22.44	24.18	−3.86	−4.28	−1.74	0.42
	CPCM (mixed)	0.00	22.64	24.32	−3.68	−4.04	−1.68	0.36
	IEFPCM (mixed)	0.00	22.68	24.21	−3.44	−4.05	−1.53	0.60
	IPCM (mixed)	0.00	23.40	24.82	−2.26	−3.12	−1.42	0.86
DHOP[d]	Gas phase	0.00	21.92	11.59	−1.33	−49.19	10.33	47.86
	Onsager model[b]	0.00	26.06	16.61	1.25	−44.65	9.45	45.90
	PCM model[b]	0.00	9.88	1.89	−17.24	−60.85	7.98	43.61
	CPCM model	0.00	10.28	2.30	−16.83	−60.53	7.98	43.69
	IEFPCM model	0.00	10.38	2.13	−16.79	−60.65	8.25	43.85
	IPCM model[b]	0.00	0.43	1.37	−17.63	−60.53	−0.94	42.89
	Microsolvation[c]	0.00	16.51	8.64	−5.33	−52.17	7.88	46.83
	PCM (mixed)	0.00	21.22	14.78	−4.62	−48.18	6.44	43.57
	CPCM (mixed)	0.00	21.66	15.41	−4.32	−48.24	6.24	43.92
	IEFPCM (mixed)	0.00	21.38	14.90	−4.60	−48.36	6.48	43.76
	IPCM (mixed)	0.00	22.26	15.43	−3.54	−47.46	6.82	43.92

[a] Reactants in each model are set to be 0 in energy, they are not necessarily the same in different models.
[b] Calculations with diethyl ether as the bulk solvent.
[c] Calculations with one dimethyl ether molecule explicitly expressed in the system.
[d] In the case of DHOP, allylic transition state and product are referred to the acyclic process.

be the simplest but reasonable analog solvent for the microsolvation model (Scheme 1) even though lithium may coordinate to two or more solvent molecules. Our results indicate that such a model can represent the trend of microsolvation efficiently. In the mixed discrete-continuum solvation, the continuum models were used for single point calculations on the microsolvation optimized geometries.

All the calculations were performed using either the GAUSSIAN 94 program package or the GAUSSIAN 98w (Windows version) program.[13] The standard 6-31++G(d,p) basis set was used (available in both programs). All stationary points were characterized as minima (with no imaginary frequency) or saddle points (with one and only one imaginary frequency) by harmonic vibrational frequency analysis at the same level. All of the transition states of the microsolvation model were located and optimized by both the synchronous transit-guided quasi–Newton method with three molecule specifications (QST3)[14] and the Berny algorithm (TS),[15] and verified to be connecting the corresponding minima (reactant and product) by a proceeding IRC calculation (six points on each side of the transition structure along the reaction path with a step size of 0.1 au) using the same basis set and theory level. All relative energies reported are of internal energies and zero-point energy (ZPE) corrections are included. All the structural parameters were obtained with CS Chem 3D PRO version 6.0.

3. Results and discussion

As expected, in all three microsolvation modeled lithiation reactions, the three components of the reactant—methyl lithium, dimethyl ether and the cyclic vinyl ether tend to form a 'pre-complex'. The pre-complex is energetically favored because the lone pairs of electrons of the two oxygen atoms (one in the cyclic vinyl ether, the other in the solvent) interact with the lithium cation.

For the lithiation reaction of DHF, the 5-membered ring system, with all the models that we used in the gas phase and ethereal solutions, vinylic lithiation is favored over the corresponding allylic process (Table 1, Figs. 2 and 3). The inclusion of solvation (long-range, short-range and combined) increases ΔE (TS).

For the lithiation reaction of DHP, the 6-membered ring system, previous gas phase geometry optimization at the Hartree–Fock level reproduced the experimental result that vinylic lithiation is favored over the corresponding allylic process by a calculated ΔE (TS) of -2.7 kcal/mol. However, with the inclusion of correlation energy, the MP2 level single point calculation predicts the allylic process.[2,16] All continuum models and even the gas phase model at the current DFT level also predict the allylic lithiation. With the microsolvation model, the current DFT calculation gives a small ΔE (TS) of -0.17 kcal/mol, favoring the vinylic

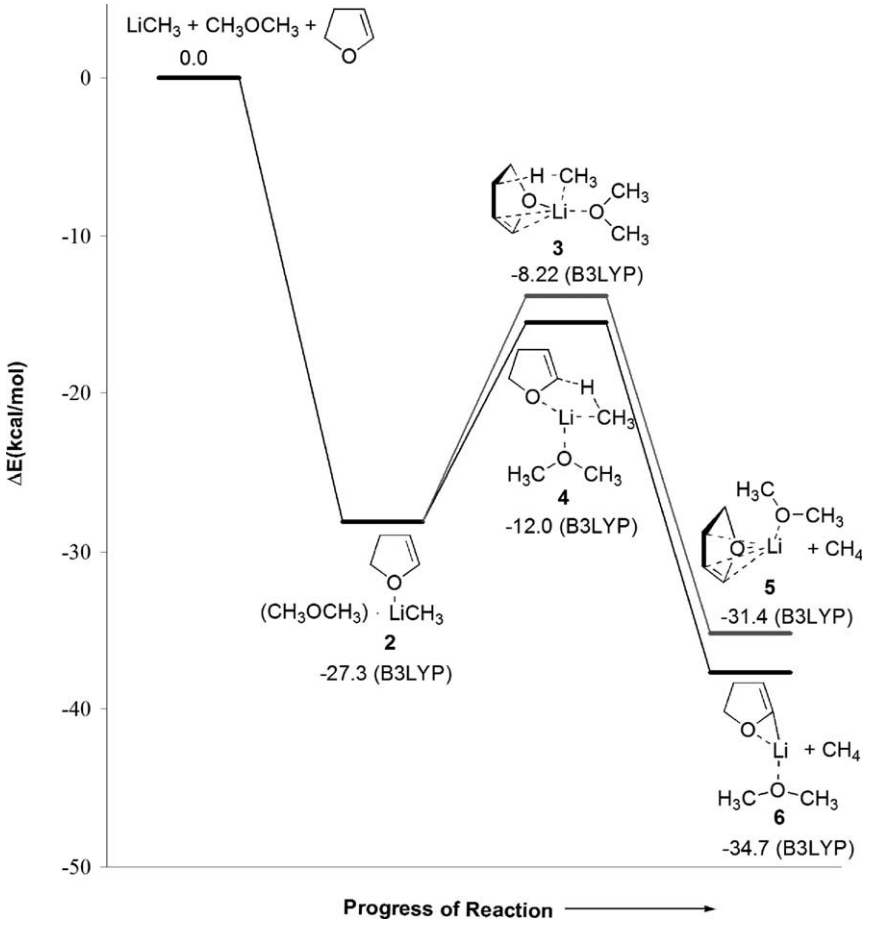


Figure 2. Progress of reaction diagram for deprotonation of DHF resulting from microsolvation geometry optimizations (B3LYP/6-31++G(d,p), relative energies are in kcal/mol).

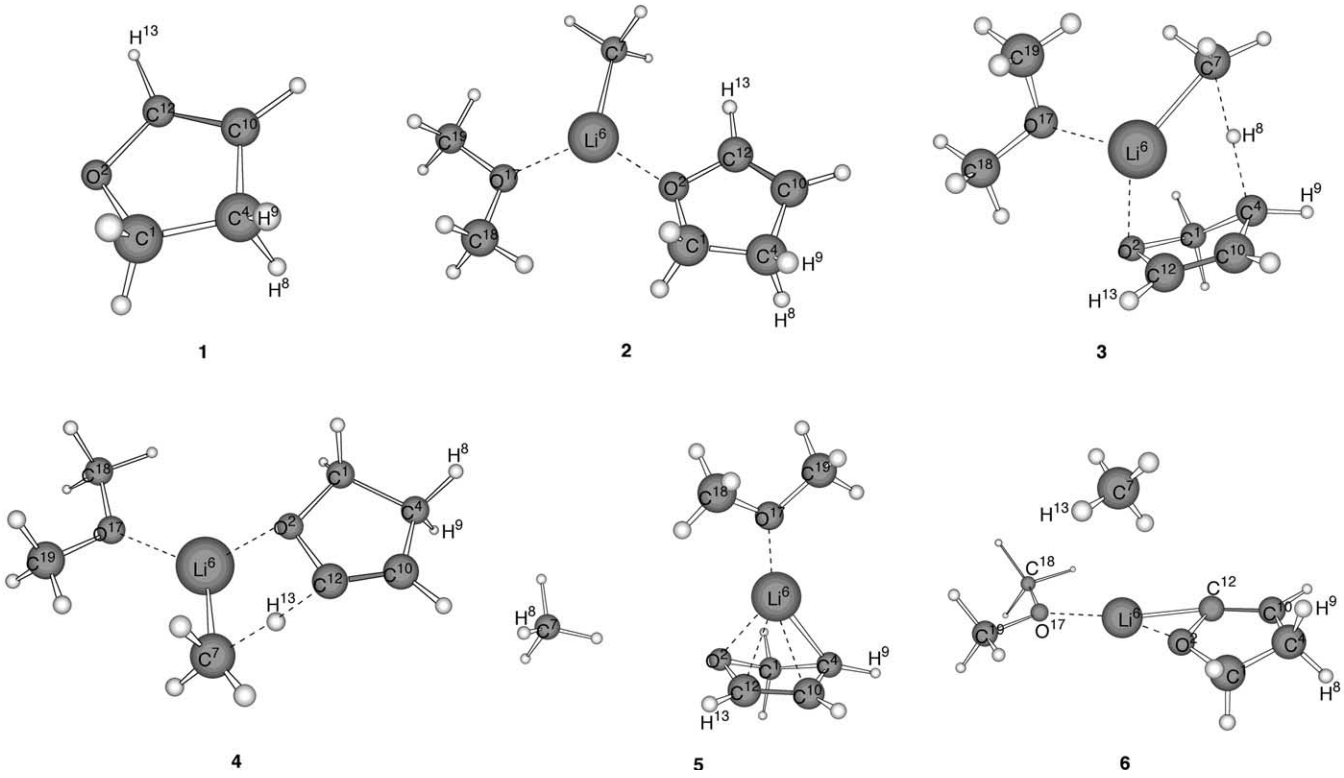


Figure 3. DFT optimized geometries of dimethyl ether microsolvated DHF system.

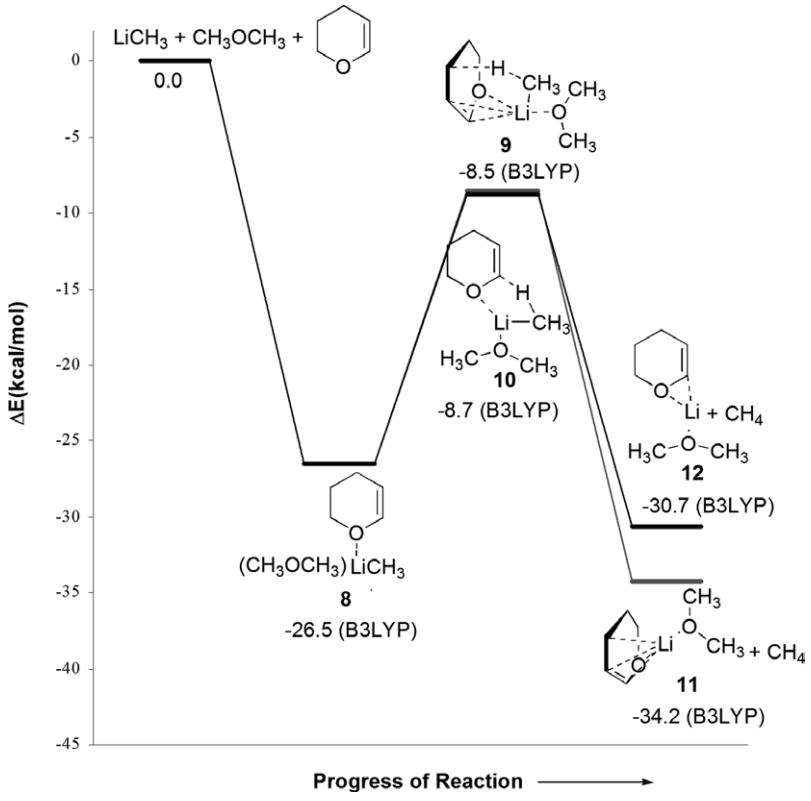


Figure 4. Progress of reaction diagram for deprotonation of DHP resulting from microsolvation geometry optimizations (B3LYP/6-31++G(d,p), relative energies are in kcal/mol).

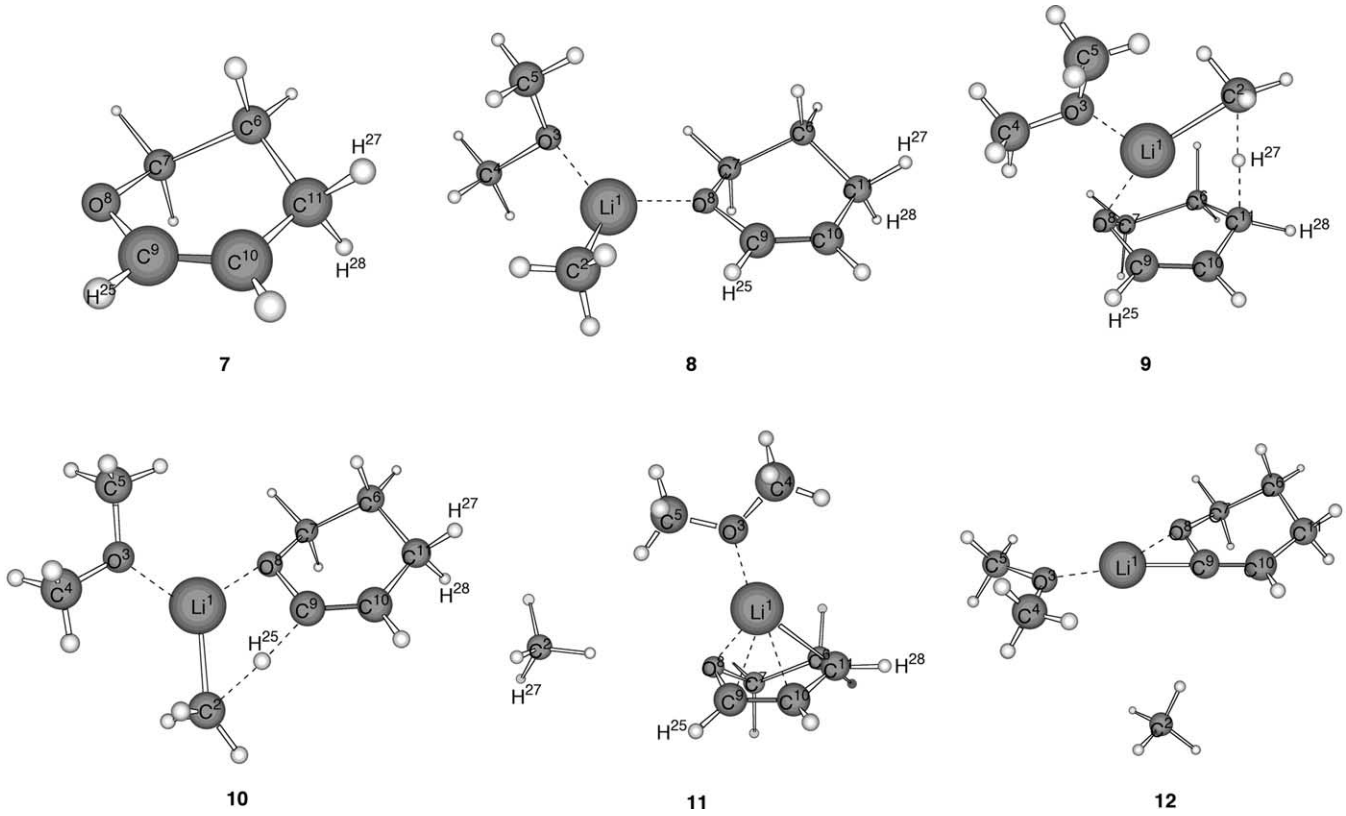


Figure 5. DFT optimized geometries of dimethyl ether microsolvated DHP system.

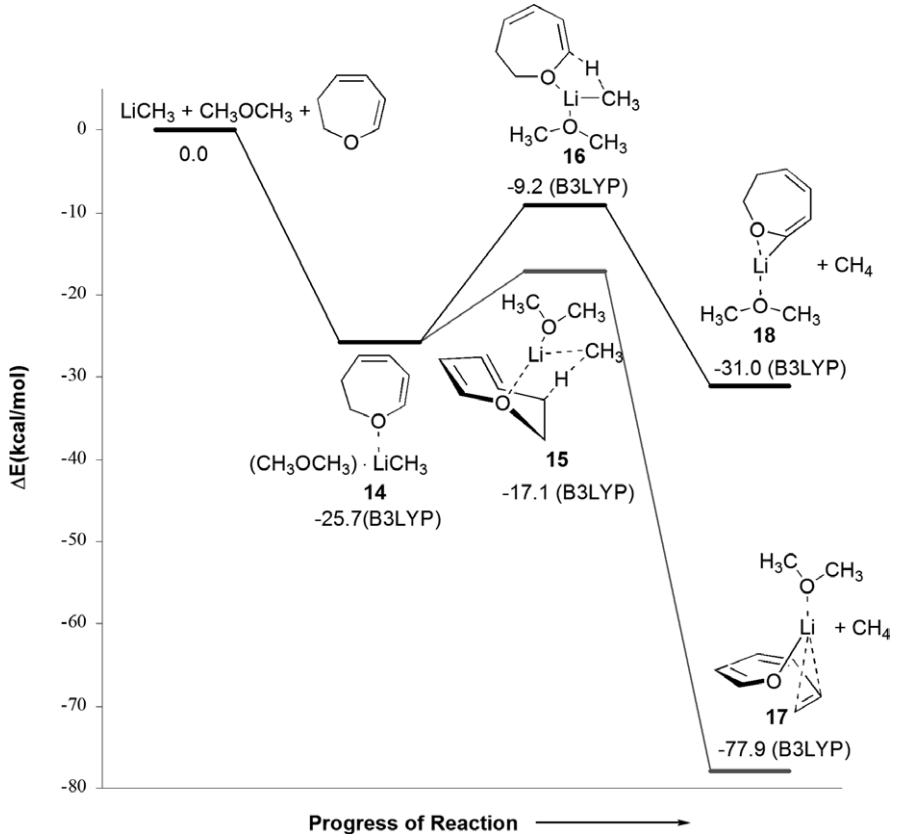


Figure 6. Progress of reaction diagram for deprotonation of DHOP resulting from microsolvation geometry optimizations (B3LYP/6-31++G(d,p), relative energies are in kcal/mol).

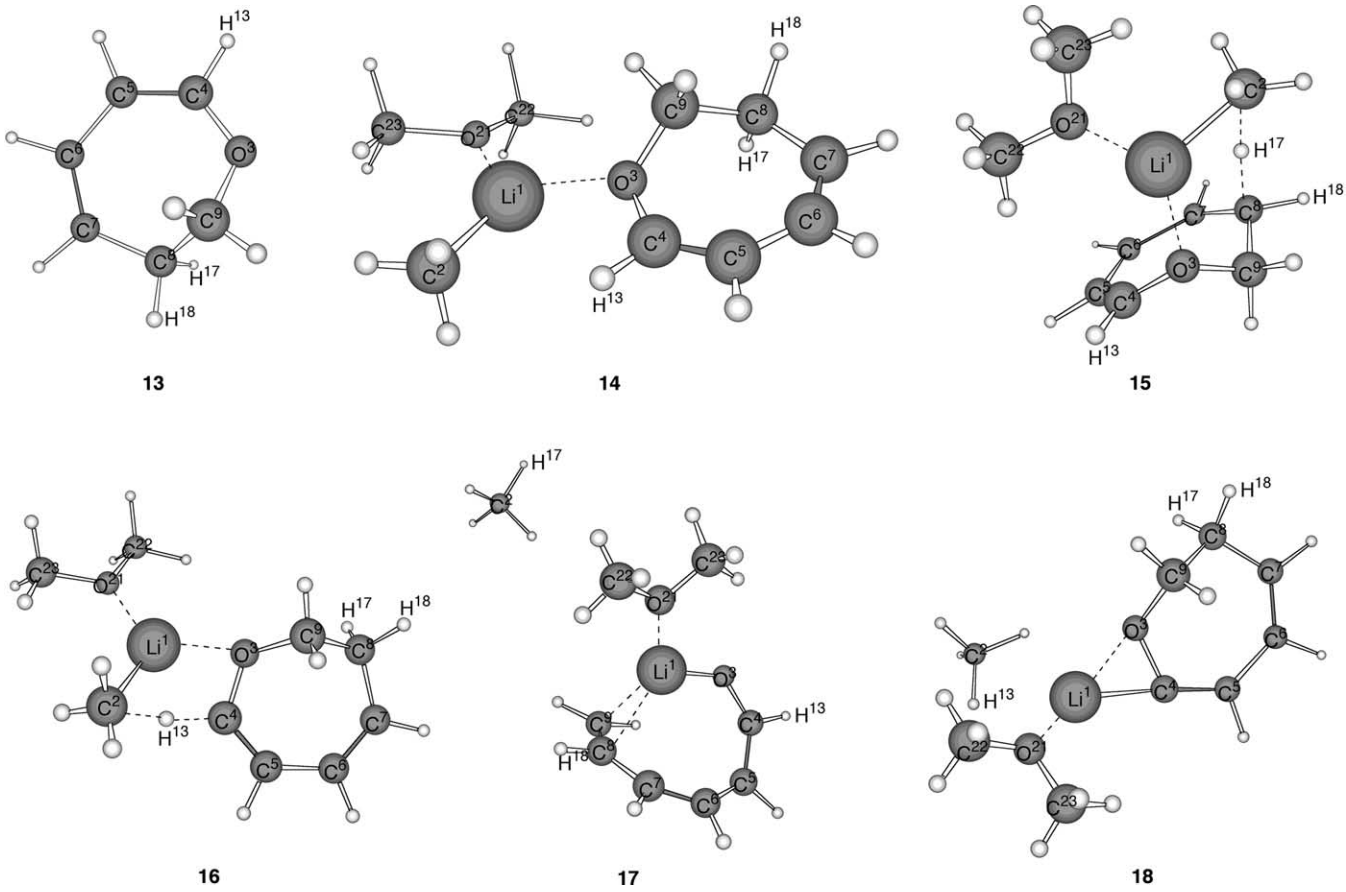


Figure 7. DFT optimized geometries of dimethyl ether microsolvated DHOP system.

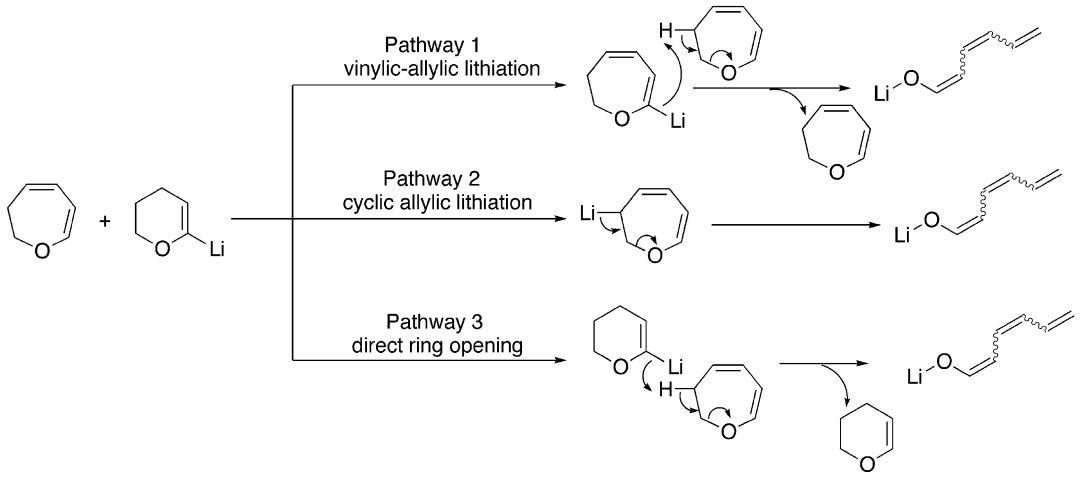
lithiation (Table 1, Figs. 4 and 5); a more reasonable ΔE (TS) of around −1.5 kcal/mol was obtained by using the mixed solvation model. Since basis set deficiency has been very likely excluded in previous studies,[16] this could suggest that the short-range solvation must be included to successfully reproduce the experimental results.

For the lithiation reaction of DHOP, the 7-membered ring system, things are more complicated. First of all, at the Hartree–Fock level with the same basis set, the allylic lithiated product in the gas phase (optimized as energy minimum) was calculated as a cyclic structure. However, when we tried to calculate the same system at MP2 and B3LYP level even with a basis set as small as 3-21G, both failed to give the cyclic form but yielded an open-chain trienolate product instead, indicating ring-opening during the gas phase lithiation process. We then 'froze' the C9–O2 bond to hold the cyclic form of the allylic lithiation product, but the calculations would not converge in a reasonable period of time as long as electronic correlation is included. The same thing happened in the microsolvation model at the current level (**17** in Figs. 6 and 7). We noticed that after reasonable rotation about the carbon–carbon single bonds our calculated allylic product lead to the actual trienolate product of previous experiments.[9] The microsolvation model indicates that the formation of the incipient trienolate structure is favored over the cyclic vinylic process by 7.88 kcal/mol in ΔE (TS). All of the reaction field solvation models at the current DFT level gave the same energetic trend of preference, except for the IPCM model (Table 1).

Scheme 2 shows three possible pathways of this reaction. Our calculation results suggest that the lithiation reaction of DHOP follows an E2 type mechanism (Scheme 2), since allylic lithiation is energetically favored and the cyclic form of the allylic product could not be formed as a minimum.

The conformations of all the allylic species are more puckered than the vinylic ones, which has also been observed in the previous studies of oxete lithiation.[5] The lithium cation is sitting atop the ring in the allylic processes, which suggests electronic delocalization. In the acyclic form of the allylic product (trienolate) of DHOP lithiation (**17**), the lithium cation only interacts with the terminal double bond. The isolated anions (gas phase) for each system are also calculated at the same theory level. Without the lithium cation, the isolated vinyl anion of DHF is 3.1 kcal/mol lower in energy than the isolated allyl anion whereas the vinyl anion of DHP is, in fact, 8.67 kcal/mol higher in energy than the allyl anion. In the case of DHOP anions, the cyclic and acyclic allyl anions are 23.36 and 44.14 kcal/mol, respectively, lower in energy than the vinyl one.

All three cyclic vinyl ethers have two hydrogen atoms attached to the allylic carbon atom. Our calculations with



Scheme 2.

the microsolvation model indicated that they are equivalent at the current DFT level of theory: the energy differences between the two allylic transition structures are 6×10^{-4} kcal/mol for DHF, 6×10^{-4} kcal/mol for DHP and 9×10^{-6} kcal/mol for DHOP, and the energy differences between the two allylic products are 0.01 kcal/mol for DHF, 0.18 kcal/mol for DHP and 0.08 kcal/mol for DHOP, all of which are negligible in this study.

Comparing the corresponding vinylic angles in the reactants and vinylic lithiation products of DHF (∠O2–C12–C10 in **2** and **6**), DHP (∠O8–C9–C10 in **8** and **12**) and DHOP (∠O3–C4–C5 in **14** and **18**), the microsolvation calculations suggest vinyl compressions of 7.5, 8.09 and 8.08°, respectively. The allylic expansions (comparing ∠C4–C10–C12 in **2** and **5**, ∠C9–C10–C11 in **8** and **11**, ∠C6–C7–C8 in **14** and **17**) are 0.3° for DHF and 5.84° for DHOP but −1.6° for DHP. The atomic charges were determined by Natural Population Analysis (NPA), based on the geometry optimized in the same solvation model.

The charges of the migrating hydrogen atoms in all the transition structures are low (+0.20–0.25 electrons) compared to the corresponding hydrogen atoms in the reactants and products, suggesting that the transition structures are multi-center processes, which agrees with previous HF level optimizations.[2]

4. Conclusions

In summary, we have successfully reproduced the experimental results of the lithiation reactions of DHF and DHP in ether solution using the DFT method (B3LYP/6-31++(d,p)). The inclusion of short-range solvation (microsolvation) is necessary for predicting the experimentally consistent regioselectivity of lithiation. The continuum solvation, on the other hand, also affects the lithiation reaction to some extent, especially in the case of DHP. The newer CPCM and IEFPCM models give very similar results to the PCM model in all three systems. In our case, the IPCM does not seem to be a good solvation model even though an isodensity surface is a more natural and intuitive shape for the solute cavity. We also examined the mechanism of the lithiation of DHOP, and the theoretical results suggest an allylic ring-opening lithiation via a direct E2 type pathway. The experimental confirmation of this mechanism will be published elsewhere.

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3-Methyl-4*H*-[1,2,4]-oxadiazol-5-one: a versatile synthon for protecting monosubstituted acetamidines

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Abstract—The utilization of 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one as a versatile protected acetamidine is demonstrated through employment in a variety of synthetic sequences. The potassium salt (**2a**) or the neutral form (**2b**) is alternatively shown to be superior for various synthetic reactions (i.e., alkylation, Michael addition, Mitsunobu) to incorporate side chains for further synthesis. The 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one moiety was found to be stable to acid or base under non-aqueous conditions. It was also found to be stable to many reagents commonly used for organic synthesis. Despite this stability, the free acetamidine may be released by mild reduction including Lindlar hydrogenation or dissolving metal reductions. Alternatively, the hydroxyl amidine may be formed via alkaline hydrolysis.

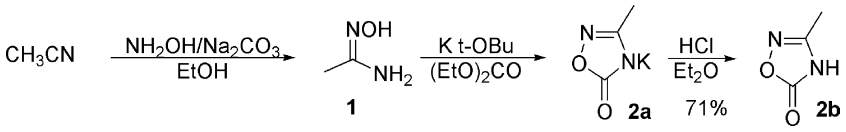
1. Introduction

Amidine groups are found in many medicinal drugs, for example, cardiovascular, anti-diabetic, antibacterial, anti-protozoal, anthelmintic, anti-inflammatory, central nervous system, antineoplastic and others.[1,2] N-monosubstituted acetamidines have been useful as arginine mimetics and they have been utilized in nitric oxide synthase (NOS) inhibitors in particular.[3,4] The basic nature of the amidine and its facile hydrolysis to the corresponding amide makes the synthesis and purification of compounds containing them troublesome. For our needs we sought a versatile method to prepare highly functionalized N-monosubstituted acetamidines. This investigation led to the introduction of the acetamidine in a protected form that enabled facile synthetic manipulations.

A survey of the literature revealed that oxadiazol-5-ones have been previously described as precursors to amidines.[5a–c,6a–d] These prior investigations did not explore the utility of this conversion as a component of a synthetic sequence. The work described here explores the synthetic utility of the use of 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one as a protected acetamidine. We have found this heterocycle to be stable to many synthetic conditions and have used it in extended synthetic schemes. The mild reaction conditions for the selective generation of acetamidines and hydroxy-acetamidines is described as well.

2. Results and discussion

The utility of 3-methyl-4*H*-[1,2,4]-oxadiazol-5-one is dependent upon a consistent route for preparation. We utilized a procedure described by Hett et al. (Scheme 1), which is suitable for the kilogram scale synthesis of the potassium salt **2a**.[7] A simple bubbling of HCl through an ether suspension of **2a** affords the protonated form of the heterocycle **2b**.



Scheme 1.

Keywords: Protected amidine; 3-Methyl-4*H*-[1,2,4]-oxadiazol-5-one.
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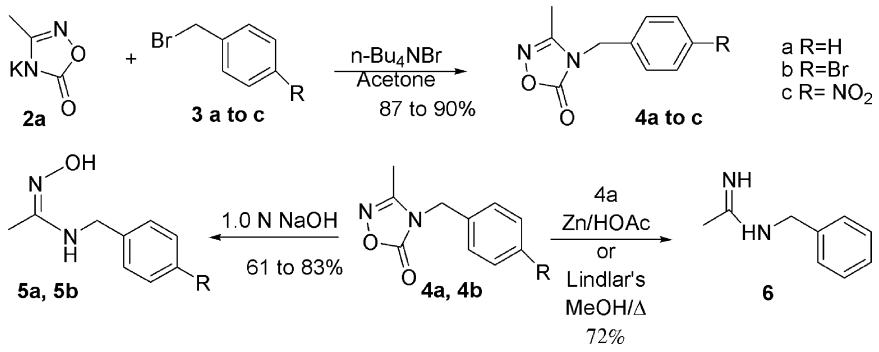


Scheme 2.

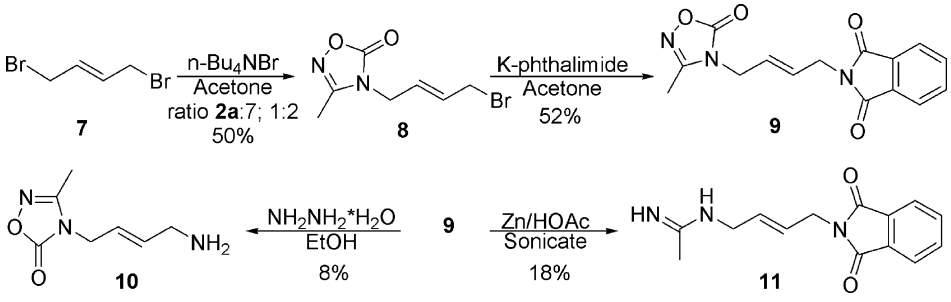
Schemes 2–4 examine the reactivity of the potassium salt **2a** with activated halides. These schemes also show the feasibility of unmasking the acetamidine in the presence of other sensitive groups and the stability of the oxadiazolone ring to further synthetic manipulations.

The potassium salt **2a** readily reacts with benzyl bromides to form the benzyl adducts (Scheme 2). The heterocycles **4a** and **4b** were subsequently hydrolyzed in aqueous hydroxide to afford the *N*-hydroxy amidines **5a** and **5b**. Heating **4a** with Lindlar's catalyst in MeOH at reflux or with zinc in HOAc at 60 °C reduced the N–O bond to afford the acetamidine.

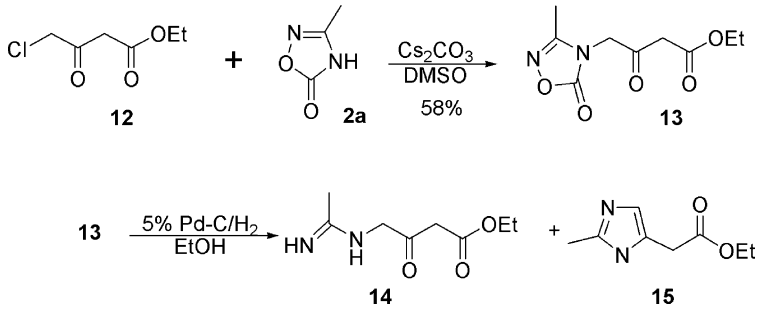
Mono-alkylation of the allylic dibromide **7** was accomplished by limiting the amount of **2a** (Scheme 3). This produced a mixture favoring the mono-alkylated derivative **8**, along with a small amount of the di-alkylated derivative that was separable by chromatography. The oxadiazolinone **8** was further elaborated to the phthalimide protected amino derivative **9** using potassium phthalimide. The phthalimide was removed with hydrazine to yield the free amine while retaining the protected amidine **10**. Alternatively, sonication of **9** in the presence of zinc and HOAc released the acetamidine **11** without altering the phthalimide. In both deprotections the double bond was retained.

A facile reaction of the α-chloroketoester **12** with **2a** afforded the α-ketoester **13** (Scheme 4). Deprotection of **13** via hydrogenation with Lindlar's catalyst in MeOH yielded the acetamidine **14** and a small amount of the imidazole **15**. The mixture was separated and it was determined that **14** slowly cyclizes to form the imidazole **15**.

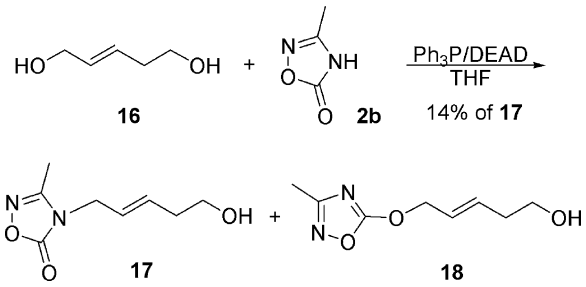
The protonated form of the heterocycle, **2b**, was found to undergo the Mitsunobu reaction with dihydroxy-olefinic alcohol **16** in a preferential reaction of the allylic alcohol to the alkyl alcohol (Scheme 5). The reaction afforded a mixture of N and O-alkylated products **17** and **18**. These isomers were separable by chromatography and the structures confirmed by NMR. Only the protonated form **2b** was successful in this reaction. Attempts to use the potassium salt **2a** directly or via in situ generation of **2b**, failed to afford the Mitsunobu product. Although the alkyl



Scheme 3.



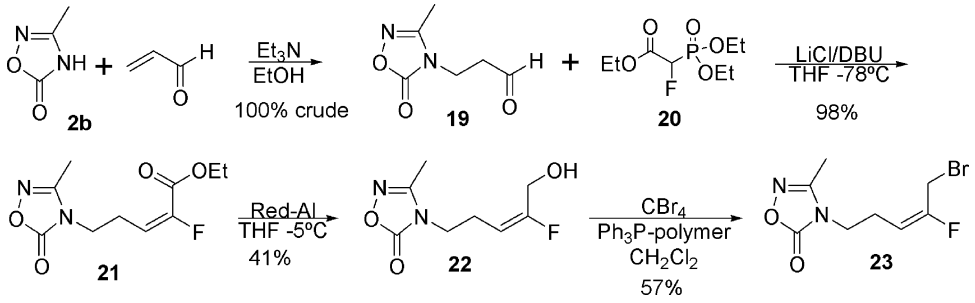
Scheme 4.



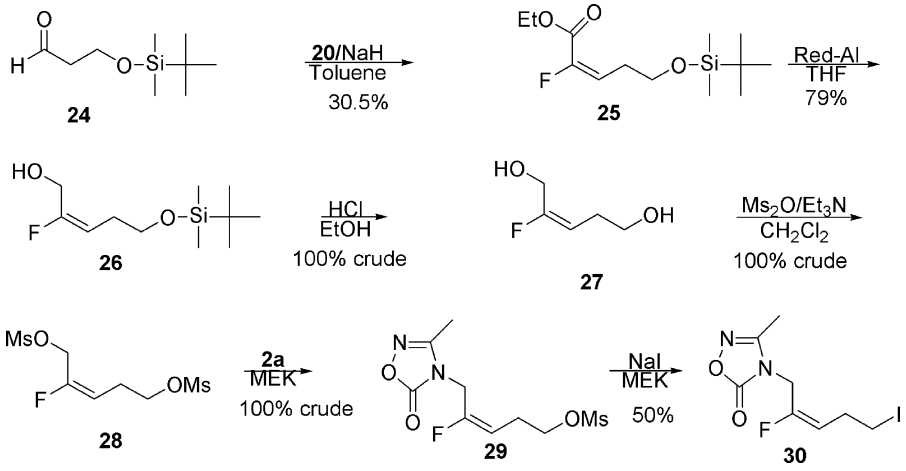
Scheme 5.

alcohols were found to be much less reactive than allylic alcohols, a mixture of O and N- alkylated products of the alkyl alcohol was observed when a large excess of Mitsunobu reagents were utilized along with extended reaction time.

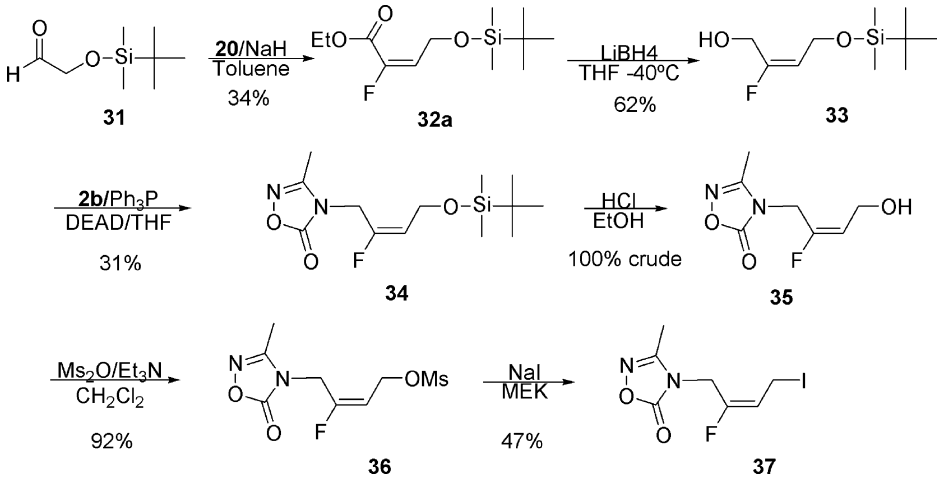
After exploring the reactivity of **2a** and **2b**, several fluoroolefins were synthesized to demonstrate the flexibility and chemical stability of the oxadiaxolinone when incorporated into a synthetic sequence. Schemes 6–8 exemplify the use of a Michael addition, alkylation and Mitsunobu reaction, respectively.



Scheme 6.



Scheme 7.



Scheme 8.

The Michael addition was successful with **2b** to afford the saturated aldehyde **19** (Scheme 6). As with the Mitsunobu reaction only the protonated form successfully produced product. The aldehyde **19** was further elaborated using Wittig conditions to the fluoro-olefinic ester **21** in high yield with no alteration of the heterocycle. The oxadiazolinone was further shown to be stable during reduction of the ester group in **21** with Red-Al to afford the alcohol **22**. The alcohol **22** was then converted to the bromide **23**, using PPh_3/CBr_4 in CH_2Cl_2, to set up for further potential elaboration.

A selective alkylation of an allyl mesylate in the presence the alkyl mesylate utilizing the potassium salt **2a** afforded **29** (Scheme 7). Further elaboration to the iodo-olefin **30** afforded an analog of **23** where the amidine precursor is transposed in relation to the halide.

The one carbon shorter homolog of **29** was prepared using a Mitsunobu reaction to yield **36** (Scheme 8). Further elaboration as for **30** afforded the corresponding homolog **37**.

3. Conclusions

3-Methyl-4*H*-[1,2,4]-oxadiazol-5-one **2** was demonstrated to be selective and versatile for the incorporation of the acetamidine in a protected form. The oxadiazolone ring was stable and robust, through multiple synthetic manipulations. Furthermore, the incorporated oxadiazolone produced products, which could be purified by silica chromatography and often by recrystallization. Catalytic reduction using Lindler's catalyst or zinc/HOAc selectively reduced the N–O bond, releasing the acetamidine in the presence of olefins and other reducible groups. The released acetamidine was often isolated pure. When purification was required, simple reverse-phase chromatography afforded clean product.

Only the protonated form of the oxadiazolone **2b** participated in Michael additions and Mitsunobu reactions while the salt **2a** participated in alkylation reactions. Both the Mitsunobu and alkylation reactions were selective for the allylic versus alkyl sites. Weak nucleophilic hydrides reduced a distal carbonyl to an alcohol without altering the oxadiazolinone. The oxadiazolinone ring was found to be stable to mild acidic conditions, but was hydrolyzed to afford the *N*-hydroxyamidine in 1 N NaOH. Hydrazine reacted with phthalimide **8** to release the amine **34** in the presence of the oxadiazolone ring.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on either a Varian Unity Plus 300 (300 MHz) or a Varian Unity Inova 400 (400 MHz) spectrometer. All NMR spectra are 400 MHz unless stated otherwise. All proton chemical shifts are recorded in ppm (δ) relative to trimethylsilane. All fluorine chemical shifts are recorded in ppm (δ) relative to a reference of $C_6H_5CF_3$ in benzene (Varian standard sample), which has a ^{19}F chemical shift of -64 ppm, with an error of <1 ppm. Column chromatography was performed using either Biotage Flash 40 or 12 system. Reverse phase chromatography was performed on a Gilson semi-preparative HPLC with a YMC Combiprep ODS-A semi-prep column eluting with acetonitrile/water (0.01% TFA) at 20 mL/min. Mass spectra were obtained on a HP series 1100MSD, and high-resolution mass spectra were obtained with a PerSeptive Biosystems Mariner TOF. All solvents and reagents were purchased from Sigma-Aldrich.

4.1.1. Preparation of 3-methyl-1,2,4-oxadiaxolin-5-one (2b). Oxadiazolone **2a**[7] (30.0 g, 0.217 mol) was suspended in Et_2O (150 mL) and cooled in an ice bath. HCl gas was bubbled through the slurry until the exotherm ceased. The mixture was stirred for 2 h, the solid filtered and the filtrate concentrated. The residue was dried under high vacuum to yield 15.5 g (71.4%) of **2b**. ^{1}H NMR (DMSO-d_6): δ 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 11.8, 162.5, 168.2; MS(CI) calcd for $C_3H_4N_2O_2$: [M+H] 101. Found: [M+H] 101; Anal. calcd for $C_3H_4N_2O_2$: C, 36.01; H, 4.03; N, 27.99. Found: C, 35.76; H, 3.99; N, 28.26.

4.1.2. 4-Benzyl-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (4a). Benzyl bromide (1.13 g, 6.59 mmol) in acetone (15 mL) was added at ambient temperature to a suspension of **2a** (1 g, 7.25 mmol), and tetrabutylammonium bromide (0.21 g, 0.66 mmol) in acetone (20 mL). The mixture was stirred 18 h, then quenched with brine and EtOAc. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated and the product was dried under vacuum to yield 1.12 g (89%) **4a** as a white solid, mp 64–65 °C. ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 4.74 (s, 2H), 7.26 (m, 2H), 7.36 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 10.9, 46.0, 127.6, 129.0, 129.5, 134.2, 156.8, 159.9; HRMS calcd for $C_{10}H_{10}N_2O_2$: [M+H] 191.0821. Found: [M+H]191.0822; Anal. calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.39; N, 14.73. Found: C, 63.22; H, 5.36; N, 14.79.

4.1.3. 4-(4-Bromobenzyl)-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (4b). 4-Bromobenzyl bromide (1.65 g, 6.59 mmol) was allowed to react as in **4a** to yielded 1.60 g (90%) of **4b** as a white solid, mp 108–109 °C. ^{1}H NMR ($CDCl_3$): δ 2.14 (s, 3H), 4.69 (s, 2H), 7.13 (d, 2H), 7.50 (d, 2H); ^{13}C NMR ($CDCl_3$): δ 10.9, 45.4, 123.5, 129.3, 132.7, 132.8, 149.5, 160.1; HRMS calcd for $C_{10}H_9N_2O_2Br$: [M+H] 268.9926. Found: [M+H] 268.9923; Anal. calcd for $C_{10}H_9N_2O_2Br$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.76; H, 3.40; N, 10.37.

4.1.4. 3-Methyl-4-(4-nitrobenzyl)-1,2,4-oxadiazol-5(4*H*)-one (4c). 4-Nitrobenzyl bromide (1.42 g, 6.59 mmol) was allowed to react as in **4a** to yielded 1.35 g (87%) of **4c** as a white solid, mp 150–152 °C. ^{1}H NMR ($CDCl_3$): δ 2.17 (s, 3H), 4.85 (s, 2H), 7.45 (d, 2H), 8.25 (d, 2H); ^{13}C NMR ($CDCl_3$): δ 10.9, 45.2, 124.8, 128.5, 141.7, 156.2; HRMS calcd for $C_{10}H_9N_3O_4$: [M+H] 236.1963. Found: [M+H] 236.1959; Anal. calcd for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 51.19; H, 3.88; N, 17.83.

4.1.5. (1*Z*)-*N*-Benzyl-*N*′-Hydroxyethanimidamide (5a). **4a** (190 mg, 1.0 mmol) was suspended in 5% NaOH

(2 mL) at 60 °C for 3 h. The mixture was neutralized with 1 N HCl to pH 7–8. The solid was collected, washed with cold water several times and air dried to yield 100 mg (61%) of **5a** as a white solid, mp 138–139 °C. ^{1}H NMR (CD_3OD): δ 1.76 (s, 3H), 4.35 (s, 2H), 7.26 (m, 5H); ^{13}C NMR (CD_3OD): δ 13.5, 45.5, 114, 126.5, 127.2, 128.4; HRMS calcd For $C_9H_{12}N_2O$: [M+H] 165.1028. Found: [M+H] 165.0987; Anal. calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.05. Found: C, 65.83; H, 7.39; N, 17.06.

4.1.6. (1*Z*)-*N*-(4-Bromobenzyl)-*N'*-hydroxyethanimidamide (5b). 4b (270 mg, 1.0 mmol) was allowed to react as in **5a** to give 200 mg (83%) of **5b** as a white solid, mp 129–130 °C. ^{1}H NMR (CD_3OD): δ 1.74 (s, 3H), 4.31 (s, 2H), 7.22 (d, 2H), 7.47 (d, 2H); ^{13}C NMR (CD_3OD): δ 13.5, 44.5, 120.1, 120.5, 128.4, 131.5; Anal. calcd for $C_9H_{11}BrN_2O$: C, 44.47; H, 4.56; N, 11.52. Found: C, 44.69; H, 5.59; N, 11.66.

4.1.7. Preparation of (iminoethyl)benzylamine (6). Method A: Oxadiazolone **4a** (380 mg, 2.0 mmol) was combined with MeOH (2 mL), HOAc (2 mL), water (2 mL) and zinc dust (570 mg, 8.7 mmol). The mixture was heated at 60 °C for 4 h. LCMS indicated product formation with no starting material. The reaction mixture was filtered and the filtrate concentrated. The crude product was purified by Reverse phase HPLC (0–100% acetonitrile with 0.01% HOAc) isolated as the HOAc salt to yield 300 mg (72%) of **6** as a clear oil. ^{1}H NMR (CD_3OD): δ 1.86 (s, 3H), 4.46 (s, 2H), 7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 17.7, 46.0, 127.6, 127.9, 128.2, 128.8, 134.7, 164.0; HRMS calcd for $C_9H_{12}N_2$: [M+H] 149.1079. Found: [M+H] 149.1041.

Method B: Oxadiazolone **4a** (190 mg, 1.0 mmol) and Lindlar's catalyst Pd–$CaCO_3$ (290 mg) were combined in MeOH (10 mL). The mixture was heated at 60 °C for 2 h. LCMS indicated a new product with **4a** consumed. The reaction mixture was filtered and washed with MeOH. The filtrate was concentrated to dryness to yield **6** quantitively.

4.1.8. 4-[(2*E*)-4-Bromobut-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (8). *Trans*-1,4-dibromo-2-butene (**7**) (50 g, 0.23 mol) was dissolved in acetone (500 mL). Oxadiazolone **2a** (16 g, 0.12 mol) was added, followed by tetrabutylammonium bromide (3.9 g, 0.012 mol). The reaction mixture was stirred at ambient temperature for 18 h, diluted with brine and the product was extracted into EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated to a yellow semi-solid residue. The product **8** was extracted from the residue into CH_2Cl_2 and concentrated to an oily residue. This residue was triturated with hot hexane to remove unreacted **7**, then chromatographed on silica, eluting with EtOAc/hexane to yield 14.2 g (50%) of **8** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.2 (s, 3H), 3.9 (d, 2H), 4.2 (d, 2H), 5.7 (d of t, 1H), 5.9 (d of t, 1H).

4.1.9. 2-[(2*E*)-4-(3-Methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)but-2-enyl]-1*H*-isoindole-1,3(2*H*)-dione (9). Bromide **8** (2 g, 8.58 mmol), tetrabutylammonium bromide (0.26 g, 0.86 mmol) and potassium phthalimide (1.9 g, 10.3 mmol) were dissolved in acetone (20 mL) and stirred for 2 h at ambient temperature. The solid was filtered and washed with H_2O (50 mL), and the filtrate was extracted with EtOAc. The organic layer was dried over $MgSO_4$, and concentrated to yield 1.32 g (52%) of **9** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.21 (s, 3H), 4.06 (d, 2H), 4.32 (d, 2H), 5.59 (m, 2H), 7.71 (m, 2H) 7.89 (m, 2H); LC–MS calc for $C_{15}H_{13}N_3O_4$: [M+H] 300. Found: [M+H] 300; Anal calcd for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 59.98; H, 4.34; N, 14.10.

4.1.10. *N*-Benzylethanimidamide (10). Phthalimide **9** (150 mg, 0.5 mmol) was dissolved/suspended in EtOH (3.0 mL). Hydrazine hydrate (50 mg, 1.0 mmol) was added and the mixture was stirred at reflux for 30 min. The reaction mixture was concentrated and the residue dissolved in dilute K_2CO_3. The insoluble material was filtered and the filtrate was chromatographed using reverse phase to yield 10 mg of **10** (7.5%) isolated as the TFA salt. ^{1}H NMR (MeOD): δ 2.25 (s, 3H), 3.55 (dd, J=6.4, 1.2 Hz, 2H), 4.29, 4.28 and 4.27, 4.270 (d of d, J=5.2, 1.2 Hz, 2H), 5.78–5.71 (m, 1H), 5.97–5.90 (m, 1H); ^{19}F NMR (MeOD): δ −77.37; HRMS calcd for $C_7H_{11}N_3O_2$: [M+H] 170.0924. Found: [M+H] 170.0916.

4.1.11. *N*-[(2*E*)-4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)but-2-enyl]ethanimidamide (11). Phthalimide **9** (150 mg, 0.5 mmol) and zinc (101 mg; 1.5 mmol) were dissolved/suspended in HOAc (10 mL) and sonicated for 10 min. The resulting mixture was filtered and concentrated. The residue was chromatographed using reverse phase chromatography to yield 96 mg (18%) of **11** isolated as the TFA salt. ^{1}H NMR (MeOD): δ 2.23 (s, 3H), 4.04 (dd, J= 11.2, 6.4 Hz, 1H), 4.23 (dd, J=5.2, 1.2 Hz, 2H), 4.31 (d of d, J=16.0, 4.8 Hz, 1H), 5.83–5.69 (m, 2H), 7.73–7.51 (m, 4H); ^{19}F NMR (MeOD): δ −77.38; HRMS calcd for $C_{14}H_{15}N_3O_2$: [M+H] 258.1164. Found: [M+H] 258.1152.

4.1.12. Ethyl 4-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)-3-oxobutanoate (13). Chloroester **12** (5.0 g, 0.03 mol) was added drop wise to a mixture of Cs_2CO_3 (13 g, 0.04 mol), NaI (50 mg) and **2a** (6 g, 0.04 mol) dissolved/suspended in DMSO (40 mL), and stirred for 3 h at ambient temperature. The reaction was quenched with NH_4Cl solution and the product extracted into EtOAc. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 5.3 g (58%) of **13** as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.33, (t, J=9.6 Hz, 3H), 2.20 (s, 3H), 3.60 (s, 2H), 4.25 (q, J=9.2 Hz, 2H), 4.63 (s, 2H); MS(CI) calcd for $C_9H_{12}N_2O_5$: [M+H] 229. Found: [M+H] 229; Anal. calcd for $C_9H_{12}N_2O_5$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.40; H, 5.46; N, 11.86.

4.1.13. Ethyl 4-(ethanimidoylamino)-3-oxobutanoate (14) and ethyl (2-methyl-1*H*-imidazol-5-yl)acetate (15). Ester **13** (80 mg; 0.35 mmol) was added to 5% Pd–C (10 mg) in EtOH (20 mL) and placed under 40 psi hydrogen gas for 4 h. The reaction mixture was filtered and concentrated at ambient temperature. The residue was chromatographed using reverse phase. Two products were isolated:

Ester **14** was the first component off the column. ^{1}H NMR (MeOD): δ 1.25 (t, J=7.2 Hz, 3H), 2.35 (s, 3H), 3.59

(s, 2H), 4.15 (q, $J=9.6$ Hz, 2H), 4.91 (s, 2H); HRMS calcd for $C_8H_{14}N_2O_3$: 187.1083, found: 187.1064.

Imidazole **15** was the second component off the column. ^{1}H NMR (MeOD): δ 1.24 (t, $J=7.2$ Hz, 3H), 2.35 (s, 3H), 3.58 (s, 2H), 4.14 (q, $J=6.0$ Hz, 2H), 6.70 (s, 1H); HRMS calcd for $C_8H_{12}N_2O_2$: [M+H] 169.0977. Found: [M+H] 169.0933.

Heating converted **14** to **15**.

4.1.14. 4-[(2*E*)-5-Hydroxypent-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (17) and (3*E*)-5-[(3-methyl-1,2,4-oxadiazol-5-yl)oxy]pent-3-en-1-ol (18). Dihydroxy-olefin **16** (109 mg, 1.0 mmol), Ph_3P (262 mg, 1.0 mmol) and **2b** (100 mg, 1.0 mmol) were dissolved in THF (5.0 mL). The reaction mixture was cooled in an ice bath before adding DEAD (174 mg, 1.0 mmol) drop wise. TLC (EtOAc) indicated that **16** was consumed and two new products were present. The reaction mixture was concentrated and chromatographed, eluting with EtOAc/hexane. The first compound to elute was identified as the O-alkylated derivative **18**, 13 mg (7%). ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 2.32 (q, $J=15$ Hz, 2H), 3.68 (t, $J=12.4$ Hz, 2H), 4.15 (dd, $J=6$, 1.2 Hz, 2H), 5.55, (pent. $J=5.6$ Hz, 1H), 5.73, (pent, Hz, $J=8.4$ Hz, 1H); MS(CI) calcd for $C_8H_{12}N_2O_3$: [M+H] 185. Found: [M+H] 185; Anal. calcd for $C_8H_{12}N_2O_3$: C, 36.01; H, 4.03; N, 27.99. Found: C, 35.76; H, 3.99; N, 28.26.

The second product to elute was the N-alkylated derivative **17**, 26 mg (14%). ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H), 2.36 (q, $J=6.4$ Hz, 2H), 3.70 (t, $J=6.0$ Hz, 2H), 4.89 (dd, $J=6.0$, 0.8 Hz, 2H), 5.80 (pent, $J=6.4$ Hz, 1H), 5.94 (pent, $J=7.2$ Hz, 1H); MS(CI) calcd for $C_8H_{12}N_2O_3$: [M+H] 185. Found: [M+H] 185; Anal. calcd for $C_8H_{12}N_2O_3$: C, 36.01; H, 4.03; N, 27.99. Found: C, 36.18; H, 4.14; N, 27.86.

Dihydroxy-olefin **16** (109 mg, 1.0 mmol) and **2b** (100 mg, 1 mol) were dissolved in THF (5.0 mL). Ph_3P–polymer (3.0 mmol/g) (500 mg, 1.5 mmol) was added and the mixture was slowly stirred while adding DEAD (174 mg, 1.0 mmol). The products were identical to the reaction with unbound Ph_3P: O-alkylated 34 mg (18%) of **18**, and N-alkylated 50 mg (27%) of **17**.

4.1.15. 3-(3-Methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)propanal (19). Oxadiazolone **2b** (729 mg, 7.24 mmol) was dissolve in ethanol (15 mL) then combined with acrolein (0.53 mL, 7.24 mmol) and triethylamine (0.10 mL, 0.723 mmol) and stirred for 18 h. The reaction mixture was partitioned between H_2O/EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated producing 1.3 g of **19** (100% crude) as a pale orange oil. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 3.04 (t, $J=6$ Hz, 2H), 3.80 (t, $J=6$ Hz, 2H), 9.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.6, 40.8, 58.6, 95.1, 157.0, 198.9; MS(CI) calcd for $C_6H_8N_2O_3$: [M+H] 157. Found: [M+H] 157.

4.1.16. Ethyl (2*E*)-2-fluoro-5-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)pent-2-enoate (21). Triethylfluorophosphonate (**20**) (52.9 g, 0.218 mol) and LiCl (10.1 g, 0.238 mol) were dissolved in THF (100 mL). DBU (33.2 g, 0.218 mol) was added drop wise over a 20 min. period. After stirring 1 h a deep orange-red color developed, where the mixture was cooled to −78 °C. Aldehyde **19** (31.2 g, 0.199 mol) dissolved in THF (60 mL) was added to the reaction mixture over a 45 min period. The mixture was stirred 4 h at −78 °C then quenched with saturated NH_4Cl solution. After warming to ambient temperature the mixture was diluted with H_2O (100 mL) and the product extracted into EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to yield 47.9 g (98%) of **21** as a dark amber oil. ^{1}H NMR ($CDCl_3$): δ 1.285 (t, $J=6.8$ Hz, 3H), 2.26 (s, 3H), 2.85 (q, $J=6.4$ Hz, 2H), 3.64 (t, $J=7.2$ Hz, 2H), 4.24 (q, $J=7.2$ Hz, 2H), 5.85 (dt, $J=19.6$, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 10.46, 14.21, 24.97, 25.02, 41.10, 41.14, 62.11, 117.01, 117.21, 148.11, 150.70, 156.55, 159.34, 160.46, 160.81; ^{19}F NMR ($CDCl_3$): δ −117.43 (d, $J=20.4$ Hz); MS(CI) calcd for $C_{10}H_{13}FN_2O_4$: [M+H] 245. Found: [M+H] 245.

4.1.17. 4-[(3*E*)-4-Fluoro-5-hydroxypent-3-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (22). Ester **21** (6.2 g, 25.4 mmol) was dissolved in THF (100 mL) and cooled to −5 °C. Red-Al 68% in toluene (8.5 mL, 27.9 mmol) was added drop wise to the cooled solution. The reaction mixture was monitored by TLC every 0.5 h until the starting material was consumed. The reaction was quenched with 75 mL of saturated Rochelle's salt. The product was extracted into CH_2Cl_2 (2×150 mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 2.1 g (41%) of **22** as an oil. ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.43 (q, $J=8.0$ Hz, 2H), 3.62–3.56 (m, 2H), 4.12 (d, $J=20$ Hz, 2H), 5.14–5.05 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 10.66, 14.38, 24.16, 24.25, 42.35, 57.50, 60.63, 103.54, 103.77, 156.55, 159.80, 162.32, 171.46; ^{19}F NMR ($CDCl_3$): δ −106.69 (dd, $J=42.0$, 30.4 Hz); MS(CI) calcd for $C_8H_{11}FN_2O_3$: [M+H] 203. Found: [M+H] 203; Anal. calcd for $C_8H_{11}FN_2O_3\cdot 0.1\,H_2O$: C, 47.10; H, 5.53; N, 13.73. Found: C, 46.96; H, 5.41; N, 13.40.

4.1.18. 4-[(3*E*)-5-Bromo-4-fluoropent-3-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (23). Alcohol **22** (800 mg, 3.98 mmol) and CBr_4 (3.28 g, 9.9 mmol) were dissolved in CH_2Cl_2 and cooled to −5 °C. Ph_3P–polymer (3.0 mmol/g) (3.98 g, 12.0 mmol) was added to the reaction mixture and stirred for 18 h. The reaction mixture was filtered and concentrated. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 600 mg (57%) of **23** as an oil. ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H), 2.46 (q, $J=12.0$ Hz, 2H), 3.68 (t, $J=6.8$ Hz, 2H), 4.10 (d, $J=22.8$ Hz, 2H), 5.35–5.26 (m, 1H);); ^{13}C NMR ($CDCl_3$): δ 10.67, 25.13, 27.85, 31.97, 41.66, 41.92, 105.47, 105.70, 156.25, 169.32; ^{19}F NMR ($CDCl_3$): δ −105.27 (dd, $J=44.0$, 22.4 Hz); MS(CI) calcd for $C_8H_{10}BrFN_2O_2$: [M+H] 265 and 267. Found: [M+H] 265 and 267; Anal. calcd for $C_8H_{10}BrFN_2O_2\cdot 0.05$ EtOAc: C, 36.55; H, 3.89; N, 10.40; F, 7.05; Br, 29.65. Found: C, 36.92; H, 3.89; N, 10.35; F, 6.69: Br, 29.75.

4.1.19. Ethyl (2*E*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluoropent-2-enoate (25a) and ethyl (2*Z*)-5-{[*tert*-butyl-(dimethyl)silyl]oxy}-2-fluoropent-2-enoate (25b). NaH (60% suspension in mineral oil) (1.7 g, 72.0 mmol) was

washed with hexane to remove the mineral oil, toluene (200 mL), **20** (17.2 g, 71.0 mmol) and **24**[8] (13.2 g; 0.07 mol) dissolved in toluene (50 mL) was reacted at 0 °C as described for Compound **21** to yield 5.9 g (30.5%) of **25a**. ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 1.33 (t, J=7.2 Hz, 3H), 2.75–2.69 (m, 2H), 3.68 (dt, J=0.8, 6.0 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 6.19 (dt, J=33.6, 7.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −121.67 (d, J=23.2 Hz); MS(CI) calcd for $C_{13}H_{25}O_3FSi$: [M+H] 277. Found: [M+H] 277.

A minor component was isolated and purified and identified as **25b** the *Z*-isomer: ^{1}H NMR ($CDCl_3$): δ 0.037 (s, 6H), 0.87 (s, 9H), 1.330 (t, J=7.2 Hz, 3H), 2.47–2.42 (m, 2H), 3.68 (dt, J=0.8, 8.0 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 6.00 (dt, J=21.2, 8.0 Hz, 1H). ^{19}F NMR ($CDCl_3$): δ −129.79 (d, J=33.2 Hz); MS(CI) calcd for $C_{13}H_{25}O_3FSi$: [M+H] 277. Found: [M+H] 277.

4.1.20. (2*E*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-fluoropent-2-en-1-ol (26). Ester **25a** (6.0 g, 21.7 mmol) dissolved in THF (70 mL), Red-Al 68% in toluene (9.2 mL, 30.0 mmol) was reacted at −5 °C as described for Compound **22** to yield 4.0 g (79%) of **26**. ^{1}H NMR ($CDCl_3$): δ 0.04 (s, 6H), 0.87 (s, 9H), 2.29–2.21 (m, 3H, 1 exchangeable), 3.63 (dt, J=1.2, 8.0 Hz, 2H), 4.20 (d, J=26.0 Hz, 2H), 5.20 (dt, J=26.0, 12.0 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −109.63 (q, 28.4 Hz); MS(CI) calcd for $C_{11}H_{23}FO_2Si$: [M+H] 235. Found: [M+H] 235; Anal. calcd for $C_{11}H_{23}FO_2Si$: C, 56.37; H, 9.89. Found: C, 56.38; H, 10.19.

4.1.21. (2*E*)-2-Fluoropent-2-ene-1,5-diol (27). Alcohol **26** (131.0 g, 0.56 mol) was dissolved in EtOH (1.5 l) and concn HCl (15 mL) was added and the mixture was stirred for 0.25 h. TLC (20% EtOAc/hexane) indicated that the starting material was consumed. The mixture was concentrated and the residue was azeotroped twice with toluene (500 mL) to produce 71.8 g (100% crude) of **27** as an oil. ^{1}H NMR ($CDCl_3$): δ 2.30–2.23 (m, 2H), 3.64 (dt, J=0.8, 8.0 Hz, 2H), 4.18 (d, J=29.6 Hz, 2H), 5.21 (dt, J=27.0, 11.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ−108.16 (q, J=30.8 Hz); MS(CI) calcd for $C_5H_9O_2F$: [M+H] 121. Found: [M+H] 121.

4.1.22. (2*E*)-2-Fluoro-5-[(methylsulfonyl)oxy]pent-2-enyl methanesulfonate (28). Dihydroxyolefin **27** (71.8 g, 0.56 mol) and Et_3N (141.4 g/195 mL, 1.4 mol) were dissolved in CH_2Cl_2 (1.0 l) and cooled in an ice bath. Ms_2O (243.4 g, 1.4 mol) was dissolved in CH_2Cl_2 (0.5 l) and added drop wise. The reaction mixture was stirred 15 min when TLC (60% EtOAc/hexane) indicated that the starting material was consumed. The reaction mixture was partitioned between H_2O/CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated to yield 164.9 g (100% crude) of **28** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.55 (q, J=10.0 Hz, 2H), 3.02 (s, 3H), 3.07 (s, 3H), 4.25 (dt, J=1.2, 8.4 Hz, 2H), 4.82 (d, J=27.6 Hz, 2H), 5.50 (dt, J=24.8, 11.2 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −107.91 (q, J=27.2 Hz); MS(CI) calcd for $C_7H_{13}O_6S_2F$: [M+NH_4] 294. Found: [M+NH_4] 294.

4.1.23. (3*E*)-4-Fluoro-5-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)pent-3-enyl methanesulfonate (29). Dimesylate **28** (164.9 g, 0.55 mol) dissolved in MEK (0.6 l) was added to a slurry of **2a** (84.8 g, 0.61 mol) in MEK (0.6 l) and heated at reflux 6.0 h where TLC (60% EtOAc/hexane) indicated that **28** was still present. Additional **2a** (17 g) was added and the mixture was stirred at reflux for an additional 2.0 h at which time the starting material was consumed. The reaction mixture was cooled and filtered and the solid washed with MEK. The filtrate was concentrated to yield 204 g (100% crude) of **29** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 2.63 (q, J=6.4 Hz, 2H), 3.01 (s, 3H), 4.26 (dt, J=0.8, 6.4 Hz, 2H), 4.31 (d, J=19.6 Hz, 2H), 5.409 (dt, J=19.6, 8.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −106.89 (q, J=21.2 Hz); MS(CI) calcd for $C_9H_{13}N_2O_5SF$: [M+H] 281. Found: [M+H] 281.

4.1.24. 4-[(2*E*)-2-Fluoro-5-iodopent-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (30). Mesylate **29** (204.8 g, 0.56 mol) was dissolved in MEK (1.2 l) and solid NaI (167 g, 1.12 mol) was added to the mixture and stirred 18 h at which time TLC (60% EtOAc/hexane) indicated that the starting material was consumed. The reaction mixture was partitioned between an equal volume of H_2O and the aqueous layer was washed with Et_2O then CH_2Cl_2 (500 mL each). The combined organic layers were washed with 1% $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica, eluting with EtOAc/hexane to yield 87.4 g (50%) of **30** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H), 2.74 (q, J=7.2 Hz, 2H), 3.20 (dt, J=0.8, 6.8 Hz, 2H), 4.31 (d, J=19.6 Hz, 2H), 5.39 (dt, J=19.6, 8.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −108.31 (q, J=21.2 Hz); MS(CI) calcd for $C_8H_{10}FIN_2O_2$: [M+H] 313. Found: [M+H] 313; Anal. calcd for $C_8H_{10}FIN_2O_2$; C, 30.79; H, 3.23; N, 8.98; I, 40.66. Found: C, 30.75; H, 2.99; N, 8.92; I, 40.41.

4.1.25. Ethyl (2*E*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluorobut-2-enoate (32a) and ethyl (2*Z*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluorobut-2-enoate (32b). NaH (60% suspension in mineral oil) (3.9 g, 0.10 mol), THF (300 mL), **20** (25 g, 0.10 mol) and **31**[9] (17.4 g; 0.1 mol) was reacted at 0 °C as described for Compound **21** to yield 8.9 g (34%) of **32a**. ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 1.25 (t, J=7.2 Hz, 3H), 4.28 (q, J=7.2 Hz, 2H), 4.64 (dd, J=3.6, 5.6 Hz, 2H), 6.01 (dt, J=19.6, 5.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −123.95 (dt, J=20.8, 3.2 Hz); MS(CI) calcd for $C_{12}H_{23}O_3FSi$: [M+H] 263. Found: [M+H] 263.

A minor component was isolated and purified and identified as the *Z*-isomer **32b**: ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 1.25 (t, J=7.2 Hz, 3H), 4.28 (q, J=7.2 Hz, 2H), 4.41 (dd, J=6.4, 1.2 Hz, 2H), 6.19 (dt, J=33.6, 6.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −127.28 (dt, J=35.2, 3.6 Hz); MS (CI) calcd for $C_{12}H_{23}O_3FSi$: [M+H] 263. Found: [M+H] 263.

4.1.26. (2*E*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-fluorobut-2-en-1-ol (33). Ester **32a** (8.7 g, 33.0 mmol) was dissolved in THF (100 mL) and cooled in an ice bath. $LiBH_4$ 2.0 M in THF (33 mL, 66.0 mmol) was added and the mixture stored at −40 °C for 18 h. The reaction was quenched with H_2O. A solid formed which was filtered and washed with THF. The filtrate was concentrated and chromatographed over silica, eluting with EtOAc/hexane to yield 4.5 g (62%) of **33**. ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H),

0.88 (s, 9H), 4.20 (dd, J=6.8, 2.4 Hz, 2H), 4.24 (d, J=19.6 Hz, 2H), 5.38 (dt, J=20.4, 7.2 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −109.28 (q, J=22.0 Hz); MS(CI) calcd for $C_{10}H_{21}O_2FSi$: [M+H] 221. Found: [M+H] 221; Anal. calcd for $C_{10}H_{21}O_2FSi$: C, 54.51; H, 9.61. Found: C, 54.44; H, 9.78.

4.1.27. 4-((2*E*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-fluorobut-2-enyl)-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (34). Alcohol **33** (25.5 g, 0.115 mol), **2b** (11.3 g, 0.1 mol) and triphenylphosphine (29.7 g, 0.11 mol) were dissolved in THF (500 mL) and cooled in an ice bath. DEAD (19.1 g/17.3 mL, 0.11 mol) was added drop wise to the reaction mixture. The reaction progress was monitored by TLC (60% EtOAc/hexane). When **33** was consumed the reaction mixture was concentrated and the residue triturated with Et_2O. The filtrate was concentrated and chromatographed over silica, eluting with EtOAc/hexane to yield 10.4 g (31%) of **34**. ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H), 0.88 (s, 9H), 2.28 (s, 3H), 4.31 (dd, J=6.4, 2.8 Hz, 2H), 4.44 (d, J=19.2 Hz, 2H), 5.53 (dt, J=20.0, 6.4 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −109.06 (q, J=20.8 Hz); MS(CI) calcd for $C_{13}H_{23}N_2O_3FSi$: [M+H] 303. Found: [M+H] 303; Anal calcd for $C_{13}H_{23}N_2O_3FSi$: C, 51.63; H, 7.67; N, 9.26. Found: C, 51.84; H, 7.82; N, 8.95.

4.1.28. 4-[(2*E*)-2-Fluoro-4-hydroxybut-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (35). Oxadiazolone **34** (10.4 g, 34.0 mmol) was dissolved in EtOH (100 mL) and concn HCl (1.0 mL) was added and the mixture stirred for 1 h. TLC (60% EtOAc/hexane) indicated that **34** was consumed. The mixture was concentrated to dryness to yield 6.9 g (100% crude) of **35**. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 4.25 (dd, J=6.8, 2.8 Hz, 2H), 4.44 (d, J=21.2 Hz, 2H), 5.65 (dt, J=20.0, 7.2 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −107.88 (q, J=21.6 Hz); MS(CI) calcd for $C_7H_9FN_2O_3$: [M+H] 189. Found: [M+H] 189.

4.1.29. (2*E*)-3-Fluoro-4-(3-methyl-5-oxo-1,2,4-oxadiazol-4(5*H*)-yl)but-2-enyl methanesulfonate (36). Alcohol **35** (6.9 g, 34.0 mmol) and Et_3N (4.0 g/5.5 mL, 40.0 mmol) were dissolved in CH_2Cl_2 (100 mL). Ms_2O (6.9 g, 40.0 mol) was added drop wise 30 min. TLC (60% EtOAc/hexane) indicated that **35** was consumed. The reaction mixture was poured into H_2O and the layers separated. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to yield 8.3 g (92%) of **36** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.06 (s, 3H), 4.42 (d, J=20.0 Hz, 2H), 4.92 (dd, J=8.0, 1.2 Hz, 2H), 5.67 (dt, J=8.7, 8.0 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −101.10 (q, J=19.6 Hz); MS(CI) calcd for $C_8H_{11}FN_2O_5S$: [M+H] 267. Found: [M+H] 267; Anal. calcd for $C_8H_{11}FN_2O_5S$: C, 36.09; H, 4.16; N, 10.52. Found: C, 36.43; H, 4.06; N, 10.41.

4.1.30. 4-[(2*E*)-2-Fluoro-4-iodobut-2-enyl]-3-methyl-1,2,4-oxadiazol-5(4*H*)-one (37). Mesylate **36** (8.3 g, 32.0 mmol) and NaI (9.8 g, 65.0 mmol) were stirred for 30 min in MEK. TLC (40% EtOAc/hexane) indicated that **36** was consumed. The reaction mixture was partitioned between Et_2O/H_2O. The aqueous layer was washed with Et_2O and the combined organic layers were washed with 1% $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated. Chromatographed over silica eluting with EtOAc/hexane to yield 4.5 g (47%) of **37** as a crystalline solid. ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.98 (dd, J=9.6, 0.8 Hz, 2H), 4.34 (d, J=19.6 Hz, 2H), 5.78 (dt, J=16.8, 7.6 Hz, 1H); ^{19}F NMR ($CDCl_3$): δ−106.08 (q, J=19.2 Hz); MS(CI) calcd for $C_7H_8FIN_2O_2$: [M+H] 299. Found: [M+H] 299; Anal. calcd for $C_7H_8FIN_2O_2$: C, 28.21; H, 2.71; N, 9.40. Found: C, 28.36; H, 3.04; N, 9.37.

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Synthesis of new unsymmetrical optically active (*s*)-(+)-naproxen dendrimers

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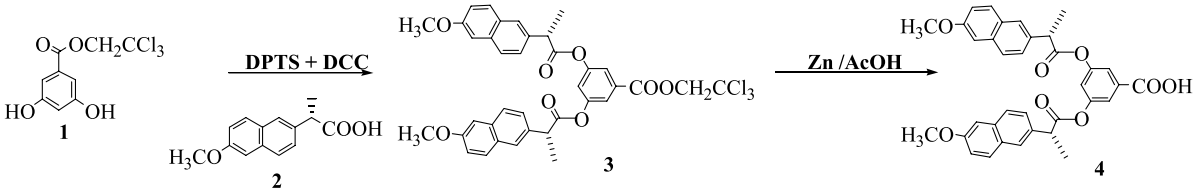
Abstract—Preparation of new unsymmetrical optically active (*s*)-(+)-naproxen dendrimers containing 2-hydroxymethyl-1,4-butanediol and 2,2-bis(hydroxymethyl)-1,4-butanediol cores is described. These polyarylester dendrimers are unsymmetrical with respect to chain lengths and aid in studying controlled drug delivery based on differential enzymatic cleavage. Synthesis of a new acid dendritic wedge containing (*s*)-(+)-naproxen is also reported.

1. Introduction

Dendrimers are macromolecules with well-defined and perfectly branched architecture, synthesized in an iterative sequence of reactions.[1–5] Unprecedented control over structural unit positioning renders these materials a wide range of applications in the areas of drug delivery, catalysis, nanostructured materials, liquid crystals, electrochemical devices, and adhesives.[6–12] Typically, dendrimers with a combination of a discrete number of functionalities in one molecule and with high densities of local active groups have attracted a lot of attention from medicinal chemists.[13] The low polydispersity provided by dendritic systems has favored their use in biomedical applications because of reproducible pharmacokinetic behavior.[14]

Owing to the advantages of dendritic therapeutics[15–21] and the promising characteristics of novel polyarylester dendrimers[22] in our initial in vitro studies, we were inspired to undertake a systematic study by introducing optically active drug molecules on the periphery of unsymmetrical dendrimers. Dendrimers built on unsymmetric cores by virtue of their unequal chain lengths are likely to get hydrolyzed by the enzymes at different rates. The differential rates of hydrolysis would release the dendrimer bound drugs gradually, thus sustaining the availability of the drug for longer periods. In addition, ester bonds are characterized by their susceptibility to hydrolysis, an attractive feature for biodegradable systems.

From the academic standpoint, study of chiral dendrimers should enable insights upon the impact of chirality on the topology of the macromolecular system in particular and molecular chirality in general. As a part of our program directed towards the development of efficient synthetic procedures for the preparation[23,24] and application of dendritic macromolecules for sustained drug release and catalysis,[23] we have given considerable attention to extending the studies to the synthesis of chiral dendrimers. Therefore, we now report the synthesis of unsymmetrical



Scheme 1.

Keywords: Dendrimers; Convergent approach; Dendritic wedge; Unsymmetrical; Polyaryl ester; Trichloroethyl protection.
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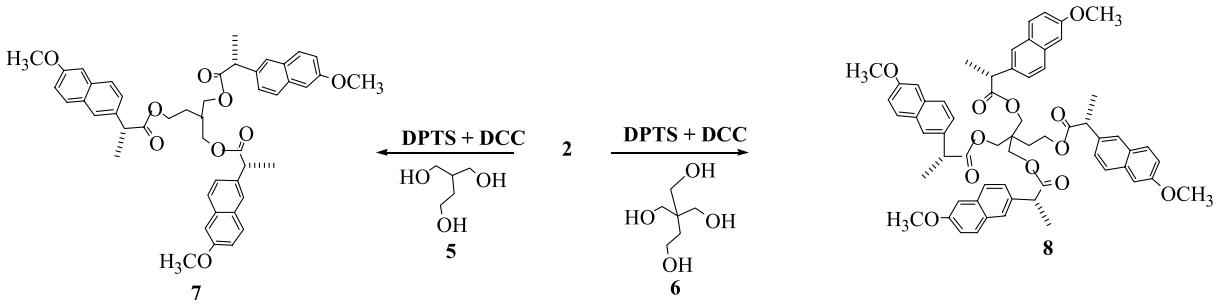


Scheme 2.

polyester dendritic scaffolds with a non-steroidal anti-inflammatory, analgesic and antipyretic drug, *s*-(+)-naproxen, on the periphery.

2. Results and discussion

By implementing a convergent approach, synthesis of new optically active naproxen dendrimers based on 2-hydroxymethyl-1,4-butanediol (**5**) and 2,2-bis(hydroxymethyl)-1,4-butanediol (**6**) was accomplished.[23,24] To begin the synthesis, 2,2,2-trichloroethyl-3,5-dihydroxybenzoate (**1**) was condensed with *s*-(+)-naproxen (**2**) using DPTS/DCC to afford the G1-ester dendritic wedge (**3**) in 68% yield (Scheme 1). The trichloroethylester of (**3**) was then removed selectively in the presence of other ester groups using zinc and acetic acid to provide the acid wedge (**4**) in 93% yield. Surprisingly, coupling of two relatively small dendrons (**4**) and bisphenol (**1**) to prepare higher generation wedges was difficult to achieve in good yields and purity.

In order to facilitate the assignments of ^{1}H NMR and ^{13}C NMR δ values in the complex dendritic structures, *s*-(+)-naproxen was reacted with triol (**5**) and tetrol (**6**) in the presence of DPTS/DCC to give the first generation dendrimers (**7**) and (**8**) in 63 and 60% yields, respectively (Scheme 2).

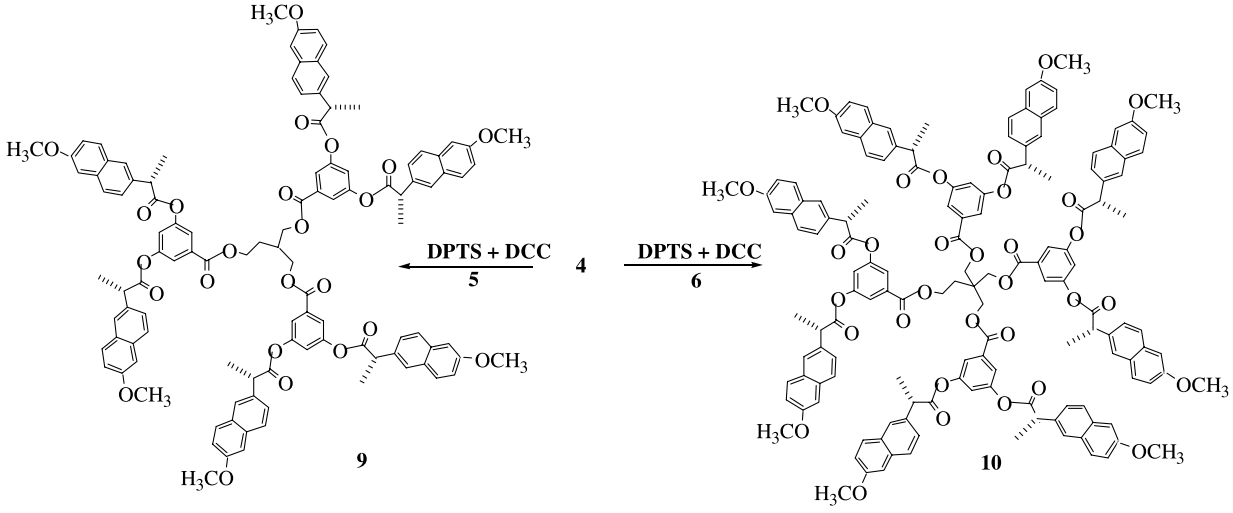
To prepare the second-generation dendrimers, the focal point acid of the convergent dendron (**4**) was reacted with the cores (**5**) and (**6**) using DPTS/DCC to give dendrimers (**9**) and (**10**) in 65 and 66% yields, respectively (Scheme 3).

In the absence of higher generation dendritic wedge, an alternative strategy was used in the preparation of third generation dendrimers (**13**) and (**14**). To achieve this, compounds (**11**) and (**12**), previously reported by us,[22] derived from the cores (**5**) and (**6**) were employed.

Accordingly, the phenolic intermediates **11** and **12** were reacted with acid dendron (**4**) in the presence of DCC/DPTS to give third-generation dendrimers **13** and **14** in 20 and 14% yields, respectively (Scheme 4).

Low yields of dendrimers **13** and **14** may be assumed to be originating from some kind of intramolecular trans-esterification reactions occurring since the reactions were performed for extended periods of time (6 days). A large number of other minor products at various stages of esterification were isolated predominantly as mixtures. In addition, compounds having relatively higher R_f values when compared to the required product were also observed. A remarkable aspect of the present work is the use of phenolic cores that are more reactive when compared to the aliphatic cores.

The present study corroborates our previous work,[22] that steric crowding could be circumvented by a fine combination of convergent approach with a little divergent synthesis. This strategy particularly helped us in achieving

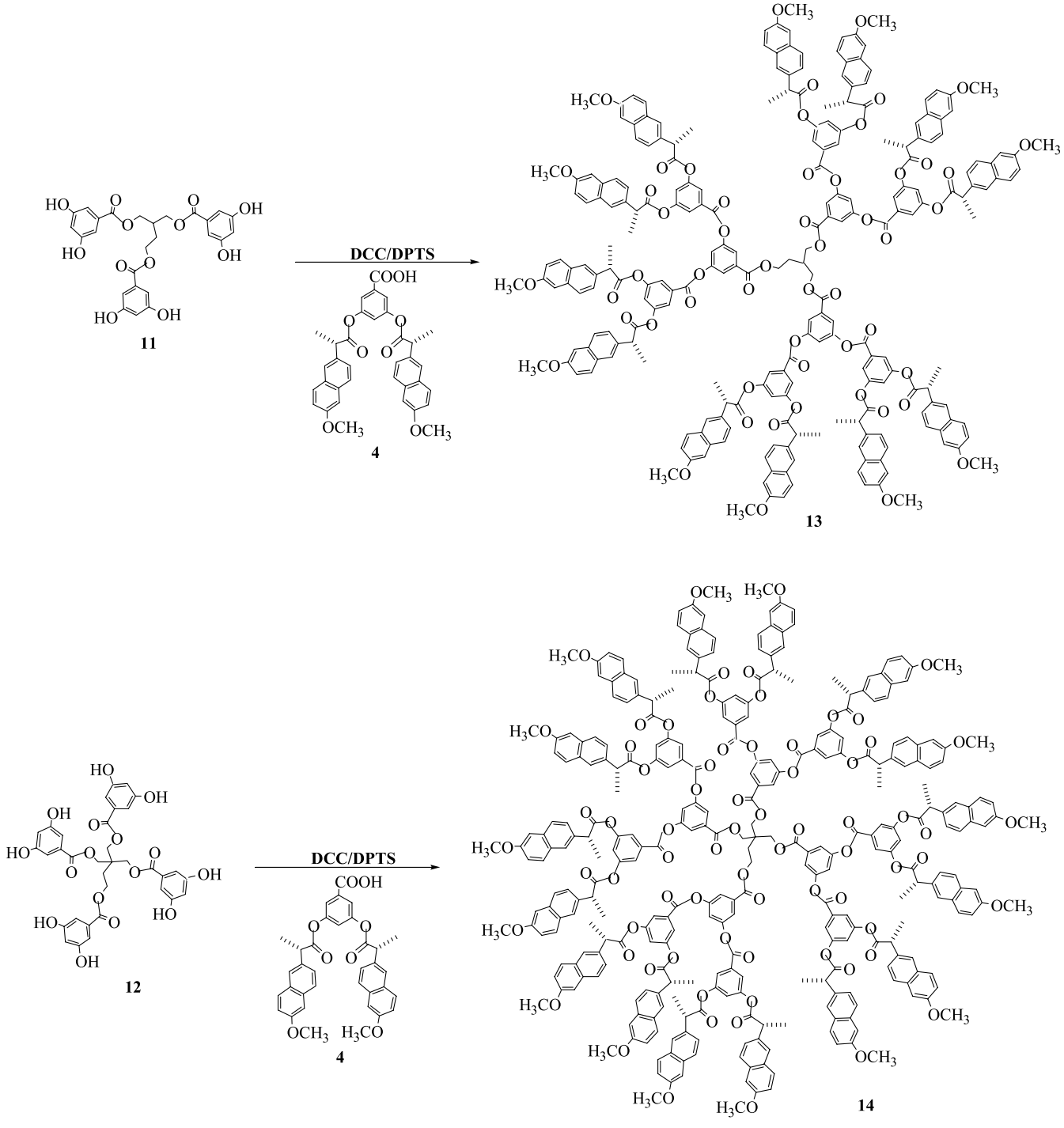


Scheme 3.

the synthesis of higher molecular weight dendrimers of third generation.

Characterization of the ester dendrimers was performed using a combination of ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry techniques. The large R_f difference between the partially and completely reacted alcoholic/phenolic groups of the core facilitated easy purification of the dendrimers. To establish the extent of reaction and the generation number from the ^{1}H NMR spectra, the integration of resonances due to ethereal hydrogens of the core (δ: 4.4) was compared with the methoxy hydrogens (δ: 3.8). Furthermore, the discrete resonances arising from aromatic and benzylic hydrogens were invaluable in detecting impurities and defects. MS techniques (FAB and MALDI) in combination with elemental analysis and NMR were used to establish the molecular weight and purity of the dendritic wedges and dendrimers.

Chiroptical property studies of the dendrimers were performed using the protocol reported by Lartigue et al.[25] The specific rotation values of higher generation dendrimers were similar (Fig. 1). On the other hand, molar rotation



Scheme 4.

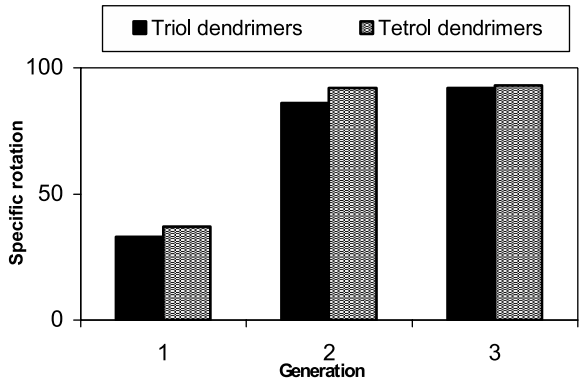


Figure 1.

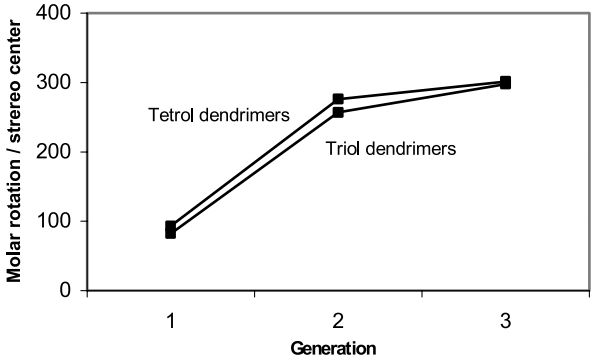


Figure 2.

increased with generation number and multiplicity of functional groups (Fig. 2). However, by dividing the molar rotation values with the number of stereogenic units, the optical rotations of higher generation dendrimers remained just about constant (Fig. 3). These observations suggest that the peripheral naproxen groups appear not to interact with each other and are conformationally more flexible for direct interaction with enzymes. In contrast, the first generation dendrimers showed lower specific rotations when compared to *s*-(+) naproxen. This discrepancy may be attributed to back folding of peripheral groups towards the core thus resulting in some kind of internal compensation. However, in the absence of molecular modeling studies the justification presented here is an assumption. To explain the topology and conformational flexibility of the dendrimers possessing chiral peripheral surface groups, some researchers[26–30] have used this kind of justification based on optical rotation.

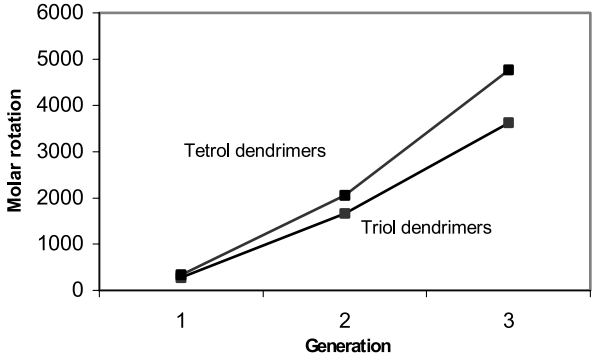


Figure 3.

3. Conclusion

The requirement for controlled drug release based on differential rates of hydrolysis has inspired the design and preparation of the chiral dendrimers having (*s*)-(+)-naproxen groups on the periphery. In vitro enzymatic hydrolysis of our dendrimers has shown some promising results. Furthermore, biological evaluation of these dendrimers with emphasis on biocompatibility of the by-products of hydrolysis will follow. Nonetheless, the dendritic systems exemplified in this paper seem to have immense potential due to their polyvalency and well-defined structures. From the synthetic standpoint, the new dendritic wedges and the route presented here demonstrate feasibility for the introduction of other diverse biodegradable polyesters and other drug molecules.

4. Experimental

4.1. General directions

^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on Varian FT (Gemini) instrument, using tetramethyl silane (TMS) as the internal standard. The chemical shifts are expressed in δ scale. The abbreviations such as s, d, t, m, b refers to singlet, doublet, triplet, multiplet and broad, respectively. The trisubstituted benzene and napthyl rings are abbreviated as Ar and Naph, respectively. Mass spectra were recorded on VG Micromass 7070 H (EI), Autospec (FAB), and Kratos Kompact SEQ (MALDI-TOF). Optical rotations were measured on JASCO DIP-370 digital polarimeter. Elemental analysis was recorded on a Perkin–Elmer 240C-CHN analyzer. The melting points reported are uncorrected and were determined using Buchi 525 instrument. Solvents were purified and dried before use. Completion of the reaction and purity of the synthesized compounds were checked by TLC performed on silica gel (acmes) plates, using iodine and H_2SO_4 for visualizing the spots.

4.1.1. 2,2,2-Trichlorethyl-3,5-di[1-(6-methoxy-2-naphthyl) ethyl carbonyloxy]benzoate (3). To a solution of (*s*)-(+)-naproxen (**2**) (15.60 g, 0.067 mol), 2,2,2-trichloroethyl-3,5-dihydroxy benzoate (**1**) (6.44 g, 0.022 mol) in dry dichloromethane (50 ml) was added 4-(dimethylamino)-pyridinium *p*-toluenesulphonate (DPTS) (1.32 g, 0.004 mol). The contents were stirred at 25 °C for 15 min under nitrogen atmosphere. Dicyclohexylcarbodiimide (DCC) (13.96 g, 0.067 mol) was then added and stirring continued at room temperature for 24 h, during this time a precipitate of dicyclohexyl urea appeared. The reaction mixture filtered and the filtrate evaporated to dryness under reduced pressure, the crude product was column chromatographed (SiO_2) eluting with initially hexane and then a mixture of EtOAc/hexane (4:1) gave **3** (10.9 g) as a white solid in 68% yield. Mp 108–110 °C. ^{1}H NMR ($CDCl_3$) δ: 1.68 (d, 6H, J=7.0 Hz; 2×CH_3CH), 3.90 (s, 6H, 2×OCH_3), 4.05 (q, 2H, J=7.0 Hz, 2×C*H*CH$_3$), 4.89 (s, 2H,

CH_2CCl_3), and 6.98–7.75 (m, 15H: 3×Ar*H*, 2×Naph*H*). ^{13}C NMR ($CDCl_3$) δ: 18.39, 45.49, 55.30, 74.54, 76.38, 105.70, 119.17, 120.45, 120.74, 125.93, 126.13, 127.90, 128.99, 129.30, 130.59, 133.90, 134.52, 151.30, 157.86, 163.42, and 172.41. MS (FAB); *m*-nitrobenzylalcohol (matrix); *m/z* (%): 710 (M^+, 61), 663 (41), 307 (100). Anal. Calcd for $C_{37}H_{31}O_8Cl_3$: C, 62.59; H, 4.40. Found: C, 62.5; H, 4.36. $[\alpha]_D^{25} = +45.6$ (*c* 1.0, $CHCl_3$).

4.1.2. 3,5-Di[(1-(6-methoxy-2-naphthyl)ethylcarbonyloxy)] benzoic acid (4). To a solution of (**3**) (3.0 g, 4.22 mmol) in THF (25 ml) was added glacial acetic acid (5 ml) and the solution was stirred at room temperature for 15 min under nitrogen atmosphere. Zinc dust (0.780 g, 0.012 mol) was then added and the contents were stirred vigorously at room temperature for 2 h. The reaction mixture was filtered and the filtrate poured into water (100 ml) and extracted with diethyl ether (2×100 ml). The combined extracts were washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was column chromatographed (SiO_2) eluting with initially benzene and then chloroform to give **4** and it was further purified by recrystallization from benzene as a white solid (2.27 g) in 93% yield. Mp 104–106 °C. ^{1}H NMR ($CDCl_3$) δ: 1.68 (d, 6H, J=7.0 Hz, 2×C*H*$_3$CH), 3.90 (s, 6H, 2×OC*H*$_3$), 4.06 (q, 2H, J=7.0 Hz, 2×C*H*CH$_3$), and 6.98–7.75 (br m, 15H: 3×Ar*H*, 2×Naph*H*). ^{13}C NMR ($CDCl_3$) δ: 18.34, 45.45, 55.22, 105.74, 119.06, 120.53, 125.90, 126.12, 127.44, 128.25, 128.97, 129.27, 131.19, 133.87, 134.51, 151.16, 157.79, 169.78, and 172.38. MS (FAB); *m*-nitrobenzylalcohol (matrix); *m/z*: 578 (M^+, 16), 212 (4), 185 (100). Anal. Calcd for $C_{35}H_{30}O_8$: C, 72.65; H, 5.23. Found C, 72.60; H, 5.19. $[\alpha]_D^{25} = +97.5$ (*c* 1.0, $CHCl_3$).

4.2. General procedure

4.2.1. First generation dendrimer (7). The title compound was prepared from triol (**5**) (400 mg, 3.3 mmol) and (*s*)-(+)-naproxen (**2**) (3.05 g, 13.2 mmol), DPTS (194 mg, 660 μmol), and DCC (2.74 g, 13.3 mmol) following the procedure as described for compound **3**. After 24 h, the crude product was column chromatographed (SiO_2), eluting with initially chloroform and then a mixture of EtOAC/$CHCl_3$ (1:9) to give **7** (1.57 g) as a white solid in 63% yield. Mp 166–170 °C. ^{1}H NMR ($CDCl_3$) δ: 1.34 (q, 2H, J=4.7 Hz, CHC*H*$_2$), 1.49 (d, 9H, J=7.0 Hz, 3×C*H*$_3$CH), 1.81 (m, 1H, C*H*CH$_2$), 3.70 (m, 3H, 3×C*H*CH$_3$), 3.80–3.92 [(m, 15H: 6H, 3×C*H*$_2$O; 9H, 3×OC*H*$_3$)], and 7.02–7.68 (m, 18H, 3×Naph*H*). ^{13}C NMR ($CDCl_3$) δ: 18.12, 27.17, 34.65, 45.28, 55.16, 62.03, 63.73, 63.85, 105.62, 118.58, 125.82, 126.03, 127.06, 128.84, 129.16, 133.63, 135.35, 157.61, 174.10, and 174.21. MS (FAB); *m*-nitrobenzylalcohol (matrix); *m/z*: (%): 779 [$(M+23)^+$, 4], 756 (M^+, 16), 185 (100). Anal. Calcd for $C_{47}H_{48}O_9$: C, 74.58; H, 6.39. Found: C, 74.53; H, 6.30. $[\alpha]_D^{25} = +37.5$ (*c* 1.0, $CHCl_3$).

4.2.2. First generation dendrimer (8). This compound was prepared from 2,2-bis(hydroxymethyl)-1,4-butanediol (**6**) (0.150 g, 1.0 mmol), *s*-(+)-naproxen (**2**) (1.150 g, 5.0 mmol), DPTS (0.058 g, 0.2 mmol) and DCC (1.030 g, 5.0 mmol) by following the above general procedure. After 24 h, the crude product was column chromatographed (SiO_2) eluting with initially hexane and then benzene to give **8** (0.60 g) as a white solid in 60% yields. Mp 124–126 °C. ^{1}H NMR ($CDCl_3$) δ: 1.23 (br s, 2H, CC*H*$_2$), 1.40 (dd, 12H, J=7.0, 7.0 Hz, 4×C*H*$_3$CH), 3.48–3.72 [m, 12H: (8H, 4×C*H*$_2$O), (4H, 4×C*H*CH$_3$)], 3.84 (two s, 12H, 4×OC*H*$_3$), and 6.69–7.60 (m, 24H, 4×Naph*H*). ^{13}C NMR ($CDCl_3$) δ: 17.79, 18.16, 29.33, 40.55, 45.16, 55.09, 60.13, 63.85, 105.54, 118.87, 125.82, 125.89, 126.00, 127.08, 128.75, 129.16, 133.60, 135.03, 135.31, 157.56, 173.56, and 173.98. MS (FAB); *m*-nitrobenzyl alcohol (matrix); *m/z* (%): 1022 [$(M+23)^+$, 8], 999 (M^+, 52), 307 (100). Anal. Calcd for $C_{62}H_{62}O_{12}$: C, 74.53; H, 6.25. Found: C, 74.58; H, 6.19. $[\alpha]_D^{25} = +33.6$ (*c* 1.0, $CHCl_3$).

4.2.3. Second generation dendrimer (9). The title compound was prepared from triol (**5**) (0.050 g, 0.41 mmol), G1-acid wedge (**4**) (0.963 g, 1.6 mmol), DPTS (0.024 g, 0.08 mmol) and DCC (0.343 g, 1.6 mmol) by following the above general procedure. After 84 h, the crude product was column chromatographed (SiO_2) eluting with initially chloroform and then a mixture of EtOAC/$CHCl_3$ (1:19) to give (**9**) (0.493 g) as a white solid in 65% yield. Mp 88–92 °C. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 2H, CHC*H*$_2$), 1.63 (d, 18H, J=7.0, 7.0 Hz, 6×C*H*$_3$CH), 1.80 (m, 1H, C*H*CH$_2$), 3.88 (s, 18H, 6×OC*H*$_3$), 4.03 (m, 6H, 6×C*H*CH$_3$), 4.33 (m, 6H, 3×C*H*$_2$O), and 6.93–7.73 [m, 45H: (9H, 3×Ar*H*), (36H, 6×Naph*H*)]. ^{13}C NMR ($CDCl_3$) δ: 18.37, 29.67, 35.02, 45.43, 55.27, 62.96, 64.68, 105.63, 119.10, 120.01, 120.10, 125.96, 126.15, 127.44, 128.93, 129.28, 131.69, 133.85, 134.57, 151.11, 151.14, 157.78, 164.49, 164.59, and 172.38. MS (MALDI); *m/z* (%): 1842 [$(M+39)^+$, 100], 1825 [$(M+23)^+$, 64], 1802 (M^+, 60). Anal. Calcd for $C_{110}H_{96}O_{24}$: C, 73.32; H 5.37. Found: C, 73.26; H 5.43. $[\alpha]_D^{25} = +92.0$ (*c* 0.4, $CHCl_3$).

4.2.4. Second generation dendrimer (10). The title compound was prepared from tetrol (**6**) (100 mg, 0.66 mmol), G1-acid wedge (**4**) (1.926 g, 3.3 mmol), DPTS (0.034 g, 0.12 mmol) and DCC (0.658 g, 3.2 mmol) by following the general procedure. After 5 days, the crude product was column chromatographed (SiO_2) eluting initially with $CHCl_3$ and then a mixture of EtOAC/$CHCl_3$ (1:19) to give dendrimer (**10**) (1.050 g) in 66% yield as a white solid. Mp 145–149 °C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (s, 2H, CC*H*$_2$), 1.60 (d, 24H, J=7.0 Hz, 8×C*H*$_3$CH), 3.83 (two s, 24H, 8×OC*H*$_3$), 3.98 (q, 8H, J=7.0 Hz, 8×C*H*CH$_3$), 4.20 (s, 6H, 3×C*H*$_2$O), 4.30 (br s, 2H, C*H*$_2$O), and 6.85–7.65 [m, 60H: (12H, 4×Ar*H*; 48H, 8×Naph*H*]. ^{13}C NMR ($CDCl_3$) δ: 18.33, 29.68, 41.17, 45.44, 55.25, 61.95, 64.68, 105.69, 119.06, 119.97, 120.30, 121.01, 125.98, 126.16, 127.43, 128.96, 129.28, 131.27, 133.86, 134.60, 151.12, 151.22, 157.77, 164.12, and 172.29. MS (MALDI); *m/z* (%): 2432 [$(M+39)^+$, 26], 2416 [$(M+23)^+$, 44], 2393 (M^+, 100). Anal. Calcd for $C_{146}H_{126}O_{32}$: C, 73.29; H, 5.31. Found C, 73.19; H, 5.41. $[\alpha]_D^{25} = +86.0$ (*c* 1.0, $CHCl_3$).

4.2.5. Third generation dendrimer (13). The title compound was prepared from (**11**) (100 mg, 189 μmol), acid wedge (**4**) (0.875 g, 1.514 mmol), DPTS (0.11 mg, 37 μmol) and DCC (311 mg, 1.514 mmol) by following the general procedure. After 6 days, the crude product was column chromatographed (SiO_2) eluting with initially

$CHCl_3$ and then a mixture of EtOAC/$CHCl_3$ (1:19) to give **13** (0.150 g) as white solid in 20% yield. Mp 83–86 °C. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 2H, $CHCH_2$), 1.65 (d, 37H, J= 7.0 Hz, 12×CH_3CH, $CHCH_2$), 3.85 (s, 36H, 12×OCH_3), 4.02 (m, 12H, 12×$CHCH_3$), 4.48 (m, 6H, 3×CH_2O), and 7.00–7.70 [m, 99H: (27H, 9×Ar*H*); (72H, 12×Naph*H*)]. ^{13}C NMR ($CDCl_3$) δ: 18.40, 24.48, 32.26, 45.47, 55.26, 63.86, 65.89, 105.70, 119.12, 120.18, 120.35, 120.46, 120.66, 125.92, 126.18, 127.49, 128.96, 129.28, 130.76, 132.05, 133.89, 134.51, 150.90, 151.29, 157.82, 162.69, 164.38, and 172.34. MS (MALDI); *m*/*z* (%): 3892 (M^+, 7). Anal. Calcd for: $C_{236}H_{192}O_{54}$. C, 72.83; H, 4.97. Found: C, 72.63; H, 5.01. $[\alpha]_D^{25} = +93.0$ (*c* 1.0, $CHCl_3$).

4.2.6. Third generation dendrimer (14). The title compound was prepared from (**12**) (100 mg, 144 μmol), acid wedge (**4**) (0.832 g, 1.44 mmol), DPTS (0.008 g, 0.028 mmol) and DCC (0.296 g, 1.44 mmol) by following the above general procedure. After 6 days, the crude product was column chromatographed (SiO_2) eluting with initially $CHCl_3$ and then a mixture of EtOAC/$CHCl_3$ (1:19) to give (**14**) (0.124 g) as a white solid in 14% yield. Mp 115–120 °C. ^{1}H NMR ($CDCl_3$) δ: 1.27 (s, 2H, CCH_2), 1.58 (d, 48H, J= 7.0 Hz, 16×CH_3CH), 3.81 (s, 48H, 16×OCH_3), 3.93 (q, 16H, J=7.0 Hz, 16×$CHCH_3$), 4.48 (b, 8H, 4×CH_2O), and 6.96–7.63 [m, 132H: (36H, 12×Ar*H*); (96H, 16×Naph*H*)]. ^{13}C NMR ($CDCl_3$) δ: 18.40, 29.68, 32.02, 45.45, 55.24, 62.02, 65.06, 105.70, 119.10, 20.40, 120.47, 120.68, 125.94, 126.18, 127.48, 128.96, 130.79, 131.55, 133.87, 134.54, 150.79, 150.92, 151.27, 157.80, 162.60, 164.06, and 172.34. Anal. Calcd for $C_{314}H_{254}O_{72}$: C, 72.82; H, 4.94. Found: C, 72.62; H, 5.03. $[\alpha]_D^{25} = +92.0$ (*c* 1.0, $CHCl_3$).

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Dearomatization of furans via [2,3]-Still–Wittig rearrangement

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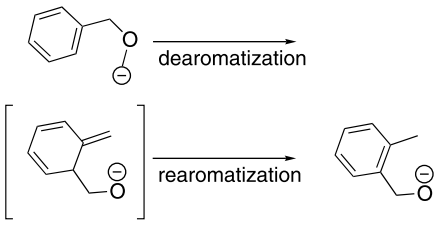
Abstract—Furans and benzofurans of type **1** were dearomatized via the [2,3]-Still–Wittig rearrangement. Enol ethers **2** could be isolated or isomerized to the corresponding furans **3**. The substitution pattern at the homofuranylic position had a strong influence on reaction behavior. Benzofurans rearranged with the greatest efficiency, and employment of a 3-substituted benzofuran (**1**; $R' = CH_3$) allowed the creation of a quaternary carbon center.

1. Introduction

The [2,3]-Wittig rearrangement is a six-electron sigmatropic process driven by the conversion of a carbon anion to an oxygen anion (Eq. 1).[1] The reaction is stereospecific with respect to the anionic carbon (inversion of stereochemistry),[2] nonbonded interactions in the transition state can lead to highly stereoselective olefin geometry,[3] and chirality transfer from the carbon–oxygen stereogenic center to the new carbon–carbon bond is efficient.[1a] These features confer upon the rearrangement a high level of synthetic utility, which has figured in a number of impressive applications to natural product synthesis.[4] An aromatic π-system can also participate in the [2,3]-rearrangement, producing a highly unstable intermediate that typically undergoes immediate rearomatization in situ (see Eq. 2).[5] However, [2,3]-Wittig variants effecting permanent destruction of an aromatic system are more elusive. The Sommelet–Hauser rearrangement of nitrogen and sulfur ylides can dearomatize benzene derivatives,[6] but no examples of the dearomatization of aromatic heterocycles via [2,3]-sigmatropic rearrangement have been reported.[7] Such a reaction could have the potential to create synthetically useful heterocyclic products with unusual architecture.

(1)



(2)

2. Results and discussion

Initial studies arose from our attempts to convert 2-substituted furans into 2,3-disubstituted furans, via a [2,3]-rearrangement pathway analogous to the reaction shown in Eq. 1. Carbanions were generated from alkylstannanes **1**[8] and submitted to Still–Wittig rearrangement conditions (Table 1).[3a] We expected to isolate the rearranged and rearomatized furyl alcohol **3b**, following spontaneous isomerization of unstable-looking intermediate **2b**. However, **2b** was surprisingly robust, surviving aqueous workup and purification by flash chromatography on silica gel. To our knowledge, intermediates analogous to **2** have never been successfully isolated from the [2,3]-Wittig rearrangement of aromatic heterocycles, and we were inspired to conduct a more detailed examination of this interesting transformation.

The [2,3]-rearrangement of anions derived from a range of stannanes **1** was carried out, and the results are presented in Table 1. Reactions proceeded with varying degrees of efficiency, giving enol ethers **2** in 20–80% yield, along with undesired 2-methoxymethyl furans **4** and 2-hydroxymethyl furans **5**. The furan analog of **1f** also underwent [2,3]-rearrangement.[9] Treatment of enol ethers **2a**–**2c**, **2e**, and **2f**

Keywords: [2,3]-Sigmatropic rearrangement; Furans; Heterocycles; Dearomatization.
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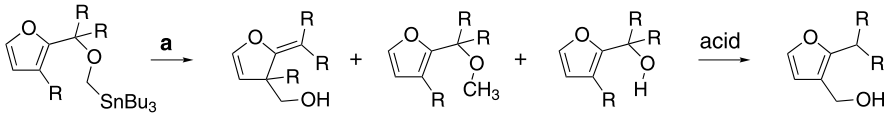
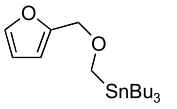
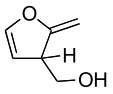
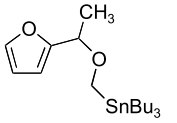
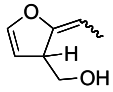
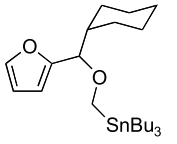
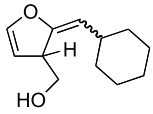
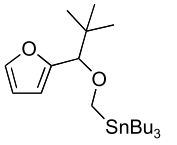
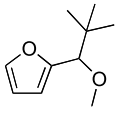
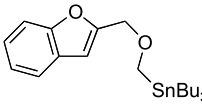
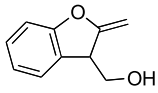
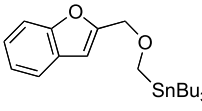
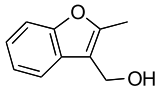
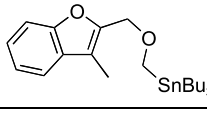
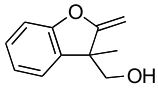
Table 1. [2,3]-Still–Wittig rearrangement of furans



1 **2** **4** **5** **3**

Entry	Stannane **1**	Reaction conditions[a]	Ratio (**2**:**4**:**5**:**3**)[b]	Product	Yield[c]
1	 **1a**	*n*-BuLi, THF, −78 °C then H_2O	7:7:0:1	 **2a**[d]	20
2	 **1b**	*n*-BuLi, THF, −78 °C then H_2O	4:1:0:trace	 **2b**[e]	50
3	 **1c**	*n*-BuLi, THF, −78 °C→−50 °C then CD_3OD	2:1:0:0	 **2c**[e]	66
4	 **1d**	*n*-BuLi, THF, −78 °C, then H_2O	**4** only	 **4d**	88
5	 **1e**	*n*-BuLi, THF, −78 °C, then H_2O	1:2:0:2	 **2e**	—
6	 **1e**	*n*-BuLi, THF, −78 °C then 10% TFA/MeOH	0:1:0:1.5	 **3e**	56
7	 **1f**	MeLi, THF, −78 °C, then MeOH	2.5:1:0:—	 **2f**	65[f]

[a] 1.0 equiv of alkyllithium.
[b] Determined by ^1H NMR.
[c] Isolated.
[d] Isolated as a 5:1 mixture of **2a**:**3a**; a small amount of rearomatization occurred during purification.
[e] A single isomer (^1H and ^{13}C NMR); geometry not known.
[f] See Ref. 11.

with 10% trifluoroacetic acid in methanol or THF effected rearomatization to give furyl alcohols **3**.[10]

Substitution at the homofuranylic position of the system retarded rearrangement. Substrates with a primary or secondary carbon at this position rearranged at −78 °C (entries 2 and 3). Cyclohexyl derivative **1c** (tertiary homofuranylic carbon) required warming to −50 °C to achieve best results, and **1d** (quaternary carbon) failed to rearrange under any conditions.

Benzofuran stannane **1e** underwent smooth [2,3]-rearrangement, but partial rearomatization to **3e** could not be avoided (entry 5). As **2e** and **3e** proved difficult to separate, a one-pot rearrangement/isomerization process was developed to convert **1e** directly into **3e** (entry 6). Finally, rearrangement of stannane **1f** proceeded without incident to give enol ether **2f**, with efficient formation of a new quaternary center.[11] It is significant that this version of the rearrangement allows the creation of intermediates that are unable to rearomatize.

Methyl ethers **4**, resulting from protodestannylation, were often present in significant quantities.[12] To determine whether a proton transfer event was competing with the [2,3]-sigmatropic rearrangement, the reaction mixture was quenched with CD_3OD and D_2O. ^1H NMR analysis of methyl ethers **4c** and **4d** showed a mixture of $-OCH_3$ and $-OCH_2D$ peaks, indicating that some extent of inter- or

intramolecular proton transfer does occur prior to the external quench.[13] Alcohol **5** is presumably the result of an α-elimination pathway, as similar processes have been observed by others.[14] However, reaction mixtures never contained significant amounts of products resulting from the (potentially competitive) [1,2]-Wittig rearrangement pathway.[5a]

Product ratios were largely unaffected by changes in reaction temperature (identical results for −90 and −78 °C) or structure of alkyllithium (*n*-BuLi, *s*-BuLi, *t*-BuLi, MeLi). Tetrahydrofuran gave better results than ether or dimethoxyethane, solvents reported to effect slower and faster Sn–Li transmetallation, respectively.[15] We sought to increase the reactivity of the carbanion by conventional means, but addition of lithium solvators (HMPA and TMEDA), and counterion exchange (Li→K) had no effect. Lithium salts (LiCl[16] and $LiClO_4$) were added to prevent postulated chelation of the organolithium to the furan oxygen, a situation that would create unfavorable geometry for rearrangement. Unfortunately, these salts seemed to interfere with transmetallation, and little rearrangement was observed. To our frustration, basic substrate architecture seemed to influence the rearrangement efficiency of furans **1a**–**1f** more profoundly than any of the reaction conditions we examined.

A set of optimization experiments on benzofuran **1e** was more fruitful (Table 2). Excess alkyllithium led to higher yields of rearranged product **3**,[17] and methyllithium gave cleaner product mixtures, simplifying purification. Alternatives to tin–lithium exchange for generating the intermediate carbanion were also explored. Treatment of the TMS methyl ether analog **1i**[18] with *n*-BuLi at low temperature led to the unexpected formation of 2-hydroxy-*trans*-cinnamaldehyde in 22% yield (entry 7).[19] Isolation of this product provides additional evidence for the undesired transfer of a proton from the furanylic position. Finally, attempts to generate the desired anion via reductive desulfurization of the phenylsulfide derivative[20] led to decomposition (entry 8).

Surprisingly, the heterocyclic substrates shown in Figure 1 did not undergo [2,3]-rearrangement under a variety of conditions. Methyl ether **4** was the major product observed when rearrangement was attempted.

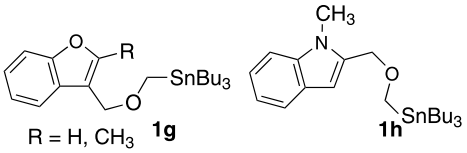
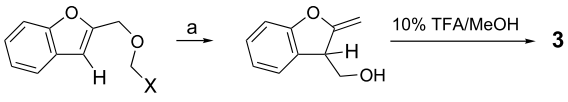


Figure 1. Substrates that did not undergo rearrangement.

Table 2. Optimization of benzofuran rearrangement



Entry	X	Reaction conditions[a]	Yield (**3**)
1	$SnBu_3$	*n*-BuLi (1.1 equiv)	56
2	$SnBu_3$	*n*-BuLi (3.0 equiv)	64
3	$SnBu_3$	*n*-BuLi (5.0 equiv)	77
4	$SnBu_3$	MeLi (1.0 equiv)	25
5	$SnBu_3$	MeLi (2.0 equiv)	80
6	$SnBu_3$	MeLi (3.0 equiv)	68
7	$SiMe_3$	*n*-BuLi (5.0 equiv)	[b]
8	SPh	LiNp[c]	0

[a] Reactions were run in THF at −78 °C.
[b] Product was 2-hydroxy-*trans*-cinnamaldehyde.
[c] Lithium naphthalenide.

3. Conclusion

In summary, we have accomplished the dearomatization of furan and benzofuran substrates via the [2,3]-Still–Wittig rearrangement with varying degrees of efficiency. Many of the enol ether products could be isolated by flash chromatography or subjected to acidic conditions to give 2,3-disubstituted furans **3**. It was also possible to form quaternary centers in this process, to give products with no available rearomatization pathway. Although the substrate scope of the rearrangement was somewhat disappointing, the rearrangement showed promising synthetic utility for benzofuran derivatives.

4. Experimental

Reactions were done in oven-dried glassware under an argon atmosphere unless otherwise noted. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under nitrogen. Dichloromethane and 1,2 dimethoxyethane were freshly distilled over calcium hydride. Tetramethylethylenediamine (TMEDA) and hexamethylphosphoramide (HMPA) were also freshly distilled over calcium hydride. Methyl lithium, *n*-butyl lithium, *s*-butyl lithium, and *t*-butyl lithium were titrated by dropwise addition to diphenylacetic acid (200 mg in 5 mL THF) under argon. Furfural was distilled under vacuum and stored in the refrigerator. Lithium chloride was stored in a nitrogen-filled glove box before use, and lithium perchlorate was dried at 60 °C for 2 h.

Column chromatography was performed on EM Science silica gel 60 (230–400) mesh. Visualization was done with *p*-anis aldehyde stain and a UV lamp. Proton and carbon NMR spectra were collected on 400 MHz spectrometers at ambient temperature. Chemical shifts δ are reported relative to $CDCl_3$. High-resolution mass spectra were measured by the Chemistry Instrumentation Center of the Department of Chemistry at the University of Buffalo.

2-Hydroxymethyl furans **1e**[21], **1f**[22], **1g**[23] (for R=H; R=Me comes from entry 6), and **1h**[24] were prepared according to literature methods. ICH_2SnBu_3 was also prepared according to a literature procedure.[25]

4.1. Preparation of 2-hydroxymethyl furan

Sodium borohydride (0.39 g, 10.4 mmol) was added to a solution of furfural (1.0 g, 10.4 mmol) in methanol at 0 °C. After 30 min the reaction was concentrated and dissolved in

ether. The organic layer was washed with water (1×) and the aqueous layer was then washed with ether (2×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to give a clear, faint yellow oil in essentially quantitative yield. Spectroscopic data were consistent with those previously reported in the literature (see www.aldrich.com).

4.2. General procedure for the synthesis of furanyl alcohols (precursors to 1b, 1c, 1d)

A solution of furfural (1.0 equiv) in diethyl ether (0.33 M) was cooled to −30 °C. The corresponding Grignard reagent (1.0 equiv) was added and TLC was used to judge completion. The reaction was then quenched with saturated ammonium chloride and warmed to room temperature. After diluting with ether, the organic layer was washed with water and brine. The organic phase was then dried with anhydrous magnesium sulfate and concentrated. Silica gel chromatography (4:1 hexane:ethyl acetate) afforded light yellow oils in essentially quantitative yield. Spectroscopic data were consistent with those previously reported in the literature: **1b**;[26] **1c**;[27] **1d**.[28]

4.3. General procedure for the synthesis of stannanes 1a–1h

KH (30% dispersion in mineral oil, 2.0 equiv) was washed with hexane (2×) under an argon atmosphere by magnetic stirring and subsequent removal of the hexane via syringe. THF (0.16 mmol/1 mL) was then added and the suspension was cooled to 0 °C. 2-Furan hydroxy methyl compounds (1.0 equiv) were then added dropwise in THF (1.7 mmol/1 mL), and the reaction was allowed to warm to room temperature for 2 h. The resulting mixture was cooled again to 0 °C and ICH_2SnBu_3 in THF (3.4 mmol/1 mL) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. Saturated ammonium chloride was used to quench the reaction, followed by dilution with ether. The layers were separated and the aqueous phase was washed one more time with ether. The combined organic extracts were dried with anhydrous magnesium sulfate and concentrated. Silica gel chromatography (100% hexane or hexane→hexane/ethyl acetate) afforded light yellow oils in 50–70% yield. Stannyl methyl ether products were identified by ^{1}H NMR.[29]

4.3.1. Preparation of 3-hydroxymethyl 2-methyl furan (3a).

Stannane **1a** (0.35 g, 0.77 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 0.48 mL, 0.77 mmol) was then added dropwise and the reaction was stirred for 20 min. H_2O (0.3 mL) was then added and the solution was allowed to warm to room temperature. The reaction mixture was then diluted with 70 mL ether, dried with anhydrous magnesium sulfate, and concentrated to a crude oil. Silica gel chromatography (92:8 dichloromethane:diethyl ether) afforded 13 mg of a light yellow oil **2a**:**3a**=5:1 as assigned by ^{1}H NMR (22%). (**2a**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (m, 1H), 5.19 (s, 1H), 4.68 (s, 1H), 4.27 (s, 1H), 3.66 (m, 3H), 1.76 (br. s, 1H).

Treatment of the product with 10% HCl (aq) or cat. AcOH in $CDCl_3$ gave furan **3a**[5c] after aqueous workup and silica gel column purification.

4.3.2. Preparation of 3-hydroxymethyl 2-ethyl furan (3b).

Stannane **1b** (0.37 g, 0.78 mmol) was dissolved in THF (5.0 mL) and cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 0.49 mL, 0.78 mmol) was then added dropwise and the reaction was stirred for 30 min. H_2O (0.5 mL) was then added and the solution was allowed to warm to room temperature. The reaction mixture was then diluted with 70 mL ether, dried with anhydrous magnesium sulfate, and concentrated to a crude oil. Silica gel chromatography (dichloromethane→92:8 dichloromethane:diethyl ether) afforded 56 mg (57%) of **2b** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (m, 1H), 5.22–5.17 (m, 2H), 3.76–3.70 (m, 3H), 1.68 (dd, J=7.2, 1.7 Hz, 3H). Treatment of the product with 10% HCl (aq) in $CDCl_3$ gave furan **3b**[30] after aqueous workup and silica gel column purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=1.8 Hz), 6.37 (d, J=1.7 Hz), 4.49 (s, 2H), 2.66 (q, J=7.6 Hz), 1.29 (br. s, 1H), 1.22 (t, J=7.6 Hz).

4.3.3. Enol ether (2c).

Stannane **1c** (0.095 g, 0.18 mmol) was dissolved in THF (1.2 mL) and cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 0.11 mL, 0.18 mmol) was then added dropwise and the reaction was stirred for 20 min at −78 °C. After warming to −50 °C for 10 min, 0.3 mL CD_3OD was added and the solution was allowed to warm to room temperature. The reaction mixture was then diluted with ether and washed with water (1×). The aqueous layer was washed with ether (1×) and the combined ether extracts were washed with brine (1×). The organic phase was then dried over anhydrous magnesium sulfate and concentrated. Silica gel chromatography (dichloromethane) afforded 22 mg (65%) of **2c** as a colorless oil. IR (thin film) 3366, 2922, 2850, 1694, 1615, 1448, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (m, 1H), 5.18 (m, 1H), 5.05 (d, J=9.4 Hz, 1H), 3.77–3.60 (m, 3H), 2.01 (m, 1H), 1.59–1.57 (m, 5H), 1.28–0.88 (m, 5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 145.4, 109.6, 103.4, 64.8, 45.6, 36.3, 34.7, 33.8, 25.9; HRMS (EI) *m/z* 194.13069 [(M^+); Calcd for $C_{12}H_{18}O_2$ 194.1301].

4.3.4. Enol ether (2e).

Stannane **1f** (0.18 g, 0.35 mmol) was dissolved in THF (2.8 mL) and cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 0.24 mL, 0.35 mmol) was then added dropwise and the reaction was stirred for 20 min. H_2O (0.5 mL) was then added and the solution was allowed to warm to room temperature. The reaction mixture was then diluted with ether and washed with water (1×). The aqueous layer was washed with ether (1×) and the combined ether extracts were washed with brine (1×). The organic phase was then dried over anhydrous magnesium sulfate and concentrated. Silica gel chromatography (two columns were run: 80:20 dichloromethane:ether, then 9:1 dichloromethane:ether) afforded 9 mg of a pure sample of **2e** as a colorless oil. IR (thin film) 3370, 2929, 2875, 1684, 1609, 1477, 1461, 1367, 1331, 1155, 936, 827, 750, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J=7.3 Hz, 1H), 7.22 (t, J=7.6 Hz, 1H), 6.99 (t, J=7.5 Hz, 1H), 6.91 (d, J=8 Hz), 4.81 (d, J=2.3 Hz, 1H), 4.38 (d, J=2.2 Hz, 1H), 4.11 (br. s, 1H), 3.87 (m, 2H), 1.77 (t, J=

6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 157.8, 128.8, 126.6, 124.3, 121.9, 109.4, 85.7, 65.7, 46.8.

4.3.5. 2-Methyl-3-hydroxymethyl benzofuran (3e). Stannane **1e** (0.18 g, 0.35 mmol) was dissolved in THF (2.8 mL) and cooled to −78 °C. MeLi (1.6 M in diethyl ether, 0.47 mL, 0.70 mmol) was then added dropwise and the reaction was stirred for 30 min. MeOH (0.4 mL), followed by 0.03 mL TFA was then added and the solution was allowed to warm to room temperature. The reaction mixture was then diluted with ether and washed with water (1×). The aqueous layer was washed with ether (1×), and the combined ether extracts were washed with saturated sodium bicarbonate (1×) and brine (1×). The organic phase was then dried over anhydrous magnesium sulfate and concentrated. Silica gel chromatography (dichloromethane→9:1 dichloromethane:ether) afforded 47 mg (80%) of **3e**[31] as a white solid.

4.3.6. Enol ether (2f). Stannane **1f** (3.65 g, 7.00 mmol) was dissolved in THF (46 mL) and cooled to −78 °C. MeLi (1.6 M in diethyl ether, 13.0 mL, 21.0 mmol) was then added dropwise and the reaction was stirred for 20 min at −78 °C. MeOH (6.0 mL) was then added and the solution was allowed to warm to room temperature. The reaction mixture was then diluted with ether and washed with water (1×). The aqueous layer was washed with ether (1×) and the combined ether extracts were washed with brine (1×). The organic phase was then dried over anhydrous magnesium sulfate and concentrated. Silica gel chromatography (4:1 hexane:ethylacetate) afforded 0.984 (80%) of **2f** as a faint yellow oil. IR (thin film) 3390, 2967, 2928, 2868, 1684, 1609, 1476, 1462, 1240, 1172, 1105, 1040, 936, 827, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.18 (m, 2H), 7.01 (t, J=7.3 Hz, 1H), 6.94 (d, J=8.0 Hz, 1H), 4.79 (d, J=2.7 Hz, 1H), 4.27 (d, J=2.7 Hz, 1H), 3.69–3.59 (m, 2H), 1.67 (t, J=7.0 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 156.8, 131.3, 128.6, 123.0, 122.0, 109.4, 84.0, 70.5, 49.7, 23.3; HRMS (EI) *m/z* 176.08308 [(M^+); Calcd for $C_{11}H_{12}O_2$ 176.0832].

General notes. Enol ether **2c** also isomerized to the corresponding furan **3c** under similar acidic conditions in moderate yield. All methyl ethers **4** were identified according to ^{1}H NMR (characteristic signal at 3.2 ppm (s, 3H)).

Acknowledgements

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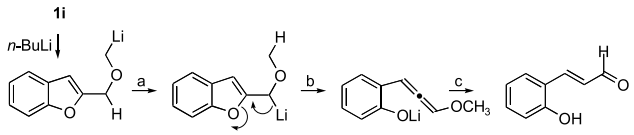

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Conformational analysis of six-membered ring dioxaphosphinanes. Part 1: Anancomeric thiophosphates

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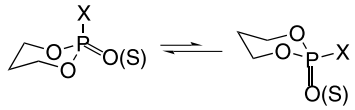
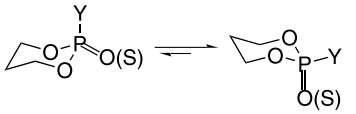
Abstract—A study of the conformation of a series of anancomeric axial and equatorial 2-aryloxy-2-thio-1,3,2λ^5-dioxaphosphinanes **2**–**12** in solution and solid state is reported. In accord to the stereoelectronic theory, aryl thiophosphates substituted with electron-withdrawing (EW) groups will tend to occupy axial positions in chair ring conformations due to the stabilizing *endo*-anomeric (n_πO–σ^*_{P-X}) hyperconjugative interaction. The antiperiplanar orientation of the orbitals involved in the stereoelectronic interaction is a requirement that is fulfiled in the axial series of compounds when the ring adopts a chair conformation. Therefore, in the equatorial series of thiophosphates, the axial seeking characteristics of aryloxy-EW groups might render the molecule with distortion of the chair conformation. An opposite trend is anticipated for the less axial seeking aryl thiophosphates substituted with electron releasing (ER) groups. A detailed analysis of the $^3J_{HH}$, $^3J_{PH}$ and $^3J_{CP}$ coupling constants allowed us to conclude that there is no contribution of high energy twist-boat conformations in the equatorial thiophosphates substituted with aryl-EW groups in solution. In consequence, single chair conformations were found in solid state for aryl thiophosphates in both configurations. X-ray geometrical analysis of bond distances and bond angles supports clearly the participation of hyperconjugative *endo*-anomeric (n_πO–σ^*_{P-OAr}) effect in the stabilization of axial series of compounds and the participation of *endo*-anomeric (n_πO–$\sigma^*_{P=S}$) effect in the stabilization of the equatorial thiophosphates in chair conformations.

1. Introduction

Six-membered ring thiophosphates are interesting systems from the conformational point of view since there are several electronic effects, as the *endo*- and *exo*-anomeric effects, that can play an important role in the conformational preferences of the substituents on phosphorus.[1–3] Steric effects in thiophosphates are not very important as in the monosubstituted cyclohexanes[4] or as in the closest heterocyclic system, the 2-substituted-1,3-dioxanes.[5] The decreased 1,3-*syn* axial steric hindrance of the substituent with the 4,6-hydrogens of the 1,3,2-dioxaphosphinane ring is due to the longer P–O (1.58 Å) *endo*-cyclic bond distances as compared to C–O in 1,3-dioxanes (1.42 Å) or C–C in cyclohexane (1.54 Å),[6] as well as the propensity of the *endo*-cyclic oxygens to adopt sp^2 hybridization instead of sp^3 that renders the ring with more flexibility than the corresponding 1,3-dioxane or cyclohexane.[7] As observed in the pentacoordinative chemistry of phosphorus compounds,[8] electronegative substituents in phosphates and thiophosphates will tend to adopt axial orientations, and electron-donating substituents, equatorial ones (Scheme 1).[9]



X = electronegative atom or group



Y = electron releasing atom or group

Scheme 1.

Keywords: Dioxaphosphinanes; Thiophosphates; Conformation; NMR; LFER correlations; X-ray crystal structures.

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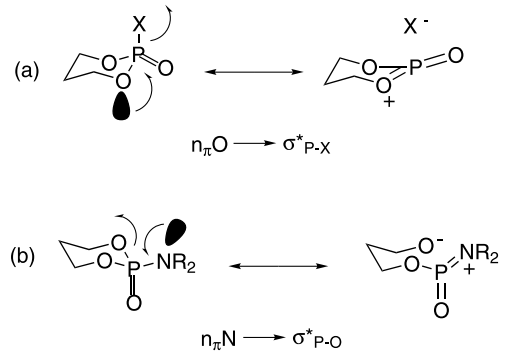
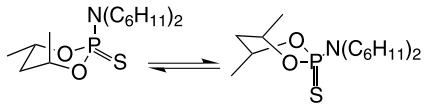


Scheme 2.

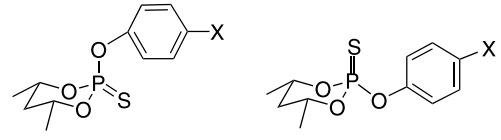
These preferences rely on stereoelectronic grounds, the *endo*-anomeric ($n_\pi O–\sigma^*_{P–X}$) effect favoring the axial conformer when the X-substituent is electronegative (such as halogen, OR, etc.), because the acceptor σ^* antibonding orbital of an electronegative substituent is lower-lying than the antibonding orbital of an electron-releasing substituent, therefore giving rise to a more stabilizing 2 electrons/2 orbitals interaction (Scheme 2a).[3,10] On the contrary, the *exo*-anomeric ($n_\pi Y–\sigma^*_{P–O\ endo\text{-cyclic}}$) hyperconjugative interaction will promote that an electron releasing substituent, such as an amine, tend to occupy the equatorial position in a dioxaphosphinane ring (Scheme 2b).[7] The equatorial isomer might also be favored by the $n_\pi O–\sigma^*_{P=S}$ *endo*-hyperconjugative intraction.[11]



Scheme 3.

From experimental point of view, van Nuffel et al.[12] have proved the participation of stereoelectronic interactions in the axial conformational preference of several phosphates and their thio derivatives, through the shortening of the *endo*-cyclic P–O bond and the lengthening of the P–X bond that is based on the resonance hybrids shown in Scheme 2. It is worth of mention that since the interconversion barrier of chair-to-twist or chair-to-boat conformations in 1,3,2-dioxaphosphinanes is very low (0.5–3.5 kcal/mol),[1] the stabilizing *endo*- or *exo*-anomeric interactions and/or the steric hindrance when the substituents are bulky, can force the molecule to adopt a twist-boat conformation in preference to the chair (Scheme 3).[7]

Reported in this work is the conformational analysis in solution and solid state of a series of axial and equatorial anancomeric aryl thiophosphates substituted with electron-withdrawing (EW) and electron-releasing (ER) groups (**2**–**12**), (Scheme 4). Spectroscopic data, as ^1H, ^{13}C and ^{31}P NMR are correlated with Hammett constants (σ_p),[13] within the context of LFER theory.[14] We analyzed thoroughly the X-ray geometrical parameters of two axial and two equatorial compounds substituted with EW or ER groups to account for the participation of the *endo*-anomeric ($n_\pi O–\sigma^*_{P–OAr}$) and ($n_\pi O–\sigma^*_{P=S}$) stabilizing interactions.



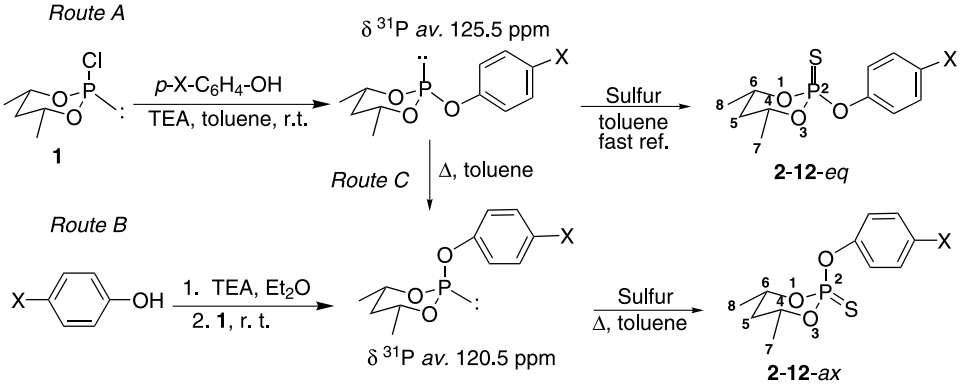
axial (ax) *equatorial (eq)*

2, X= NO_2
3, X= CN
4, X= CHO
5, X= Br
6, X= Cl
7, X= $NHCOCH_3$
8, X= H
9, X= C_6H_5
10, X= CH_3
11, X= OCH_3
12, X= NH_2

Scheme 4.

2. Results

The synthesis of both series of aryl thiophosphates **2**–**12**-*ax* and **2**–**12**-*eq* was accomplished through the stereoselective formation of the phosphite intermediates from the phosphochloridite and aryl alcohols as shown in Scheme 5. Due to the epimerization of the equatorial phosphite intermediate in the presence of an excess of phenol,[15] in route A, the *p*-X-substituted phenol was slowly added to the phosphorochloridite (**1**). On the contrary, in route B the thermodynamically more stable axial phosphite was obtained by addition of **1** to the corresponding *p*-X-substituted phenol.



Scheme 5.

Table 1. Selected ^{1}H and ^{31}P NMR chemical shifts (in ppm) for axial aryl thiophosphates **2–12** in $CDCl_3$

Chemical shifts (δ)	^{1}H				^{31}P
Compound	$H_{4,6a}$	H_{5a}	H_{5e}	$H_{7,8}$	
2-*ax* (X=NO_2)	4.76	1.86	1.90	1.42	54.3
3-*ax* (X=CN)	4.73	1.85	1.87	1.43	54.5
4-*ax* (X=CHO)	4.75	1.83	1.85	1.42	55.1
5-*ax* (X=Br)	4.75	1.82	1.87	1.42	55.5
6-*ax* (X=Cl)	4.75	1.83	1.90	1.45	55.6
7-*ax* (X=$NHCOCH_3$)	4.77	1.86	1.88	1.44	55.9
8-*ax* (X=H)	4.79	1.82	1.88	1.43	55.8
9-*ax* (X=C_6H_5)	4.81	1.83	1.88	1.44	55.8
10-*ax* (X=CH_3)	4.77	1.82	1.84	1.41	56.2
11-*ax* (X=OCH_3)	4.77	1.81	1.86	1.42	56.7
12-*ax* (X=NH_2)	[a]	[a]	[a]	[a]	56.8

[a] Undetermined (mixed with the equatorial epimer).

Table 2. Selected ^{1}H and ^{31}P NMR chemical shifts (in ppm) for equatorial aryl thiophosphates **2–12** in $CDCl_3$

Chemical shifts (δ)	^{1}H				^{31}P
Compound	$H_{4,6a}$	H_{5a}	H_{5e}	$H_{7,8}$	
2-*eq* (X=NO_2)	4.85	1.77	1.90	1.41	59.2
3-*eq* (X=CN)	4.84	1.79	1.87	1.41	59.3
4-*eq* (X=CHO)	4.79	1.54	1.69	1.34	59.5
5-*eq* (X=Br)	4.76	1.64	1.77	1.32	60.0
6-*eq* (X=Cl)	4.83	1.71	1.87	1.39	60.1
7-*eq* (X=$NHCOCH_3$)	4.80	1.75	1.85	1.38	60.4
8-*eq* (X=H)	4.83	1.70	1.89	1.39	60.4
9-*eq* (X=C_6H_5)	4.78	1.67	1.77	1.34	60.4
10-*eq* (X=CH_3)	4.80	1.59	1.72	1.34	60.9
11-*eq* (X=OCH_3)	4.73	1.63	1.75	1.31	61.0
12-*eq* (X=NH_2)	4.52	1.68	1.82	1.38	61.3

Table 3. ^{1}H NMR backbone coupling constants (in Hz) for axial aryl thiophosphates **2–12**. First-order analysis in $CDCl_3$ at 27 °C

Compound/coupling constant	$^{3}J_{H4,6aH5a}$	$^{3}J_{H4,6aH5e}$	$^{3}J_{H4,6aH7,8}$	$^{2}J_{H5aH5e}$	$^{3}J_{H4,6aP}$	$^{4}J_{H5aP}$	$^{4}J_{H5eP}$	$^{4}J_{H7,8P}$
2-*ax* (X=NO_2)	11.3	3.0	6.2	14.6	2.6	1.0	2.6	2.3
3-*ax* (X=CN)	10.5	2.5	6.4	14.8	1.2	1.5	1.3	2.5
4-*ax* (X=CHO)	8.0	2.7	6.2	13.0	1.2	[a]	1.5	2.2
5-*ax* (X=Br)	10.8	2.8	6.2	14.8	1.2	1.0	2.7	2.2
6-*ax* (X=Cl)	11.1	3.0	6.6	14.1	1.1	1.1	1.3	2.1
7-*ax* (X=$NHCOCH_3$)	12.9	2.9	6.2	13.0	1.3	1.0	1.8	2.3
8-*ax* (X=H)	10.8	2.8	6.6	14.4	1.3	1.1	2.6	2.6
9-*ax* (X=C_6H_5)	9.9	2.9	6.2	13.8	1.2	1.0	2.9	2.2
10-*ax* (X=CH_3)	10.7	3.0	6.2	14.5	1.2	1.1	2.7	2.2
11-*ax* (X=OCH_3)	10.8	3.3	6.2	14.5	1.2	1.0	3.0	2.2
12-*ax* (X=NH_2)	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]

[a] The signal was not observed.
[b] Undetermined (mixed with its equatorial epimer).

The thermal equilibration of equatorial phosphites to the axial epimers was achieved by heating them in toluene (route C). The equatorial phosphite intermediates substituted with EW groups tend to epimerize to the axial ones in shorter heating times than those substituted with ER groups. The equatorial or axial phosphites were reacted stereospecifically with sulfur to produce the thiophosphates **2–12**-*eq* or **2–12**-*ax* under the conditions shown in Scheme 5. We observed that equatorial aryl thiophosphates were obtained in a cleaner manner, without their configurational isomers, if the reaction was maintained under vigorously toluene reflux, particularly in the case of aryl-EW thiophosphates.

The conformational analysis of the axial and equatorial series of thiophosphates (**2–12**) was assessed by analysis of their spectral NMR characteristics. The chemical shifts (δ) of ^{1}H are reported in Tables 1 and 2. The correct assignment of the signals and the backbone coupling constants in the ^{1}H NMR (Tables 3 and 4) were obtained through the first-order analysis of the spectra, along with homo and heteronuclear decoupling experiments. The complete assignment of ^{13}C signals (Tables 5 and 6), was achieved by means of ^{1}H, ^{13}C correlated 2D NMR spectra, as well as inverse ^{1}H-detected HMQC and HMBC experiments. Two-dimensional techniques were particularly useful for the assignment of ^{13}C NMR signals of the configurational *p*-phenyl thiophosphates (**9**-*ax* and **9**-*eq*). The participation of the stereoelectronic interactions was analyzed in the solid state through

Table 4. ^{1}H NMR backbone coupling constants (in Hz) for equatorial aryl thiophosphates **2–12**. First-order analysis in $CDCl_3$ at 27 °C

Compound/coupling constant	$^{3}J_{H4,6aH5a}$	$^{3}J_{H4,6aH5e}$	$^{3}J_{H4,6aH7,8}$	$^{2}J_{H5aH5e}$	$^{3}J_{H4,6aP}$	$^{4}J_{H5aP}$	$^{4}J_{H5eP}$	$^{4}J_{H7,8P}$
2-*eq* (X=NO_2)	10.5	2.6	6.3	14.6	1.2	1.0	2.8	2.2
3-*eq* (X=CN)	11.2	2.7	6.6	14.5	3.3	[a]	3.6	2.0
4-*eq* (X=CHO)	10.4	2.7	6.3	14.5	2.8	1.8	2.3	2.3
5-*eq* (X=Br)	10.6	2.8	5.9	14.5	2.6	[a]	2.3	2.0
6-*eq* (X=Cl)	11.2	3.0	6.6	14.0	2.5	[a]	2.3	2.0
7-*eq* (X=$NHCOCH_3$)	10.8	2.3	6.2	14.1	2.6	[a]	2.3	2.4
8-*eq* (X=H)	10.9	2.6	6.3	14.5	2.3	[a]	2.3	2.3
9-*eq* (X=C_6H_5)	9.9	2.9	6.2	14.2	3.0	[a]	2.3	2.0
10-*eq* (X=CH_3)	11.2	2.6	6.6	14.5	2.6	2.3	2.6	2.6
11-*eq* (X=OCH_3)	10.9	2.6	6.3	14.5	2.6	[a]	2.6	2.0
12-*eq* (X=NH_2)	11.2	2.6	6.6	14.5	3.3	[a]	2.6	2.0

[a] The signal was not observed.

Table 5. Selected ^{13}C NMR signal assignments in axial aryl thiophosphates **2–12**[a]

Compound	$C_{4,6}$	C_5	$C_{7,8}$	C_i	C_o
2-*ax* (X=NO_2)	77.7 (9.1)	40.6 (4.9)	22.4 (9.6)	156.2 (6.1)	121.3 (5.4)
3-*ax* (X=CN)	77.1 (9.3)	40.3 (5.2)	22.3 (9.9)	154.3 (6.2)	121.3 (5.2)
4-*ax* (X=CHO)	76.7 (8.9)	40.2 (5.6)	22.1 (10.0)	155.4 (5.5)	120.7 (5.5)
5-*ax* (X=Br)	77.2 (8.9)	40.8 (4.8)	22.4 (9.6)	150.6 (6.4)	122.6 (4.9)
6-*ax* (X=Cl)	76.7 (10.4)	40.6 (4.9)	22.6 (9.5)	149.5 (6.3)	121.7 (5.2)
7-*ax* (X=$NHCOCH_3$)	76.8 (9.5)	42.7 (5.0)	22.5 (9.8)	147.5 (6.2)	121.9 (5.0)
8-*ax* (X=H)	76.2 (8.8)	39.9 (4.4)	21.9 (9.9)	150.5 (7.0)	119.8 (5.5)
9-*ax* (X=C_6H_5)	77.1 (8.9)	40.7 (4.7)	22.5 (9.6)	150.8 (6.5)	121.0 (5.0)
10-*ax* (X=CH_3)	76.9 (8.9)	40.7 (4.6)	22.4 (9.9)	148.8 (6.2)	120.4 (4.8)
11-*ax* (X=OCH_3)	76.9 (8.9)	40.7 (4.8)	22.4 (9.5)	144.9 (7.2)	121.7 (4.8)
12-*ax* (X=NH_2)	76.2 (9.3)	40.5 (4.7)	22.3 (9.8)	143.8 (7.8)	121.1 (5.2)

[a] Chemical shifts (δ) in ppm from TMS in $CDCl_3$. In parentheses J_{CP} in Hz.

Table 6. Selected ^{13}C NMR signal assignments in equatorial aryl thiophosphates **2–12**[a]

Compound	$C_{4,6}$	C_5	$C_{7,8}$	C_i	C_o
2-*eq* (X=NO_2)	76.1 (5.5)	40.8 (5.5)	22.1 (8.9)	155.0 (7.7)	122.1 (4.4)
3-*eq* (X=CN)	76.0 (5.5)	40.9 (6.6)	22.1 (8.9)	152.6 (6.6)	122.4 (4.4)
4-*eq* (X=CHO)	75.9 (5.4)	40.8 (5.8)	22.1 (10.0)	155.0 (6.0)	122.0 (4.4)
5-*eq* (X=Br)	75.6 (5.5)	40.9 (5.5)	22.0 (10.0)	149.5 (8.9)	123.1 (4.5)
6-*eq* (X=Cl)	76.1 (5.7)	41.3 (5.1)	22.5 (9.5)	149.4 (8.0)	123.1 (5.0)
7-*eq* (X=$NHCOCH_3$)	75.8 (5.5)	41.1 (5.5)	22.4 (9.5)	149.6 (8.1)	121.7 (4.6)
8-*eq* (X=H)	75.4 (5.5)	41.0 (4.4)	22.1 (10.0)	150.3 (7.7)	121.1 (4.4)
9-*eq* (X=C_6H_5)	75.5 (5.5)	41.0 (5.5)	22.1 (10.0)	149.9 (7.7)	121.5 (5.5)
10-*eq* (X=CH_3)	75.3 (5.5)	41.0 (5.5)	22.1 (10.0)	148.3 (7.7)	121.0 (5.5)
11-*eq* (X=OCH_3)	75.6 (5.5)	40.9 (5.6)	22.0 (10.0)	144.0 (7.7)	122.0 (4.4)
12-*eq* (X=NH_2)	75.8 (5.5)	40.8 (5.5)	21.9 (9.9)	142.6 (8.8)	121.8 (4.4)

[a] Chemical shifts (δ) in ppm from TMS in $CDCl_3$. In parentheses J_{CP} in Hz.

the X-ray diffraction analysis of four thiophosphates, two of the axial series [**2**-*ax* (X=NO_2), and **10**-*ax* (X=CH_3)] and two of the equatorial [**2**-*eq* (X=NO_2) and **11**-*eq* (X=OCH_3)]. These molecules are examples of aryl thiophosphates with EW or ER groups in both configurations.

3. Discussion

3.1. NMR analysis

As observed in Tables 1 and 2, in the axial series of thiophosphates (**2–12**), the proton H_{5a} is slightly upfield shifted (ca. 0.05 ppm) than the H_{5e}, this trend is also observed for the equatorial epimers (**2–12**). The chemical shift of protons $H_{4,6a}$ for the axial thiophosphates is at around 4.75 ppm meanwhile the same protons in the equatorial series appear at around 4.85 ppm. ^{13}C NMR chemical shifts of carbons in the heterocycle are scarcely sensitive to configuration, however a slight downfield shift (1.3 ppm in average) is observed for $C_{4,6}$ for the axial compounds, thus not giving evidence of a γ-*gauche* effect (see discussion below). The coupling constants $^{2}J_{CP}$ of $C_{4,6}$ for the axial thiophosphates are 3–5 Hz larger than the equatorial ones (Tables 5 and 6). The conformational analysis of the complete series of thiophosphates was performed with the coupling constants $^{3}J_{HH}$, $^{3}J_{HP}$ and $^{3}J_{CP}$ (Tables 3–6). Heteronuclear $^{1}H\{^{31}P\}$decoupling experiments led to simplification of the signals, therefore vicinal $^{3}J_{HP}$ were easily obtained by direct comparison with the ^{1}H NMR signals of the undecoupled spectra. For compounds (**2–11**)-*ax* the irradiation at 1.41–1.45 ppm (CH_3's at C_4, C_6) led to decoupling of the methine ($H_{4,6a}$) multiplet to an apparent doublet of double doublet (ddd) with

$^3J_{HH}$=9.9–11.3 Hz (*anti*), $^3J_{HH}$=2.5–3.3 Hz (*gauche*) and $^3J_{HP}$=1.2–2.6 Hz, these coupling constants are consistent with a chair conformation.[2,16] A similar experiment was performed for the compounds (**2**–**12**)-*eq*, irradiation at 1.31–1.41 ppm led to a double of triplets (dt) for the methine (H_{4a}) with $^3J_{HH}$=9.9–11.2 Hz (*anti*), $^3J_{HH}$=2.6–3.0 Hz (*gauche*) and $^3J_{HP}$=2.3–3.6 Hz, here also values of coupling constants suggest that in solution the series of equatorial thiophosphates are in chair conformation. On the other hand, the $^3J_{C5P}$ and $^3J_{C7,8P}$ coupling constants obtained from the ^{13}C NMR spectra of compounds (**2**–**12**) are in the range of 4.4–5.7 and 8.9–10.0 Hz, respectively, for both, axial and equatorial, series of thiophosphates (Tables 5 and 6) suggesting also a chair conformation for the six-membered ring in solution.[2,17] The fact that the $^3J_{CP}$ is not showing dependence on configuration, support the argument given by Quin[18] and Nifantiev[19] on the uses of $^3J_{CP}$ as the most useful C–P coupling constant to analyze the conformation of dioxaphosphinanes (note that in an ideal chair conformation the dioxaphosphinane dihedral angles $\omega_{C5-C4-O3-P}$ and $\omega_{C5-C6-O1-P}$ are 60° meanwhile $\omega_{C8-C6-O1-P}$ and $\omega_{C7-C4-O3-P}$ are 180°).

3.2. Electronic effects

In phosphorus compounds with aromatic rings, it has been demonstrated that EW or ER groups in the *para* position of the ring, causes polarization of charge density inducing changes in chemical shifts and coupling constants on the phosphorus and linked atoms.[20] Depending upon the aromatic organophosphorus compound, the so-called substituent-induced chemical shifts (SCS) exhibits in ^{31}P NMR one of the two possible tendencies, one that correlates ^{31}P chemical shifts directly with Hammett (σ_p) constants and the other that correlates them reversibly.[21] The factors that determine the tendency are the electronegativity of the α-atoms directly linked to phosphorus and the phosphorus hybridization,[22] and it has been observed frequently that these two factors cannot be separated for to understand the behavior.[23] Thus as expected, an EW group in aryl phosphazanes[24] provoke dishielding of the phosphorus nucleus resulting in a downfield shift of ^{31}P NMR signal. Nevertheless, the opposite behavior is observed for cinnamyl phosphonates[25] and aryl phosphates.[9a] The fundamental difference between these three types of organophosphorus compounds is that in phosphonates or phosphates the aromatic ring is in a group linked to phosphorus through a single bond; however, in aryl phosphazenes the aromatic ring is in a group linked to phosphorus through a double bond. From this observation it is evident that the transfer of charge density from the aromatic ring to phosphorus or vice versa follows a different mechanism when the transmission is through a σ or through a π bond.[26] In this work we found that the ^{31}P NMR signals of arylthiophosphates are reversibly correlated with σ_p being the correlation factor R=0.979 for the axial series of thiophosphates and R=0.982 for the equatorial. From the slope of the lines m=−1.871 for the axial series and m=−1.631 for the equatorial it can be deduced that the phosphorus of the axial isomers is more sensitive to charge polarization of the aromatic ring than the phosphorus of the equatorial ones. The reversible correlation may be explained by a change in bond distances and bond angles involving α-bonded atoms to phosphorus and the changes in torsion angles with β-atoms as proposed by Gorenstein for phosphates.[27] We will discuss this point in the structural analysis below. On the other hand, neither the ^{1}H nor the ^{13}C chemical shifts of the dioxaphosphinane ring correlate well with the Hammett (σ_p) constants. However, a good normal correlation of ^{13}C chemical shifts of the C_{ipso} with σ_p was found (R=0.926 for the axial and R=0.911 for the equatorial), C_{ipso} of NO_2 substituted arylthiophosphate being downfield shifted from C_{ipso} of OCH_3 aryl thiophosphate, as shown in Tables 5 and 6.

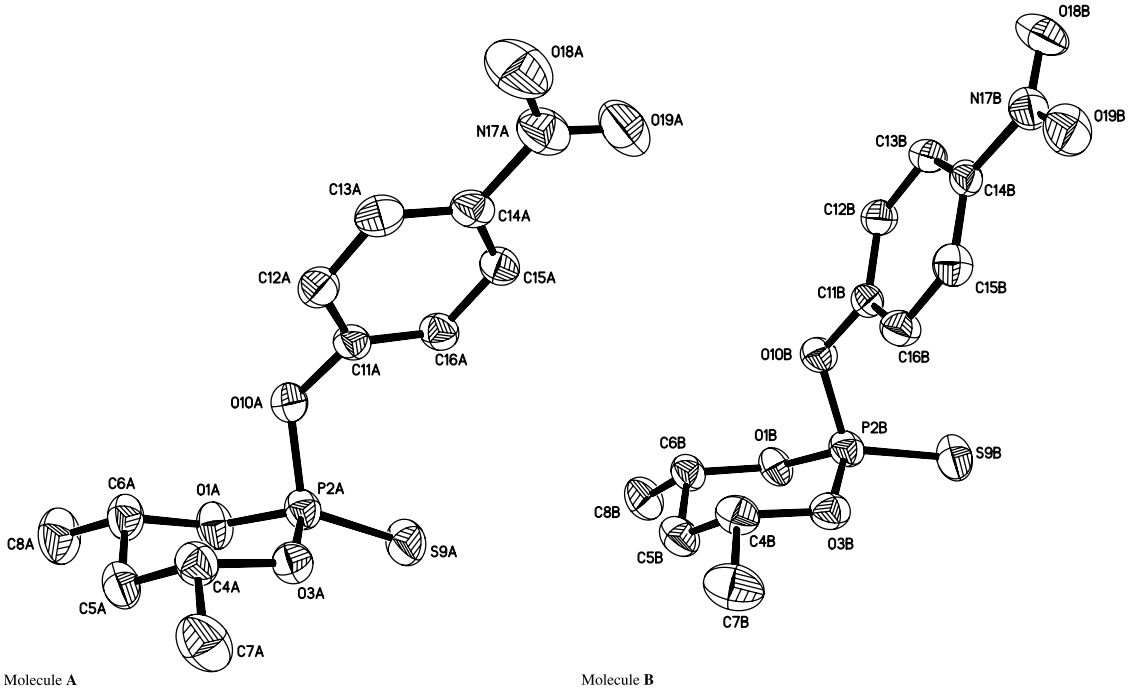


Figure 1. ORTEP drawing of *ax*-2-*p*-nitrophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (**2**-*ax*), molecule **A** and **B**.

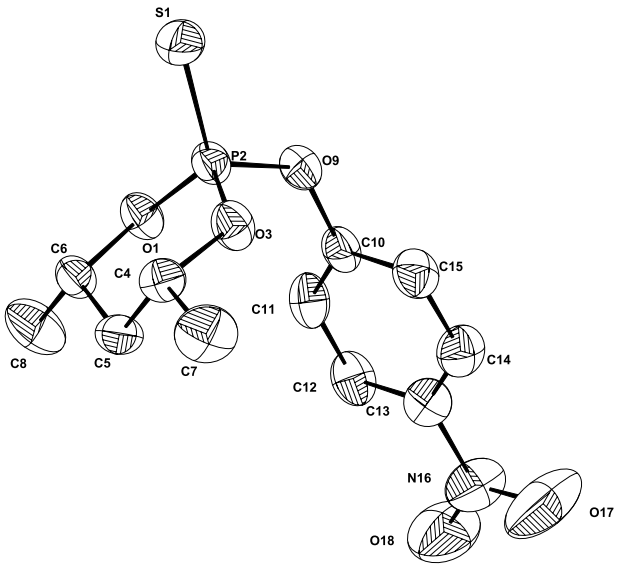


Figure 2. ORTEP drawing of *eq*-2-*p*-nitrophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (**2**-*eq*).

Based on the grounds of the stereoelectronic theory, EW groups will show more propensity to occupy axial orientations than ER groups (Scheme 2), therefore a detailed comparison of the structural parameters of the two axial **2**-*ax* (X=NO_2), and **10**-*ax* (X=CH_3) and the two equatorial **2**-*eq* (X=NO_2) and **11**-*eq* (X=OCH_3) thiophosphates not only led us to account for the participation of stereoelectronic interactions in the conformation adopted for the molecules but also for the reversible correlation found in the chemical shift of the signals of ^{31}P NMR with σ_p. We also analyzed the steric compression of the aryloxy group in the axial thiophosphates and the flexibility of the 1,3,2-dioxaphosphinane ring for to relieve the intramolecular van der Waals repulsive compression of the nonbonded substituents through compromise between the intraannular torsional strain and the Baeyer strain, as proposed for highly hindered thiophosphoramidates.[7]

3.3. Structural analysis

The ORTEP drawings obtained from the X-ray analysis of **2**-*ax*, **2**-*eq*, **10**-*ax* and **11**-*eq* are shown in Figures 1–4. Data collection and refinement parameters, bond distances, bond angles, and torsion angles are provided in Tables 7–10.

Thiophosphates **2**-*ax*, **2**-*eq* and **11**-*eq* crystallized in the monoclinic space group $P2_1/n$, $P2_1/c$ and $P2_1/a$ correspondingly, whereas **10**-*ax* crystallized in the orthorhombic *P* space group $P2_1$ *n b*. In the case of compound **2**-*ax*, two molecules were found in the asymmetric unit. Molecules A and B are not in equivalent positions, and it is interesting to note that the change of torsion angle P2–O10–C11–C12 by 74° brings with it a change in bond angle C4–O3–P2 (from 120° in molecule A to 117° in molecule B) that speaks about the high flexibility of the dioxaphosphinane ring in the OPO region ascribed to the propensity of the *endo*-cyclic oxygens to change from sp^3 to sp^2 hybridization.[7]

3.4. Torsion and bond angles

The geometry at the phosphorus center is tetrahedral for all the compounds; the sum of the four angles at the phosphorus goes from 436.04 to 439.71° (see Table 11). However, it is notable that equatorial thiophosphates are closer than the axial to the expected ideal tetrahedral angle (436°). The dioxaphosphinane ring lacks of perpendicular symmetry, the oxygens are almost flat edges [the internal COP angles are of around 119° for **2**-*ax*, **2**-*eq* and **10**-*ax* and around 116° for **11**-*eq*] and the phosphorus is a puckery end [the OPO angles are of around 106° for **2**-*ax*, **2**-*eq* and **10**-*ax* and 104° for **11**-*eq*]. There is ring flattening in the OPO region for both the axial and equatorial thiophosphates [torsion angles:

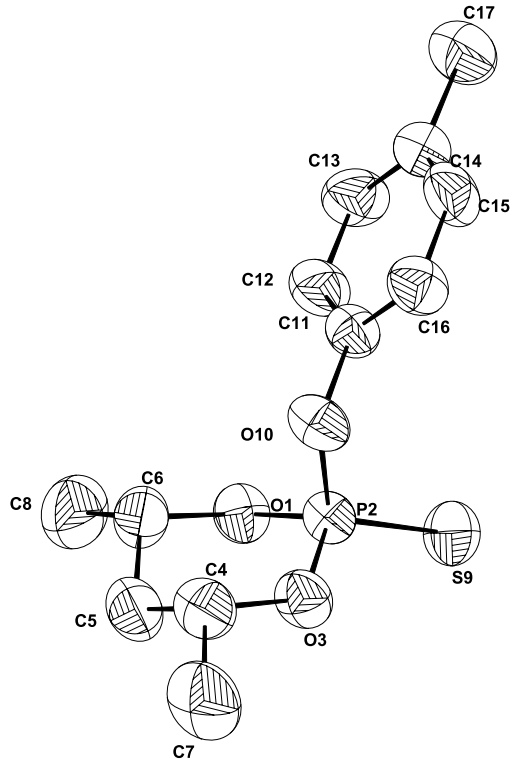


Figure 3. ORTEP drawing of *ax*-2-*p*-methylphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (**10**-*ax*).

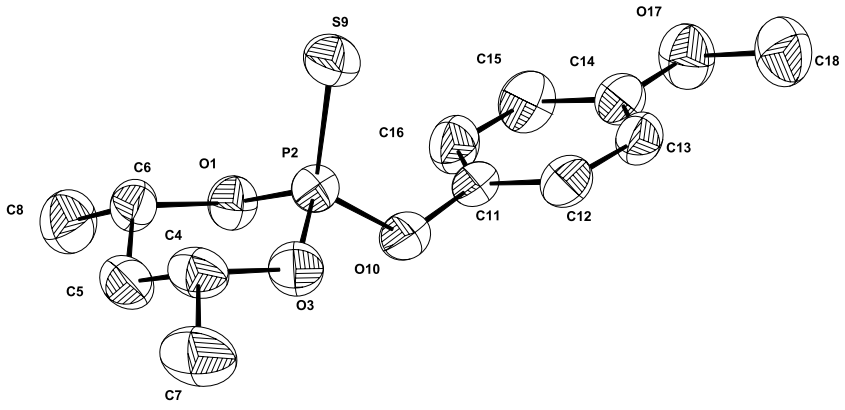


Figure 4. ORTEP drawing of *eq*-2-*p*-methoxyphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (**11**-*eq*).

(ω_{POCC5}) are in the range of 44.6–55.8°; and the internal (ω_{OPOC}) are in the range of 33.1–52.7°] being the flattening less severe for **11**-*eq* than all others. The OPO ring flattening has also been found in analog phosphates.[9a]

The Baeyer and Pitzer strain[4,29] are summarized in Table 11 for compounds **2**-*ax*, **2**-*eq*, **10**-*ax* and **11**-*eq* [calculated as the average of the internal bond angles (θ), and torsion angles (ω) of the dioxaphosphinane ring, respectively]. Taking into consideration that the bond angle in a molecule free of Baeyer strain (propane) is 112.4°, the molecule with the highest Baeyer strain is **2**-*eq* (113.1°). Contrary to what is expected, the intraannular torsion angles also decrease for **2**-*eq* more than for any other compound (51.7–54.3° vs 47.5°) leading to considerable Pitzer strain. As a consequence, there is not a very good agreement between the values of $\cos\omega$ and $-\cos\theta/(1+\cos\theta)$ for this molecule (0.68 vs 0.65) as for the others, indicating that the compromise between bond angles and torsion angles imposed by the constraint of the dioxaphosphinane ring which leads to the minimum strain in **2**-*eq*, is not perfect. We have observed that for thiophosphoramidates in conformations other than chair, the compromise between $\cos\omega$ and $-\cos\theta/(1+\cos\theta)$ is not fulfilled either.[7] Our interpretation of this result is that due to the axial seeking characteristics of the *p*-NO_2-phenoxy substituent, the molecule will tend to deform out of an ideal chair that otherwise in the case of **2**-*eq* obligates the aryloxy group to

Table 7. X-ray crystal data for compounds **2**, **10**-*ax* and **11**-*eq*[a]

	2-*ax*	**2**-*eq*	**10**-*ax*	**11**-*eq*
Formula	$C_{11}H_{14}NO_5PS$	$C_{11}H_{14}NO_5PS$	$C_{12}H_{17}O_3PS$	$C_{12}H_{17}O_4PS$
Fw	303.26	303.28	272.29	288.30
Crystal system	Monoclinic	Monoclinic	Orthorombic *P*	Monoclinic
Crystal size (mm)	0.12×0.18×0.24	0.54×0.45×0.39	0.50×0.50×0.30	0.33×0.30×0.18
Space group	$P2_1/n$	$P2_1/c$	$P2_1\ n\ b$	$P2_1/a$
Radiation	Mo Kα	Mo Kα	Mo Kα	Mo Kα
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
a (Å)	8.04550(10)	6.856(1)	9.7597(10)	7.9454(10)
b (Å)	26.9886(4)	22.911(1)	11.257(2)	20.1215(10)
c (Å)	13.06750(10)	9.128(1)	12.9736(10)	9.4777(10)
α (deg)	90.00	90.00	90.00	90.00
β (deg)	95.805(6)	91.3(11)	90.00	104.407(10)
γ (deg)	90.00	90.00	90.00	90.00
V (Å^3)	2822.88(6)	1433.3(10)	1425.4(4)	1467.6(7)
Z	8	4	4	4
$2\theta_{max}$ (deg)	4.36–49.94	11–12	4.80–53.94	11–12
ρ_{calc} (mg m^{-3})	1.427	1.41	1.269	1.30
Absorption coefficient (mm^{-1})	0.357	0.351	0.333	0.333
No. of reflections collected	5315	3475	1645	2101
No. of independent reflections	4947	3122	1645	1792
No. of observed reflections	2142	2348	1298	1285
R_1 [$F>4\sigma(F)$]	0.0380	0.037	0.0338	0.0327
wR_2	0.1002	0.047	0.0961	0.0395
R_1 (all data)	0.1587	0.057	0.0500	0.0549
wR_2	0.1377	0.048	0.1060	0.0423
GOF on F^2	0.963	1.028	1.034	1.111
Max. shift for final cycle of least-squares	0.000	0.0004	0.000	0.0002
Δ/σ	0.000	0.000	0.001	0.000
Max. peak in final difference syntheses (e/Å^3)	0.223	0.33	0.344	0.17

[a] Standard deviations are in parentheses.

Table 8. Selected bond lengths (Å) for **2**, **10**-*ax* and **11**-*eq*[a]

	2-*ax* molecule A	**2**-*ax* molecule B	**2**-*eq*	**10**-*ax*	**11**-*eq*
O1–P2	1.559(3)	1.560(2)	1.5732(12)	1.565(3)	1.572(2)
O3–P2	1.562(3)	1.574(3)	1.5691(13)	1.568(2)	1.567(2)
O10–P2	1.605(3)	1.604(3)	1.5889(14)	1.601(3)	1.578(2)
S9–P2	1.8952(15)	1.8946(16)	1.9093(7)	1.9009(13)	1.9091(10)
O1–C6	1.476(6)	1.478(4)	1.466(2)	1.500(5)	1.472(3)
O3–C4	1.481(4)	1.470(5)	1.469(2)	1.508(6)	1.470(4)
C4–C5	1.515(5)	1.515(5)	1.504(3)	1.493(7)	1.494(4)
C5–C6	1.509(6)	1.512(5)	1.497(3)	1.519(7)	1.504(4)
C6–C8	1.505(5)	1.505(5)	1.502(3)	1.487(7)	1.498(4)
C4–C7	1.506(6)	1.513(5)	1.498(3)	1.511(7)	1.509(5)
C11–O10	1.403(4)	1.395(4)	1.403(2)	1.407(4)	1.406(3)

[a] Standard deviations in parentheses.

Table 9. Selected bond angles (θ) in deg for **2**, **10**-*ax* and **11**-*eq*[a]

	2-*ax* molecule A	**2**-*ax* molecule B	**2**-*eq*	**10**-*ax*	**11**-*eq*
O1–P2–O3	106.49(14)	105.92(14)	105.72(7)	105.78(14)	104.06(11)
O1–P2–O10	98.72(15)	99.94(14)	103.39(7)	105.33(15)	102.53(11)
O1–C6–C5	107.5(3)	108.6(3)	109.71(14)	106.9(3)	109.0(2)
O3–C4–C5	109.7(3)	109.0(3)	108.20(14)	110.0(3)	109.2(2)
O3–P2–O10	105.24(14)	104.81(14)	102.39(7)	100.33(15)	98.50(11)
O1–P2–S9	114.64(12)	114.83(11)	116.24(6)	113.65(11)	115.76(8)
O3–P2–S9	112.68(12)	113.82(12)	116.23(6)	114.77(12)	116.90(9)
C4–O3–P2	120.2(2)	117.0(2)	120.33(11)	120.6(3)	116.48(18)
C6–O1–P2	118.2(2)	119.3(2)	122.57(11)	118.0(3)	116.49(16)
C6–C5–C4	112.7(3)	113.5(3)	112.27(14)	111.8(4)	114.7(2)
P2–O10–C11	126.5(2)	124.2(2)	121.4(1)	122.2(2)	124.34(17)
O10–C11–C12	116.9(3)	115.9(3)	120.10(16)	121.8(3)	118.3(3)
O10–C11–C16	121.3(4)	121.9(3)	117.67(16)	117.0(3)	120.2(3)
S9–P2–O10	117.58(11)	116.01(11)	111.24(5)	115.58(11)	116.61(9)

[a] Standard deviations in parentheses.

Table 10. Selected torsion angles (ω) in deg. for **2**, **10**-*ax* and **11**-*eq*[a,b]

	2-*ax* molecule A	**2**-*ax* molecule B	**2**-*eq*	**10**-*ax*	**11**-*eq*
S9–P2–O3–C4	−165.36	−174.17	93.03	−165.97	76.35
O10–P2–O3–C4	65.30	58.07	−145.52	69.46	−157.93
O1–P2–O3–C4	−38.85	−47.07	−37.58	−39.85	−52.66
O1–C6–C5–C4	61.66	56.05	57.24	61.99	54.84
S9–P2–O1–C6	169.23	172.06	−97.54	170.43	−77.19
O10–P2–O1–C6	−64.92	−63.10	140.29	−62.08	154.73
O3–P2–O1–C6	43.90	45.56	33.06	43.62	52.50
P2–O3–C4–C5	47.03	55.30	50.56	49.23	55.77
P2–O3–C4–C7	170.86	179.08	177.98	171.63	179.03
P2–O1–C6–C8	−179.80	−173.55	−169.53	179.79	−178.82
P2–O1–C6–C5	−56.48	−51.43	−44.60	−56.37	−55.20
C11–O10–P2–O1	−179.36	−176.28	−61.19	−82.74	98.19
C11–O10–P2–O3	70.80	74.18	48.53	167.59	−155.26
C11–O10–P2–S9	−55.59	−52.24	173.35	43.57	−29.35
C12–C11–O10–P2	−124.54	132.16	80.42	59.32	112.70
C16–C11–O10–P2	58.92	−50.53	−102.95	−123.37	−72.75
O3–C4–C5–C6	−57.14	−58.85	−61.68	−58.90	−55.09
O10–P2–O3–C4	65.30	58.07	−145.52	69.46	−157.93
O1–P2–O3–C4	−38.85	−47.07	−37.58	−39.85	−52.66
P2–O1–C6–C5	−56.48	−51.43	−44.60	−56.37	−55.20

[a] Standard deviations in parentheses.
[b] Right-hand rule.[28]

be in the equatorial position. This argument might be supported by the fact that the aryloxy group in **2**-*eq* has torsion angles [$\omega_{O10PO1C6}=140.3°$ and $\omega_{O10PO3C4}=145.5°$] that are almost 40° away from the 180° (expected for the group in equatorial orientation) and pointing towards a pseudo-axial position.

3.5. Stereoelectronic interactions

Several years ago, Gorenstein[30] coined the term '*gauche* NMR effect' to support the observation that in molecules with *gauche* segments all the atoms that conform the segment tend to be shielded, therefore upfield shifted. In

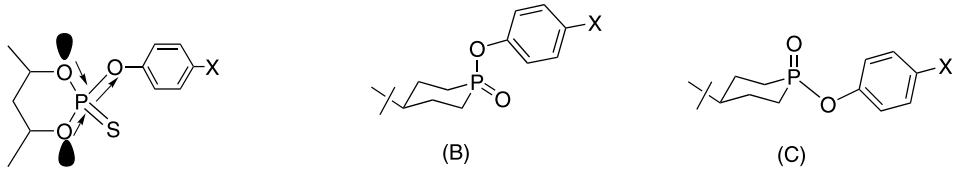
Table 11. Structural properties of **2**, **10**-*ax* and **11**-*eq*

	11-*eq*	**2**-*eq*	**10**-*ax*	**2**-*ax*	
				Molecule **A**	Molecule **B**
Geometry at phosphorus[a]	437.56	436.04	438.40	439.71	438.63
Baeyer strain[b]	111.66	113.13	112.18	112.47	112.22
Pitzer strain[c]	54.34	47.46	51.66	50.84	52.38
$\cos\omega$	0.58	0.68	0.62	0.63	0.61
$-\cos\theta/(1+\cos\theta)$	0.58	0.65	0.61	0.62	0.61

[a] Calculated as the sum of the bond angles (O1P2O3), [OP2O10(mean)], [OP2S9(mean)] and (S9P2O10) in deg.
[b] Calculated as the average value of the bond angles (O1P2O3), (O1C6C5), (O3C4C5), (C4O3P2), (C6C5C4), and (C6O1P2) in deg.
[c] Calculated as the average absolute value of the torsion angles (O1P2O3C4), (O1C6C5C4), (O3P2O1C6), (O3C4C5C6), (P2O3C4C5), and (P2O1C6C5) in deg.

cyclic six-membered ring dioxaphosphinanes the ^{31}P NMR signal of axial substituted compounds is normally upfield shifted from the equatorial,[2] thus demonstrating the participation of a *gauche* NMR effect. The ground, in which this *gauche* NMR effect relies is the decrease in the intraannular OPO bond of the dioxaphosphinanes, and it was nicely demonstrated by Gorenstein[27] that at least in phosphates there is a correlation between the OPO bond angle and the ^{31}P NMR chemical shift. We thought of the possibility to explain the observed reversibility of ^{31}P NMR shifts with σ_p or substituent-induced chemical shifts (SCS) with the changes in OPO bond angles, however unfortunately we found the opposite, that means that the compounds of the same series of thiophosphates, axial or equatorial, with smaller intraannular OPO bond are downfield shifted than those with larger OPO bond angles. For example, the OPO angle for **2**-*ax* is 106.2° and for **10**-*ax* is 105.78° and their ^{31}P NMR are shifted to 54.3 and 56.2 ppm, respectively; by the same taken, the OPO bond angle for **2**-*eq* is 105.72° and for **11**-*eq* is 104.06° and their ^{31}P NMR signals are shifted to 59.2 and 61.0 ppm, respectively. The other factor that can be disregarded from our data is that the shielding of the ^{31}P NMR signal is due to a dπ–pπ interaction involving the aryloxy group[31,32] because in such case, we would expect that an ER group as *p*-OCH_3 would enhance the orbital overlap causing an upfield shift of the signal and an EW group as *p*-NO_2 a downfield shift. Alternatively the reversibility found in SCS may be explained by an effect of a compensation of charge density to the ^{31}P nucleus given by the assistance of the free electron pairs of the *endo*-cyclic oxygens of the dioxaphosphinane ring, when an EW group is substituted in the *para* position of the phenyl ring of the aromatic thiophosphate, as shown in Scheme 6 (structure A). This hypothesis is supported by the fact that analog phosphinanes[33] where compensation of charge density on phosphorus by *endo*-cyclic α-atoms is not possible, show a normal SCS trend (Scheme 6, structures B and C).

It is worthwhile to note that the transfer of charge density by *endo*-cyclic oxygens to phosphorus give rise to the known attractive *endo*-anomeric $n_\pi O–\sigma^*_{P–OAr}$ hyperconjugative interaction for axial thiophosphates that stabilize the chair conformation with the aryl-EW group more than with the aryl-ER. On the other hand, the attractive *endo*-anomeric $n_\pi O–\sigma^*_{P=S}$ hyperconjugative interaction for equatorial thiophosphates stabilizes the P=S group in the axial position of a chair conformation more than P=O in analog equatorial phosphates.[34] Indeed, by doing an individual examination of the bond lengths (Table 8), we observed that the data indicate clearly that both *endo*-hyperconjugative interactions do participate in the stabilization of these anancomeric thiophosphates (see Scheme 2). In particular, for **2**-*ax* we found that *endo*-cyclic O1–P2 or O3–P2 bonds are shorter [1.560 Å (mean between molecule A and B) and 1.568 Å (mean between molecule A and B), respectively] than the *exo*-cyclic O10–P [1.605 Å (mean between molecule A and B)]. For **10**-*ax* we also found evidence of the $n_\pi O–\sigma^*_{P–OAr}$ *endo*-hyperconjugative interaction since the O1–P2 or O3–P2 bonds (1.565 and 1.568 Å, respectively) are shorter than O10–P2 (1.601 Å). The fact that the shortening of the *endo*-cyclic O–P bonds in **2**-*ax* (X=NO_2) is more pronounced than in **10**-*ax* (X=Me) [1.564 Å (mean) for **2**-*ax* vs 1.567 Å (mean) for **10**-*ax*] and the lengthening of the O10–P2 bond is also more important for **2**-*ax* than for **10**-*ax* [1.605 Å for **2**-*ax* vs 1.601 Å for **10**-*ax*] is in agreement with the increase in the axial seeking characteristics of aryloxy substituted with EW as compared with ER groups. On the other hand, for the equatorial thiophosphates **2**-*eq* (X=NO_2) and **11**-*eq* (X=OCH_3) the anomeric $n_\pi O–\sigma^*_{P=S}$ *endo*-hyperconjugative interaction is supported by the shortening of the *endo*-cyclic O1–P2 or



Scheme 6.

O3–P2 bonds [1.572 Å (mean) for **2**-*eq* and 1.570 Å (mean) for **11**-*eq*], although somewhat less than in the axial isomers, and slight lengthening of the P=S bonds (1.909 Å for **2**-*eq* or **11**-*eq* vs 1.895 and 1.901 Å for **2**-*ax* and **10**-*ax*, respectively). It is clear that this stereoelectronic mechanism of stabilization of the equatorial thiophosphates is less important than the axial one, because in the equilibria of mobile aryl thiophosphates the axial conformer always predominates over the equatorial.[1,2] This might be a result of the bonding electron repulsion caused by the lone pairs on sulfur when it is in the axial position.[11]

4. Conclusions

The conformational analysis of a series of axial and equatorial anancomeric *p*-X-aryloxy thiophosphates is analyzed in terms of the electronic characteristics of the *p*-substituent. The coupling constants $^{3}J_{HH}$, $^{3}J_{HP}$ and $^{3}J_{CP}$ and X-ray structures suggest that in solution and solid state, the 1,3,2-dioxaphosphinane ring is in a chair conformation regardless of configuration. We observed that there is a reverse substituent-induced chemical shifts on the ^{31}P NMR signals being the effect more pronounced for axial than for equatorial thiophosphates. These results could be explained by the compensation of charge density on phosphorus by the lone pairs on *endo*-cyclic oxygens of the dioxaphosphinane ring for thiophosphates substituted with aryl EW groups.

The structural analysis performed by X-ray on four thiophosphates, two axial and two equatorial, led to the conclusion that in all cases, the dioxaphosphinane ring is flatten in the OPO region and is lacking of perpendicular symmetry being the *endo*-cyclic oxygens flat regions of the ring and the phosphorus atom a puckery end. A thoroughful analysis of bond distances allowed to support the participation of the anomeric $n_{\pi}O–\sigma^{*}_{P–OAr}$ *endo*-hyperconjugative interaction for to stabilization of axial thiophosphates and the anomeric $n_{\pi}O–\sigma^{*}_{P=S}$ *endo*-hyperconjugative interaction for to stabilization equatorial thiophosphates, both in chair conformations.

5. Experimental

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on Jeol Eclipse 270 and Bruker Avance 300 spectrometers in $CDCl_3$ (δ 7.26, ^{1}H; δ 77.0, ^{13}C), ^{1}H at 270.2 and 300.1 MHz, ^{13}C at 67.8 and 75.5 MHz, and ^{31}P at 109.3 and 121.5 MHz, respectively. Phosphorus NMR spectra are reported in ppm downfield (+) from 85% H_3PO_4 used as external standard. Mass spectra (EI) were measured on a Hewlett Packard 5989A spectrometer using electron impact (EI) at 70 eV. The reactions were performed under an atmosphere of nitrogen in oven-dried glassware. Solvents and solutions were transferred by syringe-septum and cannula techniques. Toluene was of reagent grade and was dried and distilled immediately before use from sodium/benzophenone. Triethylamine was dried and distilled from $LiAlH_4$. Products were purified by flash column chromatography on silica gel 230–400 mesh. Yields are given for isolated products. Galbraith Laboratories, Inc., Knoxville, TN performed microanalyses of configurational isomers **3**–**9**. Microanalyses of configurational isomers **2**, **10**, **11** and **12**-*eq* were recorded in Thermo Finnigan Flash 1112 analyzer.

n-Hexane was used for recrystallization of all samples, affording crystals suitable for X-ray diffraction analysis. Crystallographic work was performed in an Enraf-Nonius CAD-4 diffractometer. Data collection: CAD-4 Software.[35] Cell refinement: CAD-4 Software. Data reduction for the axial structures **2**-*ax* and **10**-*ax*: WINGX,[36] solved by direct methods SHELXS97[37] and refined with SHELXL97.[38] Data reduction for the equatorial structures **2**-*eq* and **11**-*eq*: CRYSTALS,[39] solved and refined with CRYSTALS.[39] Molecular graphics: CAMERON[40] and dihedral angles: PLATON.[41] Crystallographic data for structures have been deposited at Cambridge Crystallographic Data Center and the deposition numbers are: CCDC 234720 for **2**-*ax*, CCDC 234719 for **10**-*ax*, CCDC 235613 for **2**-*eq*, and CCDC 235614 for **11**-*eq*.

5.1. General procedure for the preparation of intermediates arylphosphites

Route A. In a three-necked 250 mL flask, fitted with a stirbar, and rubber septa, were placed 3.64 mmol of *p*-X-phenol, and 45 mL of dry toluene. The solution was stirred at room temperature until the *p*-X-phenol was solubilized (in the case of some *p*-X-phenols as *p*-acetamido, and *p*-amino, 10 mL of acetonitrile was added in order to solubilize them), then 3.64 mmol of the phosphorochloridite **1**, followed by 3.64 mmol of triethylamine were added at once, via syringe, resulting in precipitation of triethylammonium chloride. The suspension was stirred for 5 min and the solid was filtered off through a filter tipped cannula. The solid was washed two times with 15 mL of dry toluene collecting the filtrate in a round-bottomed flask. The solvent was then removed under vacuum without heating to avoid epimerization of the equatorial phosphites to the axial ones. In all cases, products were yellowish oils.

Route B. In a three-necked 250 mL flask, fitted with dropping funnel, a stirbar, and rubber septa, were placed 3.64 mmol of *p*-X-phenol, 3.64 mmol of triethylamine, and 45 mL of dry ethyl ether. The mixture was stirred at room temperature for 30 min and 3.64 mmol of the phosphorochloridite **1** was added dropwise via syringe maintaining the stirring for additional 30 min. The solid in the resulting suspension was filtered off through a filter tipped cannula and the filtrate added to a lateral outlet round-bottomed flask equipped with a stirbar, rubber septa and reflux condenser. The solution was heated under reflux for 2 h and after cooling, the solvent was removed in a rotary evaporator. In all cases, products were yellowish oils.

Route C. In a round-bottomed 250 mL flask, fitted with reflux condenser, a stirbar, and rubber septa, were placed 3.64 mmol of the equatorial phosphites (obtained from route A) and 45 mL of dry toluene. The solution was stirred under reflux for 12–48 h until the epimerization to the axial isomers was complete. The epimerization process was followed by ^{31}P NMR (equatorial phosphites are downfield shifted than axial phosphites by around 5 ppm, see

Scheme 5). Phosphites substituted with electron releasing groups (ERG) took longer for to epimerize than those substituted with electron-withdrawing groups (EWG). After cooling, the solvent was removed under vacuum in a rotary evaporator.

5.2. General procedure for the preparation of aryl thiophosphates 2–12

In a round-bottomed 100 mL flask, fitted with a reflux condenser, a stirbar, and rubber septa, were placed 2.21 mmol of elemental sulfur. A solution of 2.21 mmol of equatorial phosphite (obtained from route A) or axial phosphite (obtained from route B or C) in 60 mL of dry toluene was added to the flask and the resulting suspension was stirred under reflux for 24 h. After cooling, the suspension was concentrated under vacuum and the residue washed with an aqueous solution of 10% sodium bicarbonate. The product was extracted with methylene chloride and the organic layer dried over sodium sulfate. The solvent was removed in a rotary evaporator and the crude product was purified by flash chromatography using hexane/ethyl acetate as eluent.

5.2.1. *ax*-2-Chloro-*cis*-4,6-dimethyl-1,3,2-λ^3-dioxaphosphinane (1). This compound was obtained from a mixture of *meso*- and *rac*-pentanediols and phosphorus trichloride by the stereoselective approach reported by us.[42]

5.2.2. *ax*-2-*p*-Nitrophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (2-*ax*). According to the general procedure described above, 1.0 g (3.69 mmol) of axial *p*-nitrophenyl phosphite (route B), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 75:25) gave 1.0 g of yellow crystals (90% yield) of mp 111–112 °C. ^{1}H NMR δ 1.42 (d, J=2.3 Hz, 6H), 1.86 (m, J=14.6, 11.3, 1.0 Hz, 1H), 1.90 (m, J=14.6, 3.0, 2.6 Hz, 1H), 4.76 (m, J=11.3, 6.2, 3.0, 2.6 Hz, 2H), 7.36 (dd, ^3J=8.9 Hz, $^4J_{HP}$=1.2 Hz, 2H), 8.24 (d, ^3J=8.9 Hz, 2H); ^{13}C NMR δ 22.4 (d), 40.6 (d), 77.7 (d), 121.3 (d, C_o), 126.0 (s, C_m), 145.1 (s, C_p), 156.2 (d, C_i); ^{31}P NMR δ 54.3. Mass spectrum (*m*/*z*) 303 (M^+), 262 (M^+-41), 236 (M^+-67), 218 (M^+-85), 171 (M^+-132), 149 (M^+-154), 123 (M^+-180), 97 (M^+-206), 69 (M^+-234), 41 (M^+-262). Anal. Calcd for $C_{11}H_{14}O_5PNS$: C, 43.57; H, 4.65. Found: C, 43.67; H, 4.85.

5.2.3. *eq*-2-*p*-Nitrophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (2-*eq*). According to the general procedure described above, 1.5 g (5.54 mmol) of equatorial *p*-nitrophenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 75:25) gave 1.52 g of pale yellow crystals (91% yield) of mp 90–91 °C. ^{1}H NMR δ 1.41(d, J=2.2 Hz, 6H), 1.77 (m, J=14.6, 10.5, 1.0 Hz, 1H), 1.90 (m, J=14.6, 2.6, 2.8 Hz, 1H), 4.85 (m, J=10.5, 6.3, 2.6, 1.2 Hz, 2H), 7.35 (dd, ^3J=9.2 Hz, $^4J_{HP}$=1.6 Hz, 2H), 8.23 (d, ^3J=8.9 Hz, 2H); ^{13}C NMR δ 22.1 (d), 40.8 (d), 76.1 (d), 122.1 (d, C_o), 125.4 (s, C_m), 145.1 (s, C_p), 155.0 (d, C_i); ^{31}P NMR δ 59.2. Mass spectrum (*m*/*z*) 303 (M^+), 262 (M^+-41), 236 (M^+-67), 218 (M^+-85), 205 (M^+-98), 171 (M^+-132), 149 (M^+-154), 123 (M^+-180), 97 (M^+-206), 69 (M^+-234), 41 (M^+-262). Anal. Calcd for $C_{11}H_{14}O_5PNS$: C, 43.57; H, 4.65. Found: C, 43.80; H, 4.51.

5.2.4. *ax*-2-*p*-Cyanophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (3-*ax*). According to the general procedure described above, 1.0 g (3.98 mmol) of axial *p*-cyanophenyl phosphite (route B), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 85:15) gave 1.04 g of the product as pale yellow crystals (93% yield) of mp 110–111 °C. ^{1}H NMR δ 1.43 (d, J=2.5 Hz, 6H), 1.85 (m, J=14.8, 10.5, 1.5 Hz, 1H), 1.87 (m, J=14.8, 2.5, 1.3 Hz, 1H), 4.73 (m, J=10.5, 6.4, 2.5, 1.2 Hz, 2H), 7.30 (dd, ^3J=9.1 Hz, $^4J_{HP}$=1.3 Hz, 2H), 7.65 (d, ^3J=9.1 Hz, 2H); ^{13}C NMR δ 22.3 (d), 40.3 (d), 77.1 (d), 108.8 (s, CN), 118.3 (s, C_p), 121.3 (d, C_o), 134.1 (s, C_m), 154.3 (d, C_i); ^{31}P NMR δ 54.5. Mass spectrum (*m*/*z*) 283 (M^+), 242 (M^+-41), 216 (M^+-67), 197 (M^+-86), 165 (M^+-118), 149 (M^+-134), 119 (M^+-164), 90 (M^+-193), 69 (M^+-234), 41 (M^+-242). Anal. Calcd for $C_{12}H_{14}O_3PNS$: C, 50.88; H, 4.98. Found: C, 50.91; H, 5.16.

5.2.5. *eq*-2-*p*-Cyanophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (3-*eq*). According to the general procedure described above, 1.5 g (5.97 mmol) of equatorial *p*-cyanophenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 1.52 g of the product as pale yellow crystals (90% yield) of mp 106–107 °C. ^{1}H NMR δ 1.41 (d, J=2.0 Hz, 6H), 1.79 (m, J=14.5, 11.2 Hz, 1H), 1.87 (m, J=14.5, 2.7, 3.6 Hz, 1H), 4.84 (m, J=11.2, 6.6, 2.7, 3.3 Hz, 2H), 8.26 (d, ^3J=8.6 Hz, 2H), 8.57 (d, ^3J=8.9 Hz, 2H); ^{13}C NMR δ 22.1 (d), 40.9 (d), 76.0 (d), 109.4 (s, CN), 118.1 (s, C_p), 122.4 (s, C_o), 133.8 (s, C_m), 152.6 (d, C_i); ^{31}P NMR δ 59.3. Mass spectrum (*m*/*z*) 283 (M^+), 242 (M^+-41), 216 (M^+-67), 197 (M^+-86), 165 (M^+-118), 149 (M^+-134), 119 (M^+-164), 90 (M^+-193), 69 (M^+-234), 41 (M^+-242). Anal. Calcd for $C_{12}H_{14}O_3PNS$: C, 50.88; H, 4.98. Found: C, 51.02; H, 5.21.

5.2.6. *ax*-2-*p*-Formylphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (4-*ax*). According to the general procedure described above, 1.0 g (3.94 mmol) of axial *p*-formylphenyl phosphite (route B), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 60:40) gave 1.01 g of the product as oil (90% yield). ^{1}H NMR δ 1.42 (d, J=2.2 Hz, 6H), 1.83 (m, J=13.0, 8.0 Hz, 1H), 1.85 (m, J=13.0, 2.7, 1.5 Hz, 1H), 4.75 (m, J=8.0, 6.2, 2.7, 1.2 Hz, 2H), 7.35 (dd, ^3J=8.6 Hz, $^4J_{HP}$=1.5 Hz, 2H), 7.87 (d, ^3J=8.6 Hz, 2H), 9.94 (s, CHO); ^{13}C NMR δ 22.1 (d), 40.2 (d), 76.7 (d), 120.7 (d, C_o), 131.7 (d, C_m), 133.3 (s, C_p), 155.4 (d, C_i), 190.8 (s, CHO); ^{31}P NMR δ 55.1. Mass spectrum (*m*/*z*) 286 (M^+), 245 (M^+-41), 219 (M^+-67), 199 (M^+-87), 167 (M^+-119), 149 (M^+-137), 138 (M^+-148), 121 (M^+-165), 97 (M^+-189), 69 (M^+-217), 41 (M^+-245). Anal. Calcd for $C_{12}H_{15}O_4PS$: C, 50.35; H, 5.28. Found: C, 50.46; H, 5.40.

5.2.7. *eq*-2-*p*-Formylphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (4-*eq*). According to the general procedure described above, 1.0 g (3.94 mmol) of equatorial *p*-formylphenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 60:40) gave 1.02 g of brown crystals (91% yield)

of mp 55–57 °C. ^{1}H NMR δ 1.34 (d, J=2.3 Hz, 6H), 1.54 (m, J=14.5, 10.4, 1.8 Hz, 1H), 1.69 (m, J=14.5, 2.7, 2.3 Hz, 1H), 4.79 (m, J=10.4, 6.3, 2.7, 2.8 Hz, 2H), 7.30 (m, 2H), 7.80 (m, 2H), 9.91 (s, CHO); ^{13}C NMR δ 22.1 (d), 40.8 (d), 75.9 (d), 122.0 (d, C_o), 131.4 (d, C_m), 133.6 (s, C_p), 155.0 (d, C_i), 190.8 (s, CHO); ^{31}P NMR δ 59.5. Mass spectrum (*m/z*) 286 (M^+), 219 (M^+-67), 199 (M^+-87), 169 (M^+-117), 149 (M^+-137), 138 (M^+-148), 122 (M^+-164), 85 (M^+-201), 69 (M^+-217), 41 (M^+-245). Anal. Calcd for $C_{12}H_{15}O_4PS$: C, 50.35; H, 5.28. Found: C, 50.35; H, 5.41.

5.2.8. *ax*-2-*p*-Bromophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (5-*ax*). According to the general procedure described above, 1.0 g (3.27 mmol) of axial *p*-bromophenyl phosphite (route B), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 85:15) gave 1.03 g of white crystals (93% yield) of mp 132–133 °C. ^{1}H NMR δ 1.42 (d, J=2.2 Hz, 6H), 1.82 (m, J=14.8, 10.8, 1.0 Hz, 1H), 1.87 (m, J=14.8, 2.8, 2.7 Hz, 1H), 4.75 (m, J=10.8, 6.2, 2.8, 1.2 Hz, 2H), 7.19 (dd, ^3J=8.9 Hz, $^4J_{HP}$=1.4 Hz, 2H), 7.49 (d, ^3J=8.9 Hz, 2H); ^{13}C NMR δ 22.4 (d), 40.8 (d), 77.2 (d), 118.3 (s, C_p), 122.6 (d, C_o), 133.1 (s, C_m), 150.6 (d, C_i); ^{31}P NMR δ 55.5 (56.0). Mass spectrum (*m/z*) 338 (M^++1), 296 (M^+-41), 270 (M^+-67), 188 (M^+-149), 172 (M^+-165), 149 (M^+-188), 69 (M^+-268), 41 (M^+-296). Anal. Calcd for $C_{11}H_{14}O_3PSBr$: C, 39.19; H, 4.19. Found: C, 39.17; H, 4.16.

5.2.9. *eq*-2-*p*-Bromophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (5-*eq*). According to the general procedure described above, 1.5 g (4.91 mmol) of equatorial *p*-bromophenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 1.54 g of white crystals (90% yield) of mp 64–65 °C. ^{1}H NMR δ 1.32 (d, J=2.0 Hz, 6H), 1.64 (m, J=14.5, 10.6 Hz, 1H), 1.77 (m, J=14.5, 2.8, 2.3 Hz, 1H), 4.76 (m, J=10.9, 6.3, 2.6, 2.3 Hz, 2H), 7.01 (dd, ^3J=8.6 Hz, $^4J_{HP}$=1.3 Hz, 2H), 7.38 (d, ^3J=8.6 Hz, 2H); ^{13}C NMR δ 22.0 (d), 40.9 (d), 75.6 (d), 118.6 (s, C_p), 123.1 (d, C_o), 132.5 (s, C_m), 149.5 (d, C_i); ^{31}P NMR δ 60.0. Mass spectrum (*m/z*) 338 (M^++1), 305 (M^+-32), 252 (M^+-85), 190 (M^+-147), 172 (M^+-165), 149 (M^+-188), 101 (M^+-236), 69 (M^+-268), 41 (M^+-296). Anal. Calcd for $C_{11}H_{14}O_3PSBr$: C, 39.19; H, 4.19. Found: C, 39.21; H, 4.28.

5.2.10. *ax*-2-*p*-Chlorophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (6-*ax*). According to the general procedure described above, 2.8 g (10.73 mmol) of axial *p*-chlorophenyl phosphite (route A-to-C), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 85:15) gave 0.72 g of white crystals (23% yield) of mp 126–128 °C. ^{1}H NMR δ 1.45 (d, J=2.1 Hz, 6H), 1.83 (m, J=14.1, 11.1, 1.1 Hz, 1H), 1.90 (m, J=14.1, 3.0, 1.3 Hz, 1H), 4.75 (m, J=11.1, 6.6, 3.0, 1.1 Hz, 2H), 7.12 (d, ^3J=8.8 Hz, 2H), 7.30 (d, ^3J=8.8 Hz, 2H); ^{13}C NMR δ 22.6 (d), 40.6 (d), 76.7 (d), 121.7 (d, C_o), 129.8 (s, C_p), 130.5 (s, C_m), 149.5 (d, C_i); ^{31}P NMR δ 55.6. Mass spectrum (*m/z*) 292 (M^+), 224 (M^+-68), 149 (M^+-143), 128 (M^+-164), 99 (M^+-193), 69 (M^+-154), 41 (M^+-251). Anal. Calcd for $C_{11}H_{14}O_3PSCl$: C, 45.14; H, 4.82. Found: C, 45.27; H, 5.04.

5.2.11. *eq*-2-*p*-Chlorophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (6-*eq*). According to the general procedure described above, 2.8 g (10.73 mmol) of equatorial *p*-chlorophenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 90:10) gave 1.54 g of white crystals (50% yield) of mp 59–60 °C. ^{1}H NMR δ 1.39 (d, J=2.0 Hz, 6H), 1.71 (m, J=14.0, 11.2 Hz, 1H), 1.87 (m, J=14.0, 3.0, 2.3 Hz, 1H), 4.83 (m, J=11.2, 6.6, 3.0, 2.5 Hz, 2H), 7.16 (d, ^3J=8.6 Hz, 2H), 7.38 (d, ^3J=8.6 Hz, 2H); ^{13}C NMR δ 22.5 (d), 41.3 (d), 76.1 (d), 122.9 (d, C_p), 123.1 (d, C_o), 130.1 (d, C_m), 149.4 (d, C_i); ^{31}P NMR δ 60.1. Mass spectrum (*m/z*) 292 (M^+), 224 (M^+-68), 149 (M^+-143), 128 (M^+-164), 99 (M^+-193), 69 (M^+-154), 41 (M^+-251). Anal. Calcd for $C_{11}H_{14}O_3PSCl$: C, 45.14; H, 4.82. Found: C, 45.17; H, 4.98.

5.2.12. *ax*-2-*p*-Acetamidophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (7-*ax*). According to the general procedure described above, 3.0 g (10.73 mmol) of axial *p*-acetamidophenyl phosphite (route A-to-C), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 85:15) gave 0.75 g of white crystals (22% yield) of mp 188–190 °C. ^{1}H NMR δ 1.44 (d, J=2.3 Hz, 6H), 1.86 (m, J=13.0, 12.9, 1.0 Hz, 1H), 1.88 (m, J=13.0, 2.9, 1.8 Hz, 1H), 2.79 (s, 3H), 4.77 (m, J=12.9, 6.2, 2.9, 1.3 Hz, 2H), 7.12 (d, ^3J=8.9 Hz, 2H), 7.49 (d, ^3J=8.9 Hz, 2H), 8.56 (s, 1H); ^{13}C NMR δ 22.5 (d), 24.7 (s), 42.7 (d), 76.8 (d), 121.9 (d, C_o), 122.6 (s, C_p), 135.1 (s, C_m), 147.5 (d, C_i), 168.4 (s); ^{31}P NMR δ 55.9. Mass spectrum (*m/z*) 315 (M^+), 273 (M^+-42), 205 (M^+-110), 187 (M^+-128), 125 (M^+-190), 108 (M^+-207), 69 (M^+-246), 43 (M^+-272). Anal. Calcd for $C_{13}H_{18}O_4PNS$: C, 49.52; H, 5.75. Found: C, 49.64; H, 5.79.

5.2.13. *eq*-2-*p*-Acetamidophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (7-*eq*). According to the general procedure described above, 3.0 g (10.73 mmol) of equatorial *p*-acetamidophenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 70:30) gave 1.54 g of pale yellow crystals (90% yield) of mp 102–104 °C. ^{1}H NMR δ 1.38 (d, J=2.4 Hz, 6H), 1.75 (m, J=14.1, 10.8 Hz, 1H), 1.85 (m, J=14.1, 2.3, 2.3 Hz, 1H), 2.14 (s, 3H), 4.80 (m, J=10.8, 6.2, 2.3, 2.6 Hz, 2H), 7.10 (dd, ^3J=8.6 Hz, $^4J_{HP}$=1.3 Hz, 2H), 7.46 (d, ^3J=8.6 Hz, 2H), 7.64 (s, 1H); ^{13}C NMR δ 22.4 (d), 24.7 (s), 41.1 (d), 75.8 (d), 121.0 (s, C_p), 121.7 (d, C_o), 135.5 (s, C_m), 149.6 (d, C_i), 168.6 (s); ^{31}P NMR δ 60.4. Mass spectrum (*m/z*) 315 (M^+), 273 (M^+-42), 229 (M^+-86), 205 (M^+-110), 187 (M^+-128), 125 (M^+-190), 108 (M^+-207), 69 (M^+-246), 43 (M^+-272). Anal. Calcd for $C_{13}H_{18}O_4PNS$: C, 49.52; H, 5.75. Found: C, 49.64; H, 5.92.

5.2.14. *ax*-2-Phenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (8-*ax*).[15] According to the general procedure described above, 1.0 g (4.42 mmol) of axial phenyl phosphite (route B), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 95:5) gave 1.05 g of white crystals (92% yield) of mp 120–122 °C. ^{1}H NMR δ 1.43 (d, J=2.6 Hz, 6H), 1.82 (m, J=13.8, 9.9,

1.0 Hz, 1H), 1.88 (m, J=14.4, 2.8, 2.6 Hz, 1H), 4.79 (m, J=10.8, 6.6, 2.8, 1.3 Hz, 2H), 7.19 (m, 3H), 7.35 (m, ^3J=8.9 Hz, 2H); ^{13}C NMR δ 21.9 (d), 39.9 (d), 76.2 (d), 119.8 (d, C_o), 125.5 (s, C_p), 129.5 (s, C_m), 150.5 (d, C_i); ^{31}P NMR δ 55.8.

5.2.15. *eq*-2-Phenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (8-*eq*).[15] According to the general procedure described above, 3.0 g (13.27 mmol) of equatorial phenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 98:2) gave 3.18 g of white crystals (93% yield) of mp 55–56 °C. ^{1}H NMR δ 1.39 (d, J=2.3 Hz, 6H), 1.70 (m, J=14.5, 10.9 Hz, 1H), 1.89 (m, J=14.5, 2.6, 2.3 Hz, 1H), 4.83 (m, J=10.9, 6.3, 2.6, 2.3 Hz, 2H), 7.20 (m, 3H), 7.35 (m, 2H); ^{13}C NMR δ 22.1 (d), 41.0 (d), 75.4 (d), 121.1 (d, C_o), 125.5 (s, C_p), 129.5 (s, C_m), 150.3 (d, C_i); ^{31}P NMR δ 60.4.

5.2.16. *ax*-2-*p*-Phenylphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (9-*ax*). According to the general procedure described above, 3.5 g (11.59 mmol) of axial *p*-phenylphenyl phosphite (route B, or the sequence A-to-C), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 98:2) gave 3.48 g of white powder (90% yield) of mp 145–146 °C. ^{1}H NMR δ 1.44 (d, J=2.2 Hz, 6H), 1.83 (m, J=13.8, 9.9, 1.0 Hz, 1H), 1.88 (m, J=13.8, 2.9, 2.9 Hz, 1H), 4.81 (m, J=9.9, 6.2, 2.9, 1.2 Hz, 2H), 7.27 (m, 2H), 7.35 (m, 1H), 7.44 (m, 2H), 7.59 (m, 4H); ^{13}C NMR δ 22.5 (d), 40.7 (d), 77.1 (d), 121.0 (d, C_o), 127.4 (s, C_m), 127.8 (s, $C_{p'}$), 128.7 (s, $C_{o'}$), 129.2 (s, $C_{m'}$), 138.5 (s, C_p), 140.5 (s, $C_{i'}$), 150.8 (d, C_i); ^{31}P NMR δ 55.8. Mass spectrum (*m*/*z*) 334 (M^+), 266 (M^+-68), 186 (M^+-148), 170 (M^+-164), 141 (M^+-193), 91 (M^+-243), 69 (M^+-265), 28 (M^+-306). Anal. Calcd for $C_{17}H_{19}O_3PS$: C, 61.07; H, 5.73. Found: C, 61.05; H, 5.44.

5.2.17. *eq*-2-*p*-Phenylphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (9-*eq*). According to the general procedure described above, 2.5 g (8.27 mmol) of equatorial *p*-phenylphenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 98:2) gave 2.51 g of white powder (91% yield) of mp 165–166 °C. ^{1}H NMR δ 1.34 (d, J=2.0 Hz, 6H), 1.67 (m, J=14.2, 9.9 Hz, 1H), 1.77 (m, J=14.2, 2.9, 2.3 Hz, 1H), 4.78 (m, J=9.9, 6.2, 2.9, 3.0 Hz, 2H), 7.19 (m, 2H), 7.28 (m, 1H), 7.36 (m, 2H), 7.48 (m, 4H); ^{13}C NMR δ 22.1 (d), 41.0 (d), 75.5 (d), 121.5 (d, C_o), 127.0 (s, $C_{m'}$), 127.3 (s, $C_{p'}$), 128.2 (s, $C_{o'}$), 128.8 (s, C_m), 138.6 (d, C_p), 140.2 (s, $C_{i'}$), 149.9 (d, C_i); ^{31}P NMR δ 60.4. Mass spectrum (*m*/*z*) 334 (M^+), 266 (M^+-68), 186 (M^+-148), 170 (M^+-164), 141 (M^+-193), 115 (M^+-219), 85 (M^+-249), 69 (M^+-265), 41 (M^+-293). Anal. Calcd for $C_{17}H_{19}O_3PS$: C, 61.07; H, 5.73. Found: C, 61.28; H, 6.00.

5.2.18. *ax*-2-*p*-Methylphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (10-*ax*). According to the general procedure described above, 1.5 g (6.25 mmol) of axial *p*-methylphenyl phosphite (route B, or the sequence A-to-C), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 1.03 g of white crystals (89% yield) of mp 138–139 °C. ^{1}H NMR δ 1.41 (d, J=2.2 Hz, 6H), 1.82 (m, J=14.5, 10.7, 1.1 Hz, 1H), 1.84 (m, J=14.5, 3.0, 2.7 Hz, 1H), 2.32 (s, CH_3), 4.77 (m, J=10.7, 6.2, 3.0, 1.2 Hz, 2H), 7.06 (dd, ^3J=8.5 Hz, $^4J_{HP}$=1.5 Hz, 2H), 7.17 (d, ^3J=8.5 Hz, 2H); ^{13}C NMR δ 20.9 (s, CH_3), 22.4 (d), 40.7 (d), 76.9 (d), 120.4 (s, C_p), 130.6 (d, C_o), 135.3 (s, C_m), 148.8 (d, C_i); ^{31}P NMR δ 56.2. Mass spectrum (*m*/*z*) 272 (M^+), 204 (M^+-68), 186 (M^+-86), 149 (M^+-123), 124 (M^+-148), 108 (M^+-164), 91 (M^+-181), 69 (M^+-203), 43 (M^+-229), 41 (M^+-231). Anal. Calcd for $C_{12}H_{17}O_3PS$: C, 52.93; H, 6.29. Found: C, 53.03; H, 6.40.

5.2.19. *eq*-2-*p*-Methylphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (10-*eq*). According to the general procedure described above, 3.5 g (14.58 mmol) of equatorial *p*-methylphenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 3.6 g of white crystals (91% yield) of mp 82–83 °C. ^{1}H NMR δ 1.34 (d, J=2.6 Hz, 6H), 1.59 (m, J=14.5, 11.2, 2.3 Hz, 1H), 1.72 (m, J=14.5, 2.6, 2.6 Hz, 1H), 2.27 (s, CH_3), 4.80 (m, J=10.9, 6.3, 2.6, 2.6 Hz, 2H), 7.03 (dd, ^3J=8.6 Hz, $^4J_{HP}$=2.0 Hz, 2H), 7.08 (d, ^3J=8.6 Hz, 2H); ^{13}C NMR δ 20.8 (s, CH_3), 22.1 (d), 41.0 (d), 75.3 (d), 121.0 (d, C_o), 129.9 (d, C_o), 135.1 (s, C_m), 148.3 (d, C_i); ^{31}P NMR δ 60.9. Mass spectrum (*m*/*z*) 272 (M^+), 204 (M^+-68), 186 (M^+-86), 149 (M^+-123), 124 (M^+-148), 108 (M^+-164), 91 (M^+-181), 69 (M^+-203), 43 (M^+-229), 41 (M^+-231). Anal. Calcd for $C_{12}H_{17}O_3PS$: C, 52.93; H, 6.29. Found: C, 52.73; H, 6.41.

5.2.20. *ax*-2-*p*-Methoxyphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (11-*ax*). According to the general procedure described above, 3.0 g (11.71 mmol) of axial *p*-methoxyphenyl phosphite (route B, or the sequence A-to-C), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 85:15) gave 2.93 g of white powder (92% yield) of mp 94–96 °C. ^{1}H NMR δ 1.42 (d, J=2.2 Hz, 6H), 1.81 (m, J=14.5, 10.8, 1.0 Hz, 1H), 1.86 (m, J=14.5, 3.3, 3.0 Hz, 1H), 3.78 (s, OCH_3), 4.77 (m, J=10.8, 6.2, 3.3, 1.2 Hz, 2H), 6.78 (dd, ^3J=8.8 Hz, $^4J_{HP}$=1.5 Hz, 2H), 6.87 (d, ^3J=8.8 Hz, 2H); ^{13}C NMR δ 22.4 (d), 40.7 (d), 56.0 (s, OCH_3), 76.9 (d), 115.0 (s, C_m), 121.7 (d, C_o), 144.9 (d, C_i), 157.29 (d, C_p); ^{31}P NMR δ 56.7. Mass spectrum (*m*/*z*) 288 (M^+), 220 (M^+-68), 202 (M^+-86), 140 (M^+-148), 124 (M^+-164), 95 (M^+-193), 69 (M^+-219), 41 (M^+-247). Anal. Calcd for $C_{12}H_{17}O_4PS$: C, 49.99; H, 5.94. Found: C, 50.06; H, 6.11.

5.2.21. *eq*-2-*p*-Methoxyphenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (11-*eq*). According to the general procedure described above, 2.5 g (9.76 mmol) of equatorial *p*-methoxyphenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 1.54 g of white crystals (90% yield) of mp 93–94 °C. ^{1}H NMR δ 1.31 (d, J=2.0 Hz, 6H), 1.63 (m, J=14.5, 10.9 Hz, 1H), 1.75 (m, J=14.5, 2.6, 2.6 Hz, 1H), 3.71 (s, OCH_3), 4.73 (m, J=10.9, 6.3, 2.6, 2.6 Hz, 2H), 6.77 (dd, ^3J=8.9 Hz, $^4J_{HP}$=1.6 Hz, 2H), 7.04 (d, ^3J=8.9 Hz, 2H); ^{13}C NMR δ 22.0 (d), 40.9 (d), 55.6 (s, OCH_3), 75.6 (d), 114.3 (s, C_m), 122.0 (d, C_o), 144.0 (d, C_i), 156.9 (d, C_p); ^{31}P NMR δ 61.0. Mass spectrum (*m*/*z*) 288 (M^+), 220 (M^+-68), 202 (M^+-86), 170 (M^+-118), 140 (M^+-148), 124 (M^+-164), 119 (M^+-169), 95 (M^+-193), 69 (M^+-219), 41 (M^+-247). Anal. Calcd

for $C_{12}H_{17}O_4PS$: C, 49.99; H, 5.94. Found: C, 49.81; H, 6.29.

5.2.22. *ax*-2-*p*-Aminophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (12-*ax*). A mixture of 1.3 g (11.86 mmol) of *p*-aminophenyl phosphites (*ax*/*eq* 7:93) was obtained through route B. The mixture was maintained at room temperature because heating led to decomposition of the intermediate phosphites. The mixture of phosphites was treated with elemental sulfur according to the general procedure described above. Flash chromatography (hexanes/ethyl acetate 35:65) was unsuccessful to purify the axial isomer, therefore it was analyzed as a mixture. ^{13}C NMR δ 22.3 (d), 40.5 (d), 76.2 (d), 116.5 (s, C_m), 121.1 (d, C_o), 144.8 (d, C_i), 143.8 (s, C_p); ^{31}P NMR δ 56.8.

5.2.23. *eq*-2-*p*-Aminophenoxy-2-thio-*cis*-4,6-dimethyl-1,3,2λ^5-dioxaphosphinane (12-*eq*). According to the general procedure described above, 4.0 g (23.73 mmol) of equatorial *p*-aminophenyl phosphite (route A), was treated with elemental sulfur. Flash chromatography (hexanes/ethyl acetate 35:65) gave 1.5 g of brown crystals (23% yield) of mp 93–94 °C. ^{1}H NMR δ 1.38 (d, J=2.0 Hz, 6H), 1.68 (m, J=14.5, 11.2 Hz, 1H), 1.82 (m, J=14.5, 2.6, 2.6 Hz, 1H), 3.25 (br, NH_2), 4.52 (m, J=11.2, 6.6, 2.6, 3.3 Hz, 2H), 6.64 (m, 2H), 6.98 (m, 2H); ^{13}C NMR δ 21.9 (d), 40.8 (d), 75.8 (d), 115.4 (s, C_m), 121.8 (d, C_o), 142.6 (d, C_i), 142.6 (s, C_p); ^{31}P NMR δ 61.3. Mass spectrum (*m*/*z*) 274 ($M^+ + 1$), 205 ($M^+ - 68$), 187 ($M^+ - 86$), 125 ($M^+ - 148$), 109 ($M^+ - 164$), 94 ($M^+ - 179$), 69 ($M^+ - 204$), 41 ($M^+ - 232$). Anal. Calcd for $C_{11}H_{16}O_3PNS$: C, 48.35; H, 5.90. Found: C, 48.52; H, 6.04.

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The facile preparation of alkenyl metathesis synthons

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Dedicated to Professor Robert H. Grubbs on the occasion of his receiving the Tetrahedron Prize for Creativity in Organic Chemistry

Abstract—We report synthetic methodology allowing the preparation of any length alkenyl halide from inexpensive starting reagents. Standard organic transformations were used to prepare straight chain α-olefin halides in excellent overall yields with no detectable olefin isomerization and full recovery of any unreacted starting material. Reported transformations can be used for the selective incorporation of pure α-olefin metathesis sites in highly functionalized molecules.

1. Introduction

Olefin metathesis has emerged as one of the primary methods for mild carbon–carbon bond formation in organic synthesis, having been widely used across many areas of chemical research. Functional group tolerant ruthenium based catalysts permit the metathesis of highly functionalized compounds that were previously incompatible with traditional catalysts.[1] The development of these stable and reactive catalysts, such as Grubbs' second-generation complex, has expanded metathesis' utility in polymer chemistry[2,3] and more recently in small molecule synthesis.[4–8] Difficult cross-metathesis and ring-closing metathesis reactions can now be accomplished allowing access to large ring systems[9] and functionalized polymer architectures.[10] The application of efficient and mild transformations such as ring closing metathesis (RCM),[11] ring opening metathesis (ROM),[12] and cross-metathesis (CM) has led to pervasive use of olefin metathesis in small molecule and polymer chemistry.[13]

In general, RCM is valuable for selective and efficient ring closures of large functionalized natural products and supramolecularly organized substrates.[14] Application of ROM in combination with CM effectively produces complex ring-opened cross-metathesis products from the coupling of cyclic and linear olefins; this method has been used to connect large molecules and is readily applied in total synthesis.[15] In addition, advances in CM and the understanding of olefin reactivity have stimulated the development of complex synthetic schemes where two or more olefins can be reacted regio- and stereoselectively forming only the target olefin in excellent yields.[16] Acyclic diene metathesis (ADMET), a special form of CM yielding polymers, has been used in materials synthesis and industrial polymer modeling.[2] This rapid rise in olefin metathesis popularity, utility, and catalyst improvement has generated the need for inexpensive, high yielding α-olefin constructs and the means of incorporating metathesis sites into various complex architectures.

We now report three facile and inexpensive synthetic routes to a family of pure α-alkenyl halide metathesis synthons possessing exact methylene run lengths. These synthetic procedures and routine purification methods afford high yields of olefins with no detectable double bond isomerization. The mild transformations reported can also be used to place olefins in highly functionalized molecules without the need for expensive starting materials.

2. Results and discussion

Metathesis ideology has fueled the development of next generation catalyst systems for the production of specific, highly functionalized target molecules for medical and consumer use. Consequently, a large scale, high-yielding α-olefin synthesis is needed to produce molecules for subsequent substitution and metathesis chemistry. Before any metathesis can occur, olefins must be incorporated into substrates where mild and inexpensive techniques would be

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preferred for the creation of target olefins. While well-known literature techniques yield α-olefins directly or transform complex substrates into metathesis active compounds, unwanted side reactions occur leading to low yields.[17,18] This makes recovery of pure starting materials difficult and expensive, while reaction products are sometimes extensively isomerized. These are common problems associated with α-olefin synthesis, and they often lead to structural defects when isomerized olefins are used in metathesis transformations.

Metathesis strategy in small molecule modification typically targets one specific regio- and stereoselective attachment of functionality to produce a high yield of a single molecule. While this facet of synthesis is important, controlling the number of methylene units between olefins is paramount when targeting specific ring size or exact structure. With this in mind, acyclic diene metathesis (ADMET) polymerization of symmetrical α,ω-diene monomers and ROMP of symmetrical cyclic olefins have become the polymerization methods of choice for the preparation of polymers with exact repeat units.

Substrate purity for metathesis reactions is essential, as structural flaws lead to low yielding ring closures, the isolation of the wrong metathesis products, or ill-defined polymer microstructure. Inclusion of internal and external olefins as starting materials in metathesis poses problems as methylene run lengths within product structure will be varied based on extent of olefin isomerization. In the case of small molecule synthesis, variable methylene content in the substrate yields different ring-sizes for RCM or incorrect methylene run lengths for ROM or CM reactions (Scheme 1). The inclusion of isomerized olefins in starting material synthesis creates ill-defined structures leading to numerous olefinic products.

The construction of ADMET monomers and isolation of exact polymer structures begins with the synthesis of pure α-olefins. Errors due to inclusion of isomerized olefins during polymer synthesis become multiplied with high olefin turnover, and ultimately these errors produce random polymer structures and ill-defined methylene run lengths between functional groups. These defects are detrimental for polymer modeling studies and lead to poor material properties relative to polymers obtained from purely α-olefins.[19] We have addressed these problems starting with the inexpensive synthesis of 1-alkenyl bromides, reagents that can be regarded as metathesis synthons in ADMET, cross-metathesis, and RCM chemistry (Scheme 1).

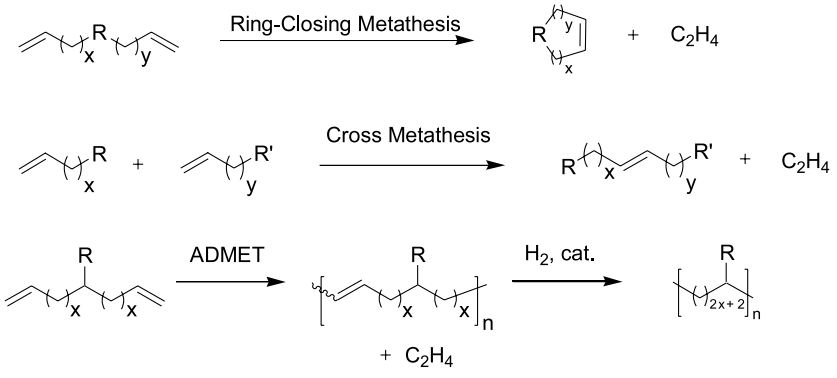
We have devised two routes to these synthons; the preparation of pure α,ω-alkenyl halides was performed either by the reduction of alkenyl esters or through the elimination of HBr from alkyl dibromides. Both routes are described herein, along with a procedure to generate long chain α-alkenyl halide synthons.

2.1. Alkenyl halide metathesis synthons from alkenyl esters

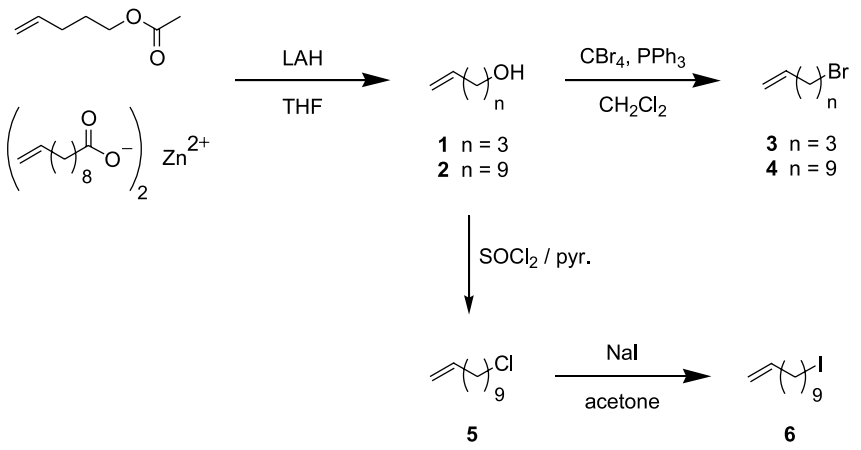
The key to success in generating ADMET, cross-metathesis and RCM dienes is found in locating a source of pure α-alkenyl halide bulk starting materials. Numerous sources of such starting materials exist based on alkenyl esters derived from fatty acids with no isomerization of the pendent olefin. These molecules can be easily reduced to their corresponding alcohols, and literature describing the reduction of various alkenyl esters extends to the 1940s including LAH reactions,[20–23] titanium mediated reductions of esters,[24,25] and polymethylhydrosilane reductions.[26] We have chosen the inexpensive conversion of an α-olefin ester or carboxylate to an alcohol using LAH in THF (Scheme 2). This method was chosen specifically for the reduction of 4-pentenyl ester as the byproduct ethanol could be easily removed via rotary evaporation.

These inexpensive reactions were done on the 100-gram scale in a large flask with sufficient volume for post reaction workup. Upon product isolation, compounds **1** and **2** were characterized via ^{1}H NMR and GC with no detectable olefin isomerization and above 90% purity. Both alkenyl alcohols were clean enough to move onto the next transformation without any further purification.

Conversion of these alkenyl alcohols to corresponding bromides was done using carbon tetrabromide and triphenyl phosphine. This reaction appears to be the most efficient route when considering all reasonable possibilities including the use of phosphorus tribromide,[27] bromine,[28] trifluoro aceticanhydride,[29] and various other conversions that first convert the alcohol to a good leaving group such as a mesylate[30,31] or a silyl ether.[32] The bromination with CBr_4 proceeded quickly and was complete almost as fast as all components could be mixed. The byproduct acid,



Scheme 1. Cross-metathesis, ring closing metathesis and the ADMET reaction.



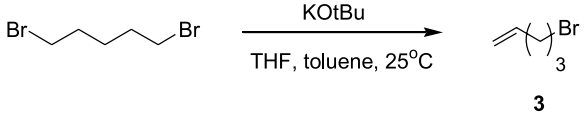
Scheme 2. Alkenyl halide synthesis.

bromoform, does not isomerize the olefin and allows for isolation of clean α-olefin in good yields.

Synthesis of chlorine-functionalized α-olefins has been previously reported and is usually performed neat via addition of $SOCl_2$ to the liquid alcohol.[21–23] We performed this conversion by adding the $SOCl_2$ to a solution of alkenyl alcohol **2** in pyridine acting as a solvent and an acid trap. Upon vacuum distillation, the alkenyl chloride **5** was obtained in good yield. Conversion of the chloride to the alkenyl iodide was performed by a Finkelstein reaction with sodium iodide in acetone.[33]

2.2. Alkenyl halide metathesis synthons via selective dihalide elimination

A method of olefin incorporation within molecules was desired in addition to the production of inexpensive starting reagents for metathesis synthesis. Mild elimination conditions were developed allowing a second method of α-olefin production that could also permit olefin incorporation in functionalized molecules where application of substitution chemistry is unavailable. Literature methods designed to prepare alkenes and alkenyl halides involve the elimination of bromo and dibromo alkanes using hexamethylphophortriamide (HMPT).[17,18] This route is expensive and potentially dangerous due to the highly carcinogenic compound HMPT. Harsh conditions and the highly reactive HMPT lead to a myriad of byproducts that interfere with purification and further, the high temperatures needed for this conversion (150 °C) can result in olefin isomerization in addition to halide elimination. One other disadvantage to this elimination chemistry is the inability to recover unreacted starting material from the complex reaction mixture. Recently, a potassium butoxide elimination has been reported affording alkenyl halides in good yield.[34] A milder, higher yielding room temperature route is presented in Scheme 3.



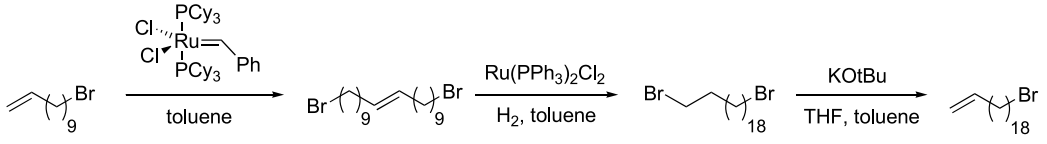
Scheme 3. A mild elimination route towards the synthesis of alkenyl bromide metathesis synthons.

Simple KO*t*Bu driven elimination in a THF/toluene solvent mixture produces the target molecules in ~65% yield. This elimination reaction is started at 0 °C and is allowed to warm to room temperature over 1 h. Upon quenching with aqueous acid, the dibromide/alkenyl bromide mixture can be easily purified affording the target molecule. The recovered dibromide can be recycled for further conversion to alkenyl bromide as necessary.

2.3. Synthesis of larger alkenyl bromide metathesis synthons

Up to this point, the incorporation of metathesis sites into target molecules has been limited by commercial availability and expense of alkenyl bromides. This is especially true when considering the preparation of longer chain alkenyl bromides, a problem that has been overcome by exploiting and extending the chemistry described in the previous sections. As an example of this strategy, we synthesized an alkenyl bromide containing 20 carbons, a molecule which is commercially unavailable.

The synthesis of extended alkenyl bromides began with the self-metathesis of **4** with Grubbs' first generation catalyst to afford **7** (Scheme 4). This dibromide was converted to **8** by exhaustive hydrogenation in a Parr bomb with Wilkinson's Rh catalyst under hydrogen pressure. The saturated 20-carbon dibromide **8** was then converted to the target



Scheme 4. The preparation of long chain alkenyl bromide metathesis synthons.

extended chain alkenyl bromide **9** using the same elimination procedure previously described for smaller alkenyl bromides. Pure compound **9** was obtained in good yield after recrystallization and column chromatography, and recovery of the pure starting reagents was accomplished during purification since very few side reactions accompany these mild transformations.

3. Conclusions

Three mild, inexpensive routes have been devised for the production of pure α-olefin containing halides as metathesis synthons. Using these methods, virtually any 1-alkenyl bromide can be made in high yields and devoid of olefin isomerization. Many of the reactions discussed here are either quantitative in nature, or the starting reagent can be easily recovered for further use.

4. Experimental

4.1. General information

All ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Varian Associates Mercury 300 spectrometer. Chemical shifts are given in ppm and referenced to residual $CHCl_3$ at 7.27 ppm (^{1}H) and 77.23 ppm (^{13}C) with 0.03 v/v% TMS as an internal standard. Splitting patterns are designated s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Gas chromatography was performed on a Shimadzu GC-17A chromatograph equipped with a RTX-5 (Restek Corp.) 15 m column and a HP-5 (Hewlett Packard) 25 m column with FID detection. Compounds were examined using mass spectrometry performed by The University of Florida Mass Spectrometry Services and elemental analysis performed by Atlantic Microlabs (Norcross, GA).

4.2. Materials

All starting materials were purchased from Aldrich except for acetic acid 4-pentenyl ester, which was supplied by TCI America. Grubbs' first generation [Ru] catalyst was synthesized as previously described by Grubbs et al.[35] Dry solvents were collected using an Aldrich keg system removing residual water by alumina filtration.

4.3. Synthesis of alkenyl alcohols

4.3.1. 4-Pentene-1-ol (1). Acetic acid pent-4-enyl ester (250 mL, 1.77 mol) was added dropwise over 2 h to a slurry of LAH (23.7 g, 0.625 mol) in diethyl ether (500 mL) at 0 °C. The solution was allowed to warm to room temperature over 1 h while stirring. The reaction was quenched via the sequential addition of 23 mL deionized water (23 mL), 15% (w/v) NaOH (23 mL), and deionized water (69 mL) waiting approximately 5 min between additions. The solution was allowed to stir the mixture became a bright white slurry. Additional ether (~125 mL) was added and the solution was filtered, dried over $MgSO_4$, and concentrated to a colorless oil. Compound **1** was obtained in 85% yield and 97% purity by GC. The ^{1}H NMR spectrum was consistent with the published spectrum.[36]

4.3.2. 10-Undecene-1-ol (2). Zinc undecylenate (250 g, 0.579 mol) was added over 30 min via powder funnel to a stirred slurry of LAH (25.0 g, 0.659 mol) in dry THF (400 mL) in a 5 L round bottom flask at 0 °C. After the addition, the solution was allowed to warm to room temperature over 1 h while stirring. The reaction was quenched via addition of deionized water (25 mL), 15% (w/v) NaOH (25 mL), and more water (75 mL) waiting approximately 15 min between additions. The solution was allowed to stir until cool, and the reaction mix appeared as a white slurry. All precipitate was filtered, and the solution was concentrated to a turbid oil. The crude mixture was dissolved in ether (100%, v/v) and stirred over $MgSO_4$ (15 g) for 45 min. The solution was filtered and concentrated to afford compound **2** as a colorless oil in 87% yield (97% pure by GC). The ^{1}H NMR spectrum was consistent with the published spectrum.[24]

4.4. Synthesis of alkenyl halides from alkenyl alcohols

4.4.1. 5-Bromo-1-pentene (3). A solution of **1** (100 g, 1.16 mol) and carbon tetratbromide (424 g, 1.27 mol) in dichloromethane (500 mL) was prepared in a 2 L flask and cooled to 0 °C. Triphenyl phosphine (333 g, 1.28 mol) was added via powder funnel in portions over 30 min with vigorous stirring. Upon addition of the phosphine, the colorless solution turned a pale brown color and was stirred for an additional 2 h at room temperature. The mixture was concentrated to a brown oil and quickly added to stirring hexane (1 L). The white precipitate was filtered, and the remaining solution was concentrated and fractionally distilled yielding compound **3** as a colorless oil (80%). The ^{1}H NMR spectrum was consistent with the published spectrum.[37]

4.4.2. 11-Bromo-1-undecene (4). Using the procedure outlined for compound **3** (above), bromide **4** was prepared using alcohol **2** (150 g, 0.881 mol), carbon tetrabromide (323 g, 0.976 mol), triphenyl phosphine (255 g, 0.976 mol), and 800 mL of dichloromethane. Fractional distillation yielded compound **4** as a colorless liquid (95%). The ^{1}H NMR spectrum was consistent with the published spectrum.[28]

4.4.3. 11-Chloro-1-undecene (5). In an argon purged 3 L round bottom flask, distilled thionyl chloride (259 g, 2.17 mol) was added dropwise over 1 h via cannula into a solution of **2** (200 g, 1.28 mol) in pyridine (50 mL). Upon compete addition, the reaction was heated to 50 °C for 2 h, cooled, and quenched via the addition of water (300 mL) and diethyl ether (300 mL) letting stir for 1 h. The remaining mixture was extracted, and the organic phase was washed with saturated $NaHCO_3$ (2×150 mL) and distilled water (100 mL). The solution was dried over $MgSO_4$, concentrated, and vacuum distilled to a colorless oil **5** (70%). The ^{1}H NMR spectrum was consistent with the published spectrum.[38]

4.4.4. 11-Iodo-1-undecene (6). Sodium iodide (40.7 g, 0.271 mol) was added to distilled **5** (30.6 g, 0.162 mol) in

acetone (150 mL) and allowed to reflux for 3 days. The reaction mixture was then cooled and flooded with ether (300 mL). The precipitate was filtered and the ether solution was washed with water (2×100 mL). The organic layer was extracted, dried with $MgSO_4$, filtered, and concentrated to a colorless oil **6** (89%). The ^{1}H NMR spectrum was consistent with the published spectrum.[39]

4.5. Synthesis of alkenyl bromides from dibromides

4.5.1. 5-Bromo-1-pentene (3). In a 1 L round bottom flask 1,5-dibromopentane (100 g, 0.434 mol) was dissolved in 450 mL of a 1:1 THF/toluene solution to favor the single eliminated product. The flask was cooled to 0 °C followed by the addition of solid KO*t*Bu (73.0 g, 0.651 mol) over 30 min. After addition, the reaction was quenched using 1 M HCl (300 mL) and the organic layer was extracted, washed with saturated Na_2CO_3 (100 mL), and dried over magnesium sulfate. The solution was concentrated and distilled yielding 44 g of compound **3** (69%). The ^{1}H NMR spectrum was consistent with the published spectrum.[37]

4.5.2. 1,20-Dibromo-eicos-10-ene (7). In an argon filled glove box, compound **4** (100 g, 429 mmol) was added to a 500 mL round bottom flask followed by Grubbs' catalyst (706 mg, 0.885 mmol, 500:1). The flask was heated at 35 °C for 24 h under a constant stream of argon. After 1 day, the flask was placed under vacuum (10 Torr) for an additional 48 h, cooled, and quenched with ethyl vinyl ether (5 mL). The crude reaction mixture was dissolved in toluene (200 mL) and precipitated into methanol (1000%, v/v) over the course of 30 min. The product was filtered as a white crystalline solid and washed with excess methanol yielding 75 g (80%). The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ (ppm) 1.20–1.50 (br, 24H), 1.88 (q, 4H, $J_1=7.0$ Hz, $J_2=7.0$ Hz, CH_2CH_2Br), 2.01 (m, 4H, allylic CH_2), 3.42 (t, 4H, $J=6.7$ Hz, CH_2Br), 5.40 (m, 2H, olefin); ^{13}C NMR ($CDCl_3$): δ (ppm) 28.4, 29.3, 29.7, 29.8, 32.8, 33.1, 34.4, 130.3; EI/HRMS: $[M]^+$ calcd for $C_{20}H_{38}Br_2$: 438.1322, found: 438.1312.

4.5.3. 1,20-Dibromo-eicosane (8). In a 125 mL Parr bomb glass sleeve, compound **7** (35 g, 80 mmol) was dissolved in a minimal amount of toluene (~80 mL). Wilkinson's Rh hydrogenation catalyst (100 mg, 0.104 mmol) was added, and the bomb was charged with 800 psi of hydrogen. The reaction was allowed to proceed for 24 h at 50 °C. Additional toluene (200 mL) was added, and upon cooling to 0 °C, the product **8** crystallized out of solution and was collected by filtration. The filtrate was concentrated (~50%), and the product was allowed to crystallize again. Upon isolation of the product from the second crystallization, both portions were combined and washed with cold toluene. Yield: 30 g (86%). The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ (ppm) 1.28 (br, 28H), 1.42 (m, 4H, $J=6.7$ Hz), 1.88 (q, 4H, $J_1=6.7$ Hz, $J_2=7.2$ Hz, CH_2CH_2Br), 3.42 (t, 4H, $J=6.9$ Hz, CH_2Br); ^{13}C NMR ($CDCl_3$): δ (ppm) 28.4, 29.7, 29.8, 30.0, 33.1, 34.4; EI/HRMS: $[M]^+$ calcd for $C_{20}H_{40}Br_2$: 440.1478, found: 440.1616.

4.5.4. 20-Bromo-eicos-1-ene (9). In a 1 L round bottom flask compound **8** (50 g, 113 mmol) was dissolved in 2:1 THF/toluene mixture producing a 1 M solution. The mixture was cooled using an ice water bath, and potassium *tert*-butoxide (19.0 g, 170 mmol) was added in 2 g portions over 30 min. After addition, the reaction turned cloudy and was allowed to stir at 0 °C for 1 h. The reaction was quenched using water (100 mL) followed by 1 M HCl (100 mL). The organic layer was extracted and washed with 1 M HCl (50 mL), saturated Na_2CO_3 (50 mL), and 50 mL of water followed by drying with magnesium sulfate. The solution was concentrated yielding 38 g of crude material. Compound **9** was purified by room temperature recrystallization from 1-butanol (5 w/v%) followed by column chromatography using hexane. Compound **9** was collected as white solid. Yield: 24 g (60%). The following spectral properties were observed: ^{1}H NMR ($CDCl_3$): δ (ppm) 1.20–1.50 (br, 30H), 1.88 (q, 2H, $J=7.2$ Hz, CH_2CH_2Br), 2.01 (q, 2H, allylic CH_2), 3.42 (t, 2H, $J=6.9$ Hz, CH_2Br), 5.09 (m, 2H, $RHC{=}CH_2$), 5.76 (m, 1H, $RHC{=}CH_2$); ^{13}C NMR ($CDCl_3$): δ (ppm) 28.4, 29.3, 29.7, 29.8, 32.8, 33.1, 34.4, 114.3, 139.4; EI/HRMS: $[M]^+$ calcd for $C_{20}H_{39}Br$: 358.2235, found: 358.2246.

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Enantiospecific synthesis of isomers of AES, a new environmentally friendly chelating agent

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Abstract—Three four-step enantiospecific syntheses of different diastereomers of AES, a new biodegradable chelating agent, are described. The stereocenters in each of the isomers are accessible from L- and D-malic and aspartic acids.

1. Introduction

Due to the increasing use of chelating agents, their environmental fate has become an important issue.[1] Approximately 50,000 tons of aminopolycarboxylates such as EDTA and DTPA are used annually; mainly in the textile, detergent and pulp and paper industries.[2] EDTA and DTPA have proven to be practically non-biodegradable in standard tests.[3] For this reason, alternative chelating agents such as the aspartic acid derivatives ethylene diamine disuccinic acid (EDDS) and iminodisuccinic acid (IDS) have become more popular as biodegradable chelating agents, particularly for detergent applications.[4]

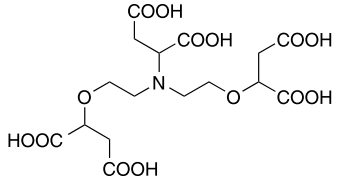
A series of novel diethanolamine derivatives such as aspartic acid ethoxysuccinate (AES) have recently been introduced as chelating agents suitable for pulp and paper applications (Fig. 1).[5] Due to its higher biodegradability, lower nitrogen content and capacity to form inert complexes with iron and manganese ions, AES is a more environmentally friendly alternative to EDTA and DTPA in the pulp and paper industry.[6] A non-selective but industrially viable route to AES via a lanthanum catalyzed Michael addition of diethanolamine to maleate has recently been described.[7] The presence of three stereogenic centers in the AES molecule gives rise to stereoisomerism. When the pseudo-symmetrical nature of the AES molecule is taken into account, one can observe that the (*S*,*S*,*R*) and the (*R*,*S*,*S*) isomers are identical to each other, as are the (*S*,*R*,*R*) and the (*R*,*R*,*S*) isomers. For this reason, there are only six possible isomers of AES, consisting of three pairs of enantiomers (Fig. 2).

Based on previous studies with the EDDS isomers,[8] the different AES isomers are expected to have different biodegradability characteristics. For full characterization of these new chelating agents, we therefore needed access to all AES isomers. Herein, we present a simple and efficient protocol for the enantiospecific synthesis of AES.

2. Results and discussion

The three chiral centers of AES are, in principle, accessible from (*R*)- and (*S*)-isomers of the readily available malic and aspartic acids. Connecting these building blocks to form the AES framework, however, is not straightforward. There are numerous possible side-reactions including the formation of lactams and lactones as well as retro-Michael reactions.

Retrosynthetic analysis of the target molecule reveals two suitable synthetic strategies which use malic and aspartic



AES (1)

Figure 1. Structure of AES (**1**).

Keywords: Aldehydes; Amino acids; Chelating agents; Reductive amination; Stereoisomerism.
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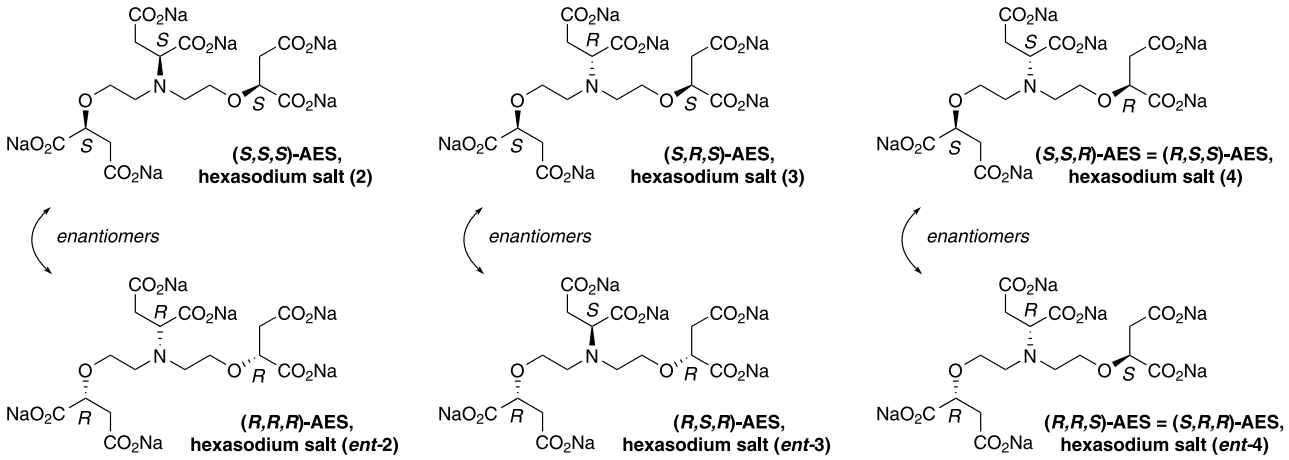
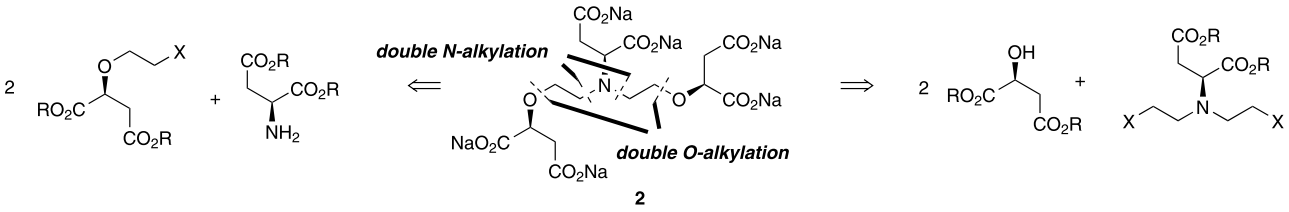


Figure 2. Structures of all AES isomers.

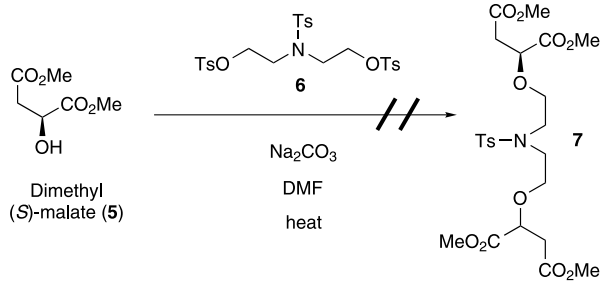


Scheme 1. Retrosynthetic analysis.

acid as starting materials: double *O*-alkylation and double *N*-alkylation (Scheme 1). Of the two disconnections, the double *N*-alkylation strategy appears more attractive since it would, at least in principle, allow the stepwise construction of the molecule by two consecutive *N*-alkylation steps. Thus, the (*S*,*S*,*R*) isomers could also be accessed by this method.

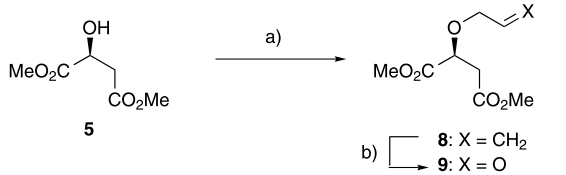
We were also further discouraged from pursuing the *O*-alkylation strategy by our initial attempts at *O*-alkylation of (*S*)-malic acid dialkyl esters with tosylated diethanolamine derivatives (Scheme 2). Instead of the desired *O*-alkylation, the reaction invariably produced the corresponding morpholines derived from the tosylate **6**.

There are several reductive amination methods available which reliably give the monoalkylation product so we decided to use this approach next to perform double *N*-alkylation of the aspartate methyl ester using a suitable malic acid derived aldehyde.[9] This approach would provide easy access to all AES isomers since the final reductive amination could then be performed with either of the enantiomeric aldehydes. However, we recognized that the requisite dialkylation reaction could be a difficult task given the low nucleophilicity of the monoalkylation product.

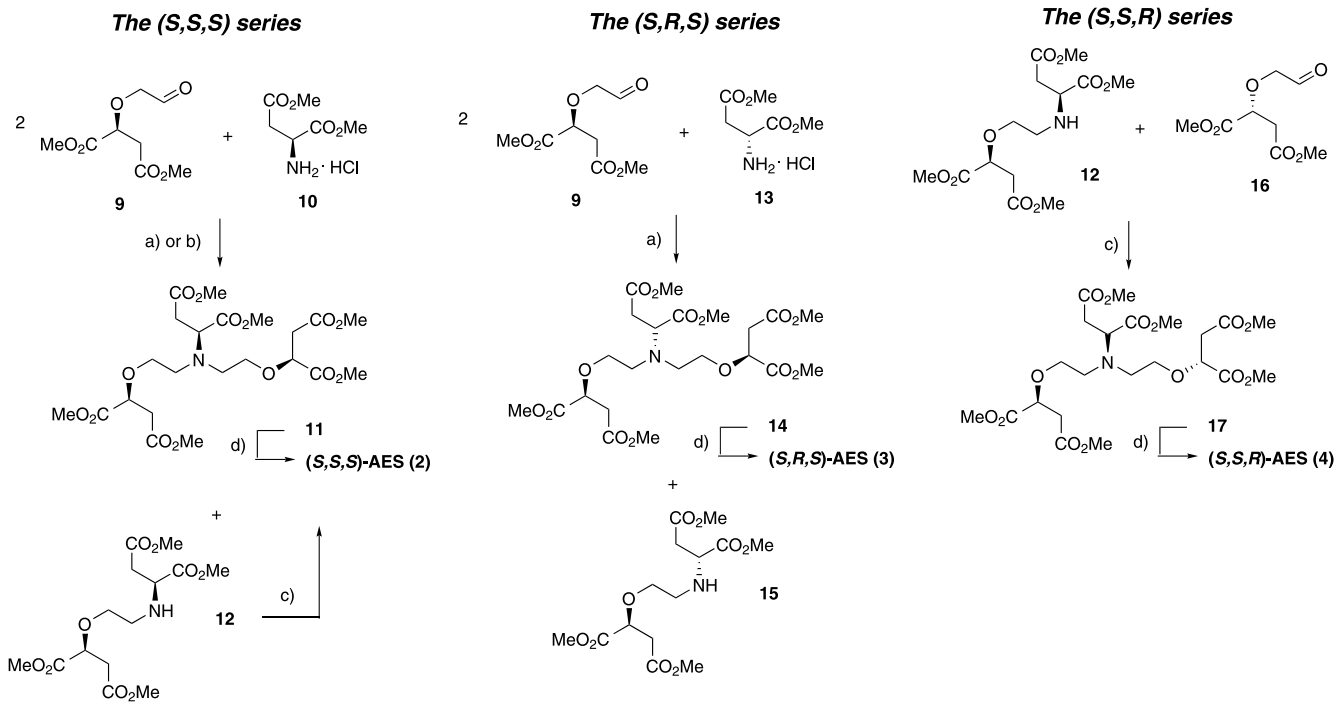


Scheme 2. Initial attempts at *O*-alkylation of dimethyl malate with diethanolamine-derived electrophiles.

For the synthesis of the key aldehyde building block **9** (Scheme 3) and its enantiomer **16** (see Scheme 4), we initially used a procedure adapted from the previous synthesis of **9** by Samuelsson and co-workers.[10] Thus, dimethyl (*S*)- or (*R*)-malate was alkylated with allyl bromide using freshly prepared Ag_2O as the bromide scavenger. We found that the amount of Ag_2O was critical for this transformation since use of more than 20 mol% excess of the reagent led to allylation of the solvent as well. After OsO_4-catalyzed dihydroxylation and subsequent cleavage of the resulting diol with sodium periodate, the aldehyde **9** was obtained in 60–65% overall yield from dimethyl malate. This procedure worked very efficiently on the small scale described by the authors (0.5 mmol). On scaleup, however, several modifications to the procedure were required. The aldehyde **9** is very prone to polymerization and decomposition, particularly when dry. Even traces of acids in deuterated chloroform were enough to completely destroy a batch of aldehyde **9** in a matter of hours! However, when pure, **9** could easily be stored in a freezer in a frozen cyclohexane matrix for several months without decomposition.



Scheme 3. Synthesis of aldehyde **9**. Reagents and conditions: (a) allyl bromide (9 equiv), Ag_2O (1 equiv), toluene, rt, 2 h; (b) OsO_4 (2 mol%), *N*-methylmorpholine-*N*-oxide (NMO, 2 equiv), 3:1 THF/H_2O, 0 °C→rt, 21 h; then $NaIO_4$ (2 equiv), 3:1 THF/H_2O, 80% from **5**.



Scheme 4. Synthesis of AES isomers. Reagents and conditions: (a) aldehyde **9** (2.6 equiv), aspartate **10** or **13** (1 equiv), $NaBH_3CN$ (2.1 equiv), MeOH, 0 °C→rt, 24 h; 40% **11**, 48% **12** or 40% **14**, 42% **15**; (b) aldehyde **9** (3.65 equiv), aspartate **10** (1 equiv), $NaBH_3CN$ (3 equiv), MeOH, 0 °C→rt, 48 h, 80% **11**; (c) aldehyde **9** or **16** (1.1 equiv), amine **12** (1 equiv), $NaBH_3CN$ (1.1–1.5 equiv), formic acid (2 equiv), MeOH, 0 °C→rt, 24 h, 40% **11** or **17** (55% **11**, 59% **17** based on recovered **12**); (d) 1 M aq. NaOH (6.8 equiv), 1:1 MeOH/THF, rt, 18 h, quant.

After considerable experimentation, we found that aldehyde **9** was obtained in 80% overall yield by filtering the crude reaction mixture through silica, concentration in vacuo, addition of brine followed by careful gradient extraction with Et_2O and CH_2Cl_2. The first Et_2O extract had to be purified by filtration through a pad of silica, however, all subsequent extracts gave pure **9** upon concentration! If further purification was needed, **9** could readily be distilled in high vacuum using a Kugelrohr apparatus. With these modifications, multigram amounts of **9** and **16** could readily be prepared.

With the aldehydes **9** and **16** in hand, the reductive amination was explored. Initial experiments using Pd/C catalysis (2.2 equiv of aldehyde, 1 equiv **10**, EtOAc or EtOH solvents) gave complex reaction mixtures with only traces of the desired alkylation products. Very poor conversions were also obtained with sodium triacetoxyborohydride. However, sodium cyanoborohydride gave more satisfactory results. If all the reagents were added at the same time to a cooled mixture of 2.5 equiv of the aldehyde, 1 equiv of amine and 2 equiv of $NaBH_3CN$, substantial decomposition of the aldehyde was observed, even at 0 °C. However, with gradual addition of the amine and the cyanoborohydride over 1.5 h, and with 2 equiv of aldehyde, the monoalkylation product **12** was obtained in 63% yield and the dialkylation product **11** in 23% yield.

Better yields of the dialkylation product were obtained with 2.5 equiv of the aldehyde (40% **11**, 48% **12**). A more dramatic improvement in yield was realized when a further portion of the aldehyde (1.3 equiv) was added to the reaction mixture after 24 h. Using this procedure, the yield of the dialkylation product climbed to 80%. However, purification of the product became progressively more difficult with increased amounts of the aldehyde. Thus, it was easier and more reliable to recycle the monoalkylated product **12** and to resubject it to the reaction conditions (in this case, 2 equiv of formic acid was added to the reaction mixture to facilitate the iminium ion formation). The overall yield of the dialkylated product after one cycle was 55%. The corresponding (*S*,*R*,*S*) isomer was synthesized in a similar manner using the (*R*)-aspartic acid dimethyl ester **13** as the starting material (Scheme 4). The hexamethylester **14** was obtained in 40% yield after one cycle, along with 42% of the monoalkylated product **15**.

To access the (*S*,*S*,*R*)-isomer, the (*S*,*S*)-tetraester **12** was treated with the (*R*)-malic acid derived aldehyde **16** (1.1 equiv). The (*S*,*S*,*R*) ester **17** was obtained in 40% yield (59% based on recovered **12**). All the hexamethyl esters were diastereomerically >95% pure according to NMR spectroscopic analysis (the ^1H and ^{13}C NMR signals, although very close, are clearly distinct in all isomers).

Finally, the corresponding sodium salts of the AES isomers were readily obtained in quantitative yields by careful saponification of the products. Here, slow addition of a slight excess of NaOH was necessary to prevent unwanted retro-Michael reactions. Using an excess of NaOH led to the partial loss of one of the malic acid groups as the fumarate. However, no isomerization could be detected in the NMR spectra. The final products were judged to be >95% diastereomerically pure by ^1H and ^{13}C NMR spectroscopy.

The three isomers of AES synthesized herein, the (*S*,*S*,*S*), the (*S*,*R*,*S*) and the (*S*,*S*,*R*) isomers, are each members of the three possible enantiomeric pairs of AES isomers. The remaining

isomers are thus enantiomeric to the ones described herein and accessible through identical procedures.

3. Conclusion

In summary, a concise and versatile synthesis of isomers of AES, a novel biodegradable chelating agent is described. The synthesis is applicable to the asymmetric synthesis of all isomers of AES in pure form and it is amenable to scaleup.

With the pure isomers **2–4** in hand, the differences in biodegradability and capacity as chelating agents can now be fully explored. These studies will be described in detail elsewhere.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Non-aqueous reagents were transferred under argon via syringe or cannula and dried prior to use. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled over CaH_2. All synthetic intermediates were azeotropically dried with toluene prior to use. Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution (6 g vanillin, 5 mL conc. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH) or with ninhydrin solution (1 g ninhydrin, 100 mL isopropanol, five drops glacial acetic acid). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted.

The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 (^1H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26) for ^1H NMR and the residual $CDCl_3$ (δ 77.0) for ^{13}C NMR spectra. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. Optical rotations were obtained with a Perkin–Elmer 343 polarimeter. High resolution mass spectrometric data were obtained by the University of Oulu Analytical Services on Micromass LCT spectrometer. The elemental analyses were performed at the Analytical Services of the Department of Chemical Technology, Laboratory of Organic Chemistry.

4.1.1. (*S*)-(2-Oxoethoxy)succinic acid, dimethyl ester 9 and (*R*)-(2-oxoethoxy)succinic acid, dimethyl ester 16. To a solution of dimethyl (*S*)-malate **5** (5.60 g, 34.6 mmol, 1 equiv) in toluene (60 mL) was added allyl bromide (27.0 mL, 312 mmol, 9 equiv) and silver (I) oxide (8.01 g, 34.6 mmol, 1 equiv). After stirring for 2 h 20 min at rt the mixture was filtered through Celite and the solvent was evaporated to give the crude product **8** (6.72 g, 96%) as a pale yellow oil. The crude product was used directly in the next reaction.

The corresponding (*R*)-isomer was synthesized according to the method for preparation of **8** described above, with the exception that 1.05 equiv of Ag_2O was used and the reaction time was 5 h. Compound **19** was obtained in quantitative yield. The NMR data of **6** and its enantiomer match those reported in the literature.

To an ice-cold solution of **8** (2.01 g, 9.94 mmol, 1 equiv) and *N*-methylmorpholine *N*-oxide monohydrate (2.26 g, 16.72 mmol, 2 equiv) in THF/H_2O 3:1 (62 mL) was added OsO_4 (2.5 wt% solution in *t*-BuOH, 2.1 mL, 0.167 mmol, 2.0 mol%). The reaction mixture was stirred for 3 h at 0 °C and then allowed to warm to rt, overnight. Solid sodium hydrogen sulfite (2.10 g) was then added and the mixture was stirred for an additional 30 min at rt. The mixture was filtered through a pad of silica (2×20 mL THF rinse) and the solvents were evaporated to give the crude diol intermediate.

The crude diol (9.94 mmol, 1 equiv) was dissolved in THF/H_2O 3:1 (107 mL) and sodium periodate (4.25 g, 19.9 mmol, 2 equiv) was added. The mixture was stirred at rt for 30 min and then filtered through silica (2×20 mL THF rinse). After concentration, brine (100 mL) and Et_2O (100 mL) were added. The layers were separated and the aqueous phase was extracted with Et_2O (2×75 mL).The combined organic layers were dried (Na_2SO_4), filtered and concentrated, and the crude product was purified by dry flash chromatography (4×8 cm silica, EtOAc/hexanes stepwise gradient from 0 to 100% EtOAc, final flush with pure MeOH) to give a first batch, 0.44 g (22%), of the aldehyde. The aqueous layer was further extracted with CH_2Cl_2 (6×100 mL). These extracts were combined, dried (Na_2SO_4) and concentrated to give pure aldehyde **9** (1.27 g, 63%). Total yield of **9** 1.71 g, 84% (80% from **5**). **9**: viscous, colorless oil, $[\alpha]_D^{22}=-62.8$ (*c* 0.9, CH_2Cl_2), lit.[10] $[\alpha]_D^{22}=-44.1$ (*c* 0.5, $CHCl_3$). A reliable comparison of the rotation in $CHCl_3$ could not be made because the aldehyde decomposed relatively easily in dry $CHCl_3$! The NMR spectral data corresponded to those reported in the literature[10] but were best recorded with a trace of added Et_3N.

The aldehyde **9** could be stored in a frozen cyclohexane matrix at −20 °C for several months without appreciable decomposition. If necessary, it could be purified by Kugelrohr distillation (0.1 mmHg, bp 80–90 °C).

The corresponding enantiomeric aldehyde **16** was prepared using the same procedure from dimethyl (*R*)-malate in 61% overall yield. Its NMR spectra were identical to that of **9**. $[\alpha]_D^{22}=+56.8$ (*c*0.8, CH_2Cl_2).

4.1.2. (2*S*,2′*S*′,2″*S*)-{2-[[2′-(1″,2″-Bis-methoxycarbonyl-ethoxy)-ethyl]-(1′,2′-bis-methoxycarbonyl-ethyl)-amino]-ethoxy}-succinic acid hexamethyl ester (11) and (2*S*,2′*S*)-2-[2′-(1′,2′-bis-methoxycarbonyl-ethylamino)-ethoxy]-succinic acid tetramethyl ester (12). To a solution of aldehyde **9** (480 mg, 2.35 mmol, 2.35 equiv) in MeOH (1.8 mL) at 0 °C was added L-aspartic acid dimethyl ester hydrochloride **10** (197.6 mg, 1.00 mmol, 1 equiv) and $NaBH_3CN$ (94.3 mg, 1.50 mmol, 1.5 equiv) in three equal portions at 30 min intervals. After the last addition, the

resulting suspension was allowed to warm to rt over 18 h. The mixture was cooled to 0 °C and more **9** (265 mg, 1.30 mmol, 1.3 equiv) dissolved in MeOH (1.2 mL) was added, followed by $NaBH_3CN$ (94.3 mg, 1.50 mmol, 1.5 equiv). The reaction mixture was allowed to gradually warm to rt over 5 h. After a total reaction time of 48 h, the mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the crude product was purified by flash chromatography (silica gel, 85% EtOAc in hexanes+1.5% triethylamine). Yield of **11** 428 mg, 80%. **11:** colorless viscous oil, $[\alpha]_D^{22}=-82.7$ (*c*1.0, CH_2Cl_2); IR (film) 3634, 3462, 2998, 2955, 1737, 1438, 1371, 1279, 1169, 1128, 1002, 849, 782, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.29 (dd, $J=5.1$, 7.5 Hz, 2H), 3.96 (t, $J=7.5$ Hz, 1H), 3.77 (s, 6H), 3.70 (s, 9H), 3.67 (td, $J=6.3$, 9.7 Hz, 2H), 3.68 (s, 3H), 3.44 (td, $J=6.2$, 9.5 Hz, 2H), 2.90–2.74 (m, 8H), 2.73 (dd, $J=7.5$, 16.1 Hz, 1H), 2.58 (dd, $J=7.5$, 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 172.6, 171.8, 171.7, 170.5, 75.5, 70.8, 61.6, 52.2, 52.1 (2), 51.9, 51.7, 51.6, 37.6, 35.6; ESI MS calcd for (M^++H) $C_{22}H_{36}NO_{14}$ 538.2136, found 538.2147, $\Delta=2.1$ ppm.

An alternative procedure to access both amination products proceeded as follows: to a solution of aldehyde **9** (436 mg, 2.13 mmol, 2.6 equiv) in MeOH (1.8 mL) at 0 °C was added **10** (160 mg, 0.81 mmol, 1 equiv) and $NaBH_3CN$ (107 mg, 1.70 mmol, 2.1 equiv), both in three equal portions at 45 min intervals. The resulting suspension was stirred for 3 h at 0 °C, after which time it was allowed to warm to rt and stirred overnight. The reaction mixture was then treated and purified as described above to afford **11** (152 mg, 35%) and **12** (143 mg, 51%). Resubjection of **12** to the reductive amination conditions with 2 equiv formic acid (see the procedure below) afforded **11** in 40% yield based on **12**, raising the total yield of **11** to 55% (based on **10**).

Compound **12**: colorless oil, $[\alpha]_D^{22}=-47.3$ (*c* 0.7, CH_2Cl_2); IR (film) 3338, 2955, 1739, 1661, 1438, 1367, 1279, 1198, 1171, 1132, 998, 850, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.34 (dd, $J=4.8$, 8.1 Hz, 1H), 3.78 (s, 3H), 3.77 (ddd, $J=3.8$, 6.1, 10.4 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.70 (t, $J=5.9$ Hz, 1H), 3.57 (ddd, $J=3.8$, 9.8 Hz, 3.8 Hz, 1H), 2.92–2.70 (m, 3H), 2.76 (dd, $J=6.9$, 15.2 Hz, 2H), 2.67 (dd, $J=6.9$, 16.1 Hz, 1H), 1.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 173.8, 171.8, 171.3, 170.5, 75.3, 70.9, 57.6, 52.2, 52.1, 52.0, 51.8, 47.2, 37.7, 37.6; ESI MS calcd for (M^++Na) $C_{14}H_{23}NO_9Na$ 372.1271, found 372.1264, $\Delta=1.7$ ppm.

4.1.3. (2*S*,2′*R*,2″*S*)-{2-[[2′-(1″,2″-Bis-methoxycarbonyl-ethoxy)-ethyl]-(1′,2′-bis-methoxycarbonyl-ethyl)-amino]-ethoxy}-succinic acid hexamethyl ester (14) and (2*S*,2′*R*)-2-[2′-(1′,2′-bis-methoxycarbonyl-ethylamino)-ethoxy]-succinic acid tetramethyl ester (15). The hexamethyl ester **14** was synthesized as described above for **11** and **12**. Yield of **14**: 40% and **15**: 42%. **14**: colorless viscous oil, $[\alpha]_D^{22}=+1.8$ (*c* 0.6, CH_2Cl_2); IR (film) 3634, 3465, 3000, 2955, 1737, 1438, 1370, 1276, 1170, 1128, 1002, 850, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.28 (dd, $J=5.3$, 7.3 Hz, 2H), 3.94 (t, $J=7.4$ Hz, 1H), 3.76 (s, 6H), 3.71 (s, 3H), 3.70 (s, 6H), 3.68 (s, 3H), 3.66 (td, $J=6.0$, 9.8 Hz, 2H), 3.44 (td, $J=6.4$, 9.6 Hz, 2H), 2.89–2.74 (m, 8H), 2.73 (dd, $J=7.4$, 16.0 Hz, 1H), 2.59 (dd, $J=7.4$, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 172.6, 171.8, 171.7, 170.5, 75.5, 70.6, 61.4, 52.14, 52.12 (2), 51.9, 51.7, 51.6, 37.6, 35.7; ESI MS calcd for (M^++H) $C_{22}H_{36}NO_{14}$ 538.2169, found 538.2136, $\Delta=6.1$ ppm. **15**: colorless oil, $[\alpha]_D^{22}=-25.6$ (*c*0.9, CH_2Cl_2); IR (film) 3419, 2956, 1739, 1646, 1439, 1368, 1279, 1198, 1172, 1133, 1044, 999, 857, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.29 (dd, $J=4.8$, 8.1 Hz, 1H), 3.77 (ddd, $J=4.2$, 5.5, 9.5 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.66 (t, $J=6.5$ Hz, 1H), 3.52 (ddd, $J=3.8$, 7.5, 9.7 Hz, 1H), 2.90–2.63 (m, 5H), 2.64 (dd, $J=6.5$, 16.0 Hz, 1H), 2.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 173.7, 171.7, 171.3, 170.5, 75.4, 71.0, 57.6, 52.1, 52.0, 51.9, 51.7, 47.3, 37.7, 37.6; ESI MS calcd for (M^++H) $C_{14}H_{24}NO_9$ 350.1451, found 350.1443, $\Delta=2.4$ ppm.

4.2. General procedure for reductive amination of 12 with formic acid

A solution of aldehyde **16** (584 mg, 2.86 mmol, 1.1 equiv) and tetramethylester **12** (900 mg, 2.58 mmol, 1 equiv) in MeOH (5.0 mL) was cooled to 0 °C. $NaBH_3CN$ (180 mg, 2.86 mmol, 1.1 equiv) and formic acid (0.19 mL, 5.0 mmol, 2 equiv) were added at 0 °C in one portion. The suspension was stirred for 3 h, after which time it was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 (50 mL) and sat. $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the crude product was purified by flash chromatography (85% EtOAc in hexane + 1–1.5% triethylamine) to give **17** (550 mg, 40%) and recovered **12** (170 mg, 19%).

This procedure was also used for the conversion of the reductive amination product **12** into **11**.

4.2.1. (2*S*,2″*S*,2″*R*)-{2-[[2′-(1″,2″-Bis-methoxycarbonyl-ethoxy)-ethyl]-(1′,2′-bis-methoxycarbonyl-ethyl)-amino]-ethoxy}-succinic acid hexamethyl ester (17). Pale yellow oil, $[\alpha]_D^{22}=-27.61$ (*c* 0.7, CH_2Cl_2); IR (film) 3456, 3155, 3002, 2955, 1736, 1438, 1370, 1280, 1171, 1129, 1002, 909, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.29 (dd, $J=3.0$, 5.0 Hz, 1H), 4.27 (dd, $J=3.0$, 5.0 Hz, 1H), 3.94 (t, $J=7.5$ Hz, 1H), 3.76 (s, 6H), 3.71 (s, 3H), 3.70 (s, 6H), 3.67 (s, 3H), 3.71–3.63 (m, 2H), 3.46–3.40 (m, 2H), 2.90–2.73 (m, 8H), 2.72 (dd, $J=7.6$, 16.2 Hz, 1H), 2.58 (dd, $J=7.3$, 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 172.6, 171.8, 171.7, 171.6, 170.5, 75.5, 70.8, 70.6, 61.5, 52.2, 52.1 (2), 51.9, 51.6, 51.5, 37.6, 35.6; ESI MS calcd for (M^++Na) $C_{22}H_{35}NO_{14}Na$ 560.1955, found 560.1951, $\Delta=0.8$ ppm.

4.3. General procedure for saponification of the hexamethyl esters

To a solution of hexamethyl ester **11** (133 mg, 0.25 mmol, 1 equiv) in 1:1 MeOH/THF-solution (1.2 mL) was added 1 M NaOH (1.70 mL, 1.70 mmol, 6.8 equiv). The mixture

was stirred at rt for 18 h and then concentrated to give crude **2** as a tan solid. The excess NaOH was removed by precipitation of the product from H_2O (0.5 mL) by adding ethanol (2 mL), affording **2** (153 mg, quant., calculated as $C_{16}H_{17}NO_{14}Na_6 \cdot H_2O \cdot (C_2H_5OH)_{0.5}$) as a white solid.

The same procedure was used for the synthesis of **3** and **4**, starting from **14** and **17**, respectively.

4.3.1. (2*S*,2′*S*,2″*S*)-2-{2′-[[2′-(1″,2″-Dicarboxy-ethoxy)-ethyl]-(1′,2′-dicarboxy-ethyl)-amino]-ethoxy}-succinic acid, hexasodium salt (2). White powder, melting range 340–385 °C (dec.), $[\alpha]_D^{22} = -13.7$ (*c* 0.5, H_2O); IR (KBr) 3429, 2967, 1591, 1409, 1308, 1196, 1107, 881, 686 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 4.11 (dd, $J=3.2$, 9.6 Hz, 2H), 3.67–3.51 (m, 5H), 2.90–2.76 (m, 4H), 2.64–2.34 (m, 8H); ^{13}C NMR (D_2O, 400 MHz) δ 180.1, 179.4, 79.3, 67.4, 64.4, 50.9, 41.5, 37.3; ESI MS calcd for ($M^+ - Na$) $C_{16}H_{17}NO_{14}Na_5$ 562.0138, found 562.0117, $\Delta = 3.6$ ppm. Anal. calcd for $C_{16}H_{17}NO_{14}Na_6 \cdot H_2O \cdot (C_2H_5OH)_{0.5}$: C, 32.60; H, 3.54; N, 2.24. Found: C, 32.27; H, 3.24; N, 1.95.

4.3.2. (2*S*,2′*R*,2″*S*)-2-{2′-[[2′-(1″,2″-Dicarboxy-ethoxy)-ethyl]-(1′,2′-dicarboxy-ethyl)-amino]-ethoxy}-succinic acid, hexasodium salt (3). White powder, melting range 320–370 °C (dec.), $[\alpha]_D^{22} = -2.8$ (*c* 0.8, H_2O); IR (KBr) 3419, 2180, 1586, 1409, 1308, 1197, 1108, 877 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 4.06 (dd, $J=3.4$, 9.2 Hz, 2H), 3.70 (dd, $J=5.5$, 8.1 Hz, 1H), 3.64 (ddd, $J=5.0$, 8.7, 9.7 Hz, 2H), 3.78–3.42 (m, 2H), 2.77–2.52 (m, 9H), 2.61 (dd, $J=3.4$, 15.4 Hz, 2H), 2.46 (dd, $J=9.2$ Hz, 15.4 Hz, 2H), 2.38 (ddd, $J=5.4$, 9.8, 15.3 Hz, 1H); ^{13}C NMR (D_2O, 400 MHz) δ 180.1, 179.4, 79.1, 67.2, 63.8, 50.7, 41.5, 35.2; ESI MS calcd for ($M^+ + H$) $C_{16}H_{18}NO_{14}Na_6$ 586.0113, found 586.0095, $\Delta = 3.2$ ppm. Anal. calcd for $C_{16}H_{17}NO_{14}Na_6 \cdot H_2O \cdot (C_2H_5OH)_{0.5}$: C, 32.60; H, 3.54; N, 2.24. Found: C, 32.52; H, 3.39; N, 2.07.

4.3.3. (2*S*,2′*S*,2″*R*)-2-{2′-[[2′-(1″,2″-Dicarboxy-ethoxy)-ethyl]-(1′,2′-dicarboxy-ethyl)-amino]-ethoxy}-succinic acid, hexasodium salt (4). White powder, melting range 300–310 °C (dec.), $[\alpha]_D^{22} = -9.7$ (*c* 0.7, H_2O); IR (KBr) 3434, 2970, 1603, 1385, 1307, 1193, 1105, 880, 683 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 4.08 (dd, $J=3.5$, 6.0 Hz, 1H), 4.06 (dd, $J=3.6$, 5.9 Hz, 1H), 3.65 (dd, $J=5.6$, 8.5 Hz, 1H), 3.63–3.59 (m, 1H), 6.31 (t, $J=6.3$ Hz, 2H), 3.46 (td, $J=5.7$, 1.0 Hz, 1H), 2.82–2.69 (m, 4H), 2.58 (dd, $J=4.4$, 15.2 Hz, 1H), 2.57 (dd, $J=6.5$, 15.3 Hz, 1H), 2.57 (dd, $J=6.2$, 15.4 Hz, 1H), 2.44 (dd, $J=9.7$, 15.2 Hz, 1H), 2.44 (dd, $J=9.6$, 15.3 Hz, 1H), 2.40 (dd, $J=5.9$, 15.5 Hz, 1H); ^{13}C NMR (D_2O, 400 MHz) δ 180.8, 180.2, 180.1, 179.8, 179.4, 179.3, 79.3, 79.2, 67.5, 67.1, 63.9, 50.7, 50.6, 41.6, 41.5, 36.3; ESI MS calcd for ($M^+ + H$) $C_{16}H_{18}NO_{14}Na_6$ 586.0113, found 586.0123, $\Delta = 1.7$ ppm. Anal. calcd for $C_{16}H_{17}NO_{14}Na_6 \cdot (H_2O)_{2.5} \cdot (C_2H_5OH)_{0.5}$: C, 31.25; H, 3.86; N, 2.14. Found: C, 31.05; H, 3.74; N, 2.02.

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Dinucleotides containing two allyl groups by combinations of allyl phosphotriesters, 5-allyl-, 2′-*O*-allyl- and 2′-*arabino*-*O*-allyl uridine derivatives as substrates for ring-closing metathesis

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Abstract—Five different dinucleotides, each containing two allyl groups in various positions, were prepared and studied as substrates for ring-closing metathesis reactions. These dinucleotides were designed from appropriate nucleoside building blocks combining four different positions for the allyl group; the allyl phosphotriester linkage, 5-allyl-2′-deoxyuridine, and *ribo*- as well as *arabino*-configured 2′-*O*-allyluridine. Thus, convenient procedures for these building blocks were developed. From the dinucleotides, two new cyclic nucleotide structures were obtained; one connecting two adjacent nucleobase moieties and the other forming an unsaturated four-carbon linkage between the phosphate moiety and the adjacent pyrimidine nucleobase. The latter cyclic dinucleotide was also prepared with a saturated four-carbon linkage using a tandem ring-closing metathesis–hydrogenation procedure. This compound was found to be significantly more stable towards a nucleophilic ring-opening than its unsaturated counterpart.

1. Introduction

The application of ring-closing olefin metathesis (RCM) for the preparation of medium and large rings has been a major tool in organic and bioorganic chemistry.[1] In particular, the introduction of highly efficient and functional group tolerant ruthenium-based catalysts by Grubbs and co-workers has made metathesis technology generally attractive.[2] A large number of heterocyclic rings have been constructed by RCM,[1,3] and recently, the application of RCM for the synthesis of phosphorus heterocycles has been specifically reviewed.[4] In a bioorganic context, cyclic peptide or peptide mimetic structures have been achieved by RCM reactions.[5] In view of this, we have focused on the application of RCM in nucleic acid chemistry,[6–10] and as a result, conformationally restricted bi- and tricyclic nucleoside monomers[6] as well as di- and trinucleotides with large cyclic structures have been achieved.[7–10] In addition, other research groups have recently prepared different nucleoside derivatives by RCM based strategies.[11]

In the studies of nucleic acid chemical biology, a significant number of conformationally restricted nucleic acid fragments have been designed.[12] As a relatively new approach, however, the relationship between structure and function of nucleic acid secondary and tertiary structures[13] has motivated the preparation of nucleic acids with covalent intra- and interstrand linkages.[14] Sekine and co-workers have introduced a number of cyclic nucleotide and dinucleotide structures for mimicking nucleic acid secondary structures.[15] In these cases, linkages have been established between the 2′-position and the nucleobase in the two adjacent nucleosides in a dinucleotide or between the nucleobase and the adjacent phosphate moiety.[15] Recently, another example of a conformationally restricted dinucleotide for this purpose with a linkage between the phosphate and the adjacent 5′-position has been introduced.[16] In all these cases, the covalent linkages have been obtained by conventional phosphoramidite chemistry,[17] disulfide bond formation and/or peptide/amide bond formation.[14–16] We have concentrated on the development of a general methodology based on RCM for the construction of this type of conformationally restricted nucleic acid fragments. Thus, we have synthesised a series of diastereomeric dinucleotides with phosphotriester internucleotide linkages containing seven-membered rings.[7] These were prepared by an RCM reaction on a dinucleotide substrate in which two terminal double bonds have been introduced by a 5′-*C*-vinyl moiety and an allyl phosphotriester linkage.[7] In a

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similar way, a ring connecting the phosphotriester linkage in a dinucleotide with a nucleobase has been demonstrated,[8,9] and two adjacent phorphortriester linkages have been linked in a cyclic trinucleotide structure.[8] Thus, a tandem RCM and hydrogenation procedure efficiently mediated the preparation of cyclic dinucleotides with a butylene nucleobase phosphotriester connection, which was unobtainable by a conventional hydrogenation method.[9] In this paper, some of these results are reported with all experimental details, and the general study on exploring the scope of ring-closing metathesis in the construction of cyclic dinucleotides with large rings is continued. Thus, four different positions of terminal double bonds were investigated, the appropriate nucleoside building blocks were prepared, and a selection of the possible dinucleotides were synthesised and investigated as substrates for RCM. Hereby, two cyclic dinucleotide structures were obtained.

2. Results and discussion

Four different positions for the allyl groups were deduced for incorporation into dinucleotides; the allyl phosphotriester linkage **A**, 5-allyl-2′-deoxyuridine **B**, 2′-*O*-allyluridine **C**, and 2′-*arabino*-*O*-allyluridine **D** (Fig. 1). Among these, **A** and a 5-allyluridine counterpart of **B** have been applied in our earlier studies.[7,8] From these four different allyl positions, a series of 12 different dinucleotides might be constructed; (5′–3′) **AB**, **AC**, **AD**, **BB**, **BC**, **BD**, **CB**, **CC**, **CD**, **DB**, **DC** and **DD**, as **A** cannot logically be placed in the 3′-end of the dinucleotides. Nevertheless, we decided to make only a section of five of these dinucleotides representing all of the four different allyl positions in at least two dinucleotides each. Thus, **AB**,[9] **AD**, **BB**, **CB** and **CD** were produced and investigated as substrates for RCM reactions.

In order to make dinucleotides with an allyl phosphotriester linkage **A**, the phosphoramidite **1** (Scheme 1) was formed in two steps from thymidine as shown in the literature.[7,18]

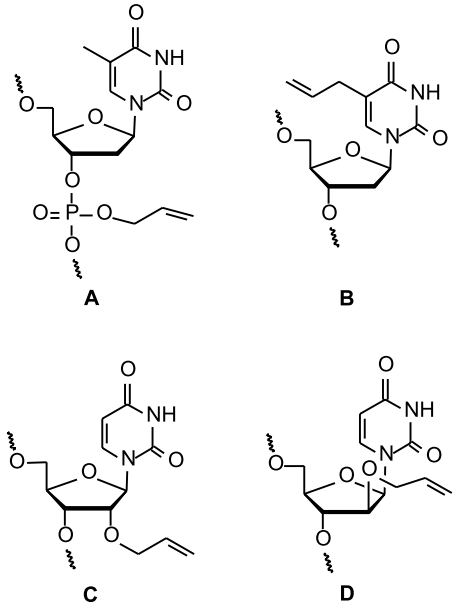
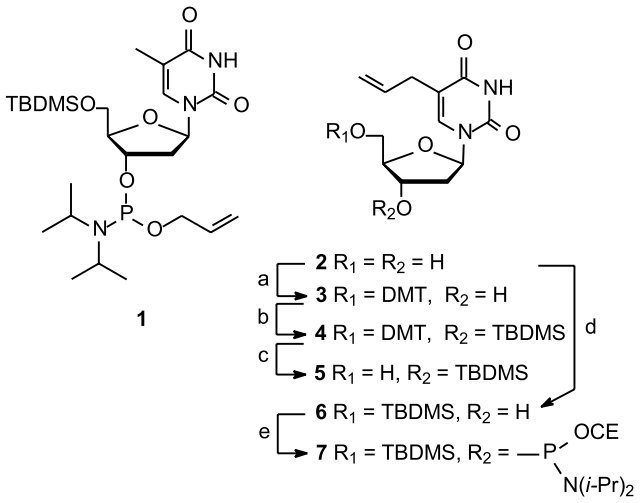


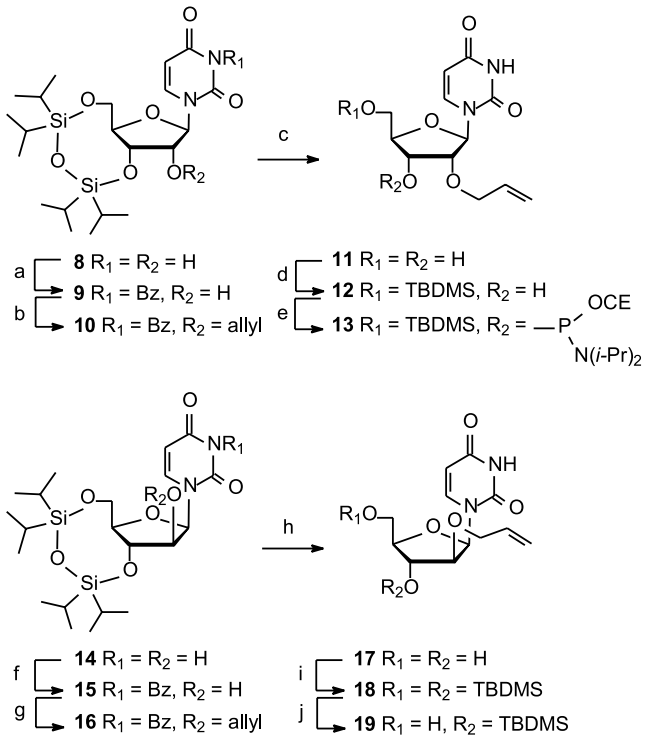
Figure 1. The four different positions for allyl groups in this study.



Scheme 1. Reagents and conditions: (a) DMTCl, $AgNO_3$, pyridine, 84%; (b) TBDMSCl, $AgNO_3$, pyridine, 86%; (c) *p*-TsOH, CH_2Cl_2, CH_3OH, 0 °C, 88%; (d) TBDMSCl, $AgNO_3$, pyridine, 42%; (e) CEOP(N(*i*-Pr)$_2$)$_2$, 4,5-dicyanoimidazole, CH_2Cl_2, CH_3CN, 75%. DMT=4,4′-dimethoxytrityl, TBDMS=*tert*-butyldimethylsilyl, CE=2-cyanoethyl.

Hereby, the appropriate building block for incorporation of **A** into dinucleotides by standard phosphoramidite chemistry[17] was formed. For the 5-allyluracil alternative **B**, 5-allyl-2′-deoxyuridine **2** was synthesised from 2′-deoxyuridine in two steps using a known procedure based on the formation of an organomercuri-intermediate followed by a transmetallation with Li_2PdCl_4 and allylation with allylchloride in methanol.[19] Subsequently, **2** was converted to the 3′-protected derivative **5** in three steps, that is, selective 5′-*O*-tritylation to give **3**, 3′-*O*-silylation to give **4**, both reactions accelerated by silver nitrate, and finally acidic detritylation to give the product **5** in 64% yield over the three steps (Scheme 1). Hereby, the building block for incorporating **B** in the 3′-end of the dinucleotides was formed.[9] Furthermore, **2** was selectively protected at the 5′-position as a silyl ether to give **6** and converted to the 3′-phosphoramidite **7** using a phosphordiamidite reagent and 4,5-dicyanoimidazole[20] as an activating reagent. This formed the building block for incorporating **B** in the 5′-end of the dinucleotides.

The formation of 2′-*O*-allyl-ribonucleosides, **C**, is well described in the literature.[21–24] Thus, Sproat et al. synthesised 2′-*O*-allyluridine[21] via a neutral palladium(0) catalysed allylation method[25] combined with a 5′,3′-TIPDS protection of the two alcohols and a 4-*O*-(2,6-dichlorophenyl) protection of the uracil moiety.[21] Later, it was demonstrated that the allylation can be performed with a simpler and cheaper 3-*N*-(4-*tert*-butylbenzoyl) group as protection of the uracil moiety.[22] Recently, also a 4-*O*-(2,6-dimethylphenyl) protection of the uracil has been successfully applied in the same reaction.[23] On the other hand, a conventional Williamson type allylation, that is, allyl bromide and sodium hydride, has been used with 5′-*O*-MMT-3′-*O*-TBDMS-uridine as substrate.[24] Thus, an allylation can be performed without a protecting group for the uracil, and we decided to attempt the same reaction with TIPDS-protected uridine **8** (Scheme 2). However, this led to only 20% of the 2′-*O*-allyl derivative due to a partial basic cleavage of the silyl ether moieties. Subsequently, we



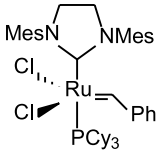
Scheme 2. Reagents and conditions: (a) BzCl, Bu_4NBr, CH_2Cl_2, aq Na_2CO_3, 77%; (b) allylethylcarbonate, tris(benzylidenacetone)dipalladium(0), bis(diphenylphosphino)butane, THF, 92%, reflux; (c) i. TBAF, THF, ii. aq NH_3, CH_3OH, 95%; (d) TBDMSCl, $AgNO_3$, pyridine, 79%; (e) CEOP(Cl)N(*i*-Pr)$_2$, EtN(*i*-Pr)$_2$, CH_2Cl_2, 65%; (f) i. TMSCl, Et_3N, CH_2Cl_2, ii. BzCl, EtN(*i*-Pr)$_2$, pyridine, iii. *p*-TsOH, CH_2Cl_2, 81%; (g) as (b), (h) as (c), 75%, two steps; (i) TBDMSCl, imidazole, DMF, 83%; (j) 80% aq AcOH, 73%. TBDMS=*tert*-butyldimethylsilyl, TMS=trimethylsilyl, CE=2-cyanoethyl.

decided to apply the neutral palladium(0) catalysed allylation method[25] with **8**. Thus, in this first attempt, nucleobase protection was avoided and, as expected, only the 3-*N*,2′-*O*-dialkylated product, or even the 3-*N*-monoalkylated product, was obtained. Therefore, we decided to follow the procedure by Sproat and co-workers[22] but with a conventional 3-*N*-benzoyl protection of the uracil instead of the 3-*N*-(4-*tert*-butylbenzoyl) group. Thus, the TIPDS-protected uridine **8** was treated with benzoyl chloride in a known phase transfer reaction with DCM/Na_2CO_3(aq) and tetrabutylammonium bromide as phase transfer catalyst to give **9** in 77% yield (Scheme 2).[26,27] The palladium(0) catalysed allylation procedure[25] applied with **9** afforded **10** in 92% yield. Subsequently, desilylation with TBAF in THF followed by debenzoylation with 25% ammonia in methanol gave 2′-*O*-allyluridine **11** in 95% yield, that is a conveniently 67% overall yield from **8**. Finally, **11** was reprotected as a silyl ether at the 5′-position to give **12** and converted to the 3′-phosphoramidite **13** by standard methods (Scheme 2). Hereby, the building block for incorporating **C** in the 5′-end of the dinucleotides was formed.

The formation of 2′-*O*-allyl-arabinouridine, **D**, has also been described in the literature.[28] However, only the conventional Williamson ether formation has been demonstrated using 5′,3′-*bis*-*O*-tetrahydropyranyl protected arabinouridine without protection of the uracil moiety to afford the 2′-*O*-allyl product in 40% yield.[28] Therefore, we decided to use the same procedure for allylation as applied with the *ribo*-configured uridine. Thus, the known TIPDS-protected *arabino*-configured uridine **14**[29] was treated with benzoyl chloride using the same phase transfer conditions as before but in this case only 34% yield of the 3-*N*-benzoylated product **15** was obtained due to a formation of a significant amount of the 3-*N*,2′-*O*-dibenzoylated product. Therefore, an in situ trimethylsilyl protection of the 2′-*O*-position was accomplished before a conventional *N*-benzoylation to give, after mild acidic desilylation, **15** in 81% yield over the three steps (Scheme 2). The palladium based allylation[22,25] afforded **16**, and after complete deprotection, the target 2′-*O*-allyl-arabinouridine **17** was obtained in 76% yield from **15**. Hereby, **17** has been obtained in approximately 53% overall yield from arabinouridine, that is, 45% from uridine counting the two step conversion of the 2′-configuration.[30] In comparison, the reported method,[28] albeit in fewer steps, gave **17** in only approximately 17% overall yield from uridine. Finally, **17** was reprotected as its *bis*-silyl ether **18** in 83% yield and selectively deprotected using mild acid to give **19** in 73% yield as the appropriate building block for incorporating **D** in the 3′-end of the dinucleotides.

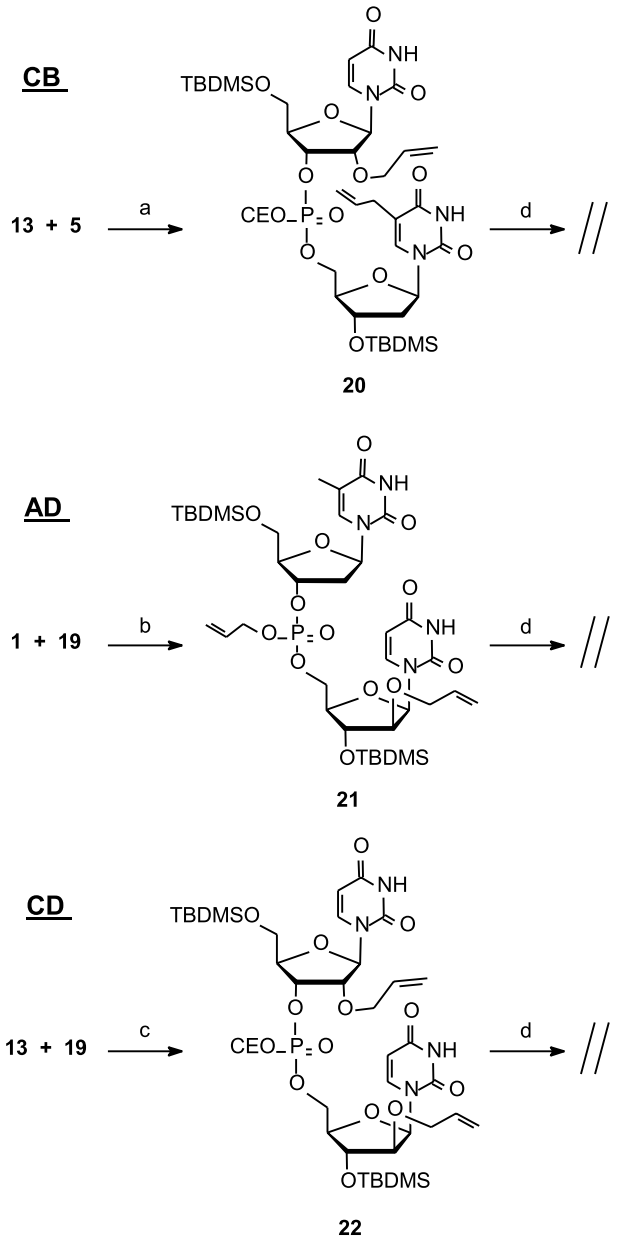
The five different protected dinucleotides **20**–**24** were made by the same general method using standard phosphoramidite chemistry[17] (Schemes 3–5). Thus, the appropriate 5′-alcohols and 3′-phosphoramidites were coupled with 1*H*-tetrazole as the activator followed by oxidation with *t*BuOOH. This oxidation reagent was efficient and easily handled, and the alternative standard reagent iodine was avoided due to the presence of double bonds. The general procedure afforded the dinucleotides in 60% to 100% yields. In all cases, the expected mixtures of two phosphorus epimers were obtained in approximately equimolar ratios as estimated from ^{1}H and ^{31}P NMR.

Subsequently, all the protected dinucleotides **20**–**24** were investigated as substrates for RCM reactions using 5–15 mol% of Grubbs second-generation catalyst **X** (Mes=2,4,6-trimethylphenyl, Cy=cyclohexyl),[2] in dichloromethane or 1,2-dichloroethane under reflux. We only investigated this catalyst, as this is by far the most generally successful according to the literature[1–4] as well as the most successfully applied in our lab for the synthesis of other dinucleotides with large rings.[7–10] We did not make a thorough investigation of a range of solvents, as dichloromethane and 1,2-dichloroethane have been the only successful solvents in our previous studies on nucleoside and nucleotide substrates.[6–10]



X

Of the five different dinucleotide substrates, however, neither **20**, **21** or **22** were good substrates for RCM reactions under these conditions (Scheme 3). In the case of **21** the substrate was converted to a highly polar material indicating polymerisation products, whereas both **20** and **22** could be re-isolated from the reaction mixtures. In the latter case,

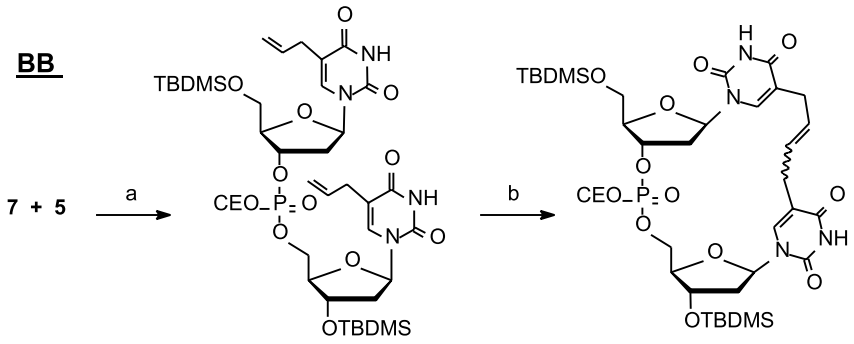


Scheme 3. Reagents and conditions: (a) i. 1*H*-tetrazole, CH_2Cl_2, CH_3CN, ii. *t*-BuOOH, CH_2Cl_2, CH_3CN, toluene, 100%; (b) 1*H*-tetrazole, CH_3CN, ii. *t*-BuOOH, CH_2Cl_2, toluene, 85%; (c) 1*H*-tetrazole, CH_2Cl_2, CH_3CN, ii. *t*-BuOOH, CH_2Cl_2, CH_3CN, toluene, 78%; (d) 5–15 mol% **X**, CH_2Cl_2/$ClCH_2CH_2Cl$/THF, reflux. TBDMS = *tert*-butyldimethylsilyl, CE = 2-cyanoethyl.

however, solubility problems forced us to investigate other solvents; toluene, ethyl acetate, acetonitrile/dichloromethane and THF, and with the latter, traces of a cyclised product was indicated from MS. On the other hand, the dinucleotide **23** was slowly converted to a ring-closed product **25** (Scheme 4). The best result was obtained with 5 mol% of the catalyst in dichloromethane at reflux from which **25** was isolated in 23% yield as a mixture of four stereoisomers in an approximately 1:1:4:6 ratio as deduced from the ^{31}P NMR spectrum. This indicates that both *E* and *Z*-configured products were obtained and also that the ratios are dependent on the configuration of the phosphorus and that the two isomers in the substrate reacted in different rates. Thus, 27% of the starting material was re-isolated with an approximately 1:10 ratio of phosphorus epimers. Nevertheless, the formation of a ring-closed product was also confirmed by MS showing the expected loss of ethylene, and by ^{1}H NMR demonstrating the conversion of terminal to internal double bonds.

Finally, the dinucleotide **24**[9] turned out to be the most efficient substrate for RCM. Thus, a treatment with 5 mol% of the catalyst in dichloromethane afforded **26** in 58% yield as a mixture of two phosphorus epimers in an equimolar ratio as deduced from ^{31}P NMR (Scheme 5). Again the product was also confirmed by MS and ^{1}H NMR showing the loss of ethylene and the conversion of terminal to internal double bonds. Thus, this RCM reaction was performed very smoothly, as it has also been demonstrated for its 3′-ribonucleosidic analogue.[8] Thus, **26** was the most easily obtained of the five projected cyclic dinucleotides, and subsequently, **26** has been further investigated for its stability towards ammonia.[9] Thus, ammonia is a standard reagent used in the final deprotection step in oligonucleotide synthesis, and as an allylic phosphotriester, **26** was expected to be labile towards nucleophiles. Thus, in an analytical experiment treating **26** with 32% aqueous ammonia for 24 h at room temperature, the allylic phosphotriester was found to react completely with ammonia at the allylic CH_2 group located next to the phosphate to give a zwitterionic ammonia adduct **27** as a dinucleotide with an achiral phosphordiester linkage in which also both TBDMS ethers were hydrolysed.[9] In order to increase the stability of the phosphotriester, we decided to prepare the saturated analogue of **26**. Thus, **24** was applied in a tandem RCM and hydrogenation reaction[31] by performing the RCM reaction as described earlier followed by hydrogenation of the reaction mixture in a Parr-bomb with 1000 psi H_2 at 50 °C. This gave the cyclic dinucleotide **28** in 63% yield as an equimolar mixture of two phosphorus epimers.[9] The protecting groups were subsequently removed by an acidic treatment to give the cyclic dinucleotide **29** in a quantitative yield. This dinucleotide was considerably more stable towards ammonia, as experiments showed that treatment with 32% NH_3(aq) at room temperature for 24 h resulted in only 10% conversion to the dinucleotide **30** as indicated by ^{31}P NMR and MS. A harsher treatment with 32% NH_3(aq) at 55 °C for 5 days resulted, however, in a complete conversion to the ammonia adduct **30**.

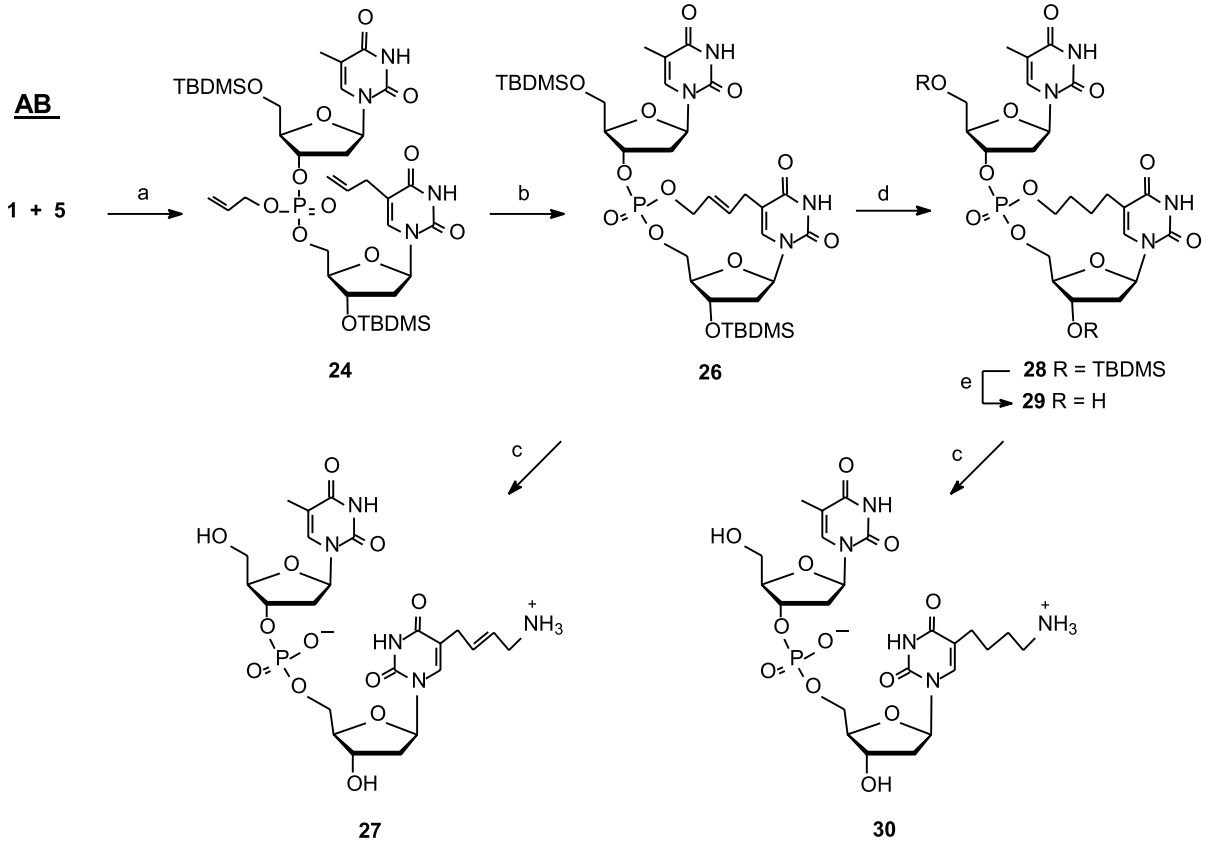
In summary, the present study has demonstrated that not all the five dinucleotide substrates were found to be substrates for RCM reactions. It could be argued, of course, that a longer range of catalysts and solvents should be included in the study. However, Grubbs second-generation catalyst **X** was in all cases tested by us[6–10,32] found to be superior to the first-generation catalyst ($(Cy_3P)_2RuCl_2CHPh$).[2] The recently commercialised Hoveyda–Grubbs second-generation catalyst[33] was not available, when most of the presented experiments were conducted. On the other hand, not even this catalyst has been found to be superior to **X** with dinucleotide substrates in our lab.[32] In the case of **21** Grubbs first-generation catalyst has been attempted, but only polymerisation was observed once again. Concerning solvents, we have attempted toluene in other studies[6–8] but this solvent has been incompatible with our nucleotide substrates. Furthermore, the major subject of this study has



Scheme 4. Reagents and conditions: (a) i. 1*H*-tetrazole, CH_3CN, ii. *t*-BuOOH, CH_3CN, toluene, 60%; (b) 5 mol% **X**, CH_2Cl_2, 23%, reflux. TBDMS=*tert*-butyldimethylsilyl, CE=2-cyanoethyl.

been to explore and compare different potential positions for introducing allyl groups into nucleotide building blocks and to compare different dinucleotides as RCM substrates. Thus, if a given substrate reacts very slowly with **X** or seems to prefer a polymerisation metathesis instead of a ring-closing reaction, no perspectives were seen in exploring a long range of reaction conditions. Therefore, we must conclude that only two of the five substrates, **23** and **24** could be transferred into the envisioned cyclic dinucleotides. Thus, the cyclic structures **25** and **26/29** can be used in the design of oligonucleotides that are conformationally restricted and potentially useful for targeting and mimicking nucleic acid secondary structures.

When comparing the four different building blocks **A**–**D** in Figure 1, all four have been very conveniently obtained and incorporated into dinucleotides. Thus, as an interesting spin-off from this study, very convenient procedures for preparing the two epimeric 2′-*O*-allyluridine **11** and 2′-*O*-allyl-arabinouridine **17** have been developed. Especially in the latter case, our procedure has surpassed the existing literature method. However, the efficient RCM reactions have been obtained only with **A** and **B**. Thus, taking in account our former studies,[7,8] the allyl group on the phosphotriester linkage is very reactive towards the catalyst and very well-positioned for performing ring-closing reactions. The 2′-*O*-*ribo* position of the allyl group, **C**, on



Scheme 5. Reagents and conditions: (a) 1*H*-tetrazole, CH_3CN, then *t*-BuOOH, toluene, 64%; (b) 5 mol% **X**, CH_2Cl_2, reflux, 58%; (c) 32% aq NH_3; (d) From **24**, 5 mol% **X**, CH_2Cl_2, reflux, then 1000 psi H_2, 50 °C, 63%; (e) 90% aq TFA, 100%. TBDMS=*tert*-butyldimethylsilyl.

the other hand, seems to be problematic. However, in other studies by us[32] and others,[11e] this position has been used to form cyclic nucleotide structures with large rings, and the reasons for the failure of **20** and **22** might be found in the particular conformational properties of these substrates. Similarly, the 2′-*O*-*arabino* position of the allyl group, **D**, has failed as demonstrated by the dinucleotides **21** and **22**. Nevertheless, reactivity between this allyl group and the catalyst is proven by the fact, that **21** is converted by polymerisation, probably by cross metathesis. Therefore, the reason for **21** being a bad substrate for RCM should be found in its conformational limitations making it impossible for the two double bonds (and their ruthenium [2+2]adducts) to approach and react in an intramolecular reaction. The 5-position of the pyrimidine, **B**, seems to be a good position for reaction with the catalyst **X**, and the possibility of making the very large ring structure in compound **25**, the largest of the projected rings in this study, might be partly driven by an ability to stack between the two pyrimidines. Furthermore, the planar geometry of these probably reduces any steric problems compared to the other positions for allyl groups. Nevertheless, also in this case, the reactivity is limited by geometry as illustrated by the fact that different reactivity was observed for the two phosphorus epimers. Thus, even though the selection of five dinucleotides that we choose for RCM studies led to the examination of each of the four allyl positions **A**–**D**, we cannot exclude the possibility that very efficient substrates and subsequent cyclic dinucleotides could be found with other combinations of **A**–**D**.

As evident from the present results, the butylene nucleobase to phosphotriester connection obtained in **29** has been efficiently obtained from the tandem RCM hydrogenation strategy. Further effort can now be put into separating the two phosphorus epimers of this compound and incorporating these into oligonucleotides. The stability of **29** towards ammonia supports these plans. Of the long range of possible cyclic dinucleotides investigated by this study, **29** is the most easily obtained and the obvious choice for further studies. Furthermore, the synthesis of other cyclic dinucleotides, constructed from allyl phosphotriester linkages and/or other positions for terminal alkene moieties[10,32] are in progress.

3. Conclusion

Five different dinucleotides combining four nucleotide building blocks with different allyl substituents have been explored as substrates for RCM reactions. Two cyclic dinucleotide structures were obtained and the one further elaborated to give a stable butylene connection between a nucleobase and a phosphate internucleotide linkage. Even though not all projected cyclisations could be performed in practice, more general knowledge within the scopes and limitation of the RCM based methodology towards conformationally restricted nucleic acid fragments has been obtained. Thus, we envision a large potential for constructing a plethora of cyclic dinucleotide structures mimicking a large range of nucleic acid secondary structures, and we expect the present RCM methodology to be a general future tool in nucleic acid chemical biology.

4. Experimentals

4.1. General

All commercial reagents were used as supplied. When necessary, reactions were performed under an atmosphere of nitrogen. Column chromatography was carried out on glass columns using silica gel 60 (0.040–0.063 mm). NMR spectra were recorded on a Varian Gemini 2000 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz, ^{13}C NMR spectra at 75.5 MHz, and ^{31}P NMR spectra at 121.5 MHz. Values for δ are in ppm relative to tetramethylsilane as internal standard or 85% H_3PO_4 as external standard. Fast-atom bombardment mass spectra (FAB-MS) were recorded in positive ion mode on a Kratos MS50TC spectrometer and MALDI mass spectra were recorded on an Ionspec Ultima Fourier Transform mass spectrometer. Microanalyses were performed at The Microanalytical Laboratory, Department of Chemistry, University of Copenhagen. Assignments of NMR spectra are based on 2D spectra and follow standard nucleoside style; that is, the carbon next to the nucleobase is assigned C-1′. For dinucleotides, the upper (5′) nucleotide is depicted U1 or T1 and the lower nucleoside U2 or T2.

4.1.1. Preparation of 5-allyl-2′-deoxy-5′-*O*-dimethoxytrityluridine (3). 5-Allyl-2′-deoxyuridine **2**[19] (0.700 g, 2.61 mmol) was coevaporated twice with anhydrous pyridine and redissolved in anhydrous pyridine (40 mL) in a darkened flask. $AgNO_3$ (0.557 g, 3.28 mmol) was added and the mixture was stirred for 5 min. DMTCl (1.099 g, 3.24 mmol) was added and the reaction mixture was stirred for 4 h, concentrated under reduced pressure and coevaporated with toluene. The residue was dissolved in ethyl acetate (50 mL), washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (2×50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (1–4% CH_3OH and 1% pyridine in CH_2Cl_2) to give the product as a white foam (1.280 g, 86%) (Found C, 68.59; H, 6.07; N, 4.75%; $C_{33}H_{34}N_2O_7 \cdot 1/2H_2O$ requires C, 68.38; H, 6.08; N, 4.83%); mp=79–82 °C; R_f 0.23 (5% CH_3OH in CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 2.24–2.44 (2H, m, H-2′), 2.51–2.77 (2H, m, 5-CH_2), 3.33–3.43 (2H, m, H-5′), 3.78 (6H, s, OCH_3), 4.06 (1H, m, H-4′), 4.53 (1H, m, H-3′), 4.76–4.82 (2H, m, CH=CH_2), 5.60 (1H, m, CH=CH_2), 6.41 (1H, m, H-1′), 6.83 (4H, m, Ph), 7.16–7.41 (9H, m, Ph), 7.47 (1H, s, H-6), 9.33 (1H, s, NH); ^{13}C NMR ($CDCl_3$) δ 30.5 (5-CH_2), 40.8 (C-2′), 55.2 (OCH_3), 63.5 (C-5′), 72.4 (C-3′), 84.8 (C-1′), 86.1 (Ph), 86.8 (C-4′), 113.23 (Ph), 113.71 (C-5), 116.65 (CH=CH_2), 125.3, 127.1, 127.9, 128.1, 128.2, 129.0, 130.1, 134.3, 135.4 (Ph), 135.4 (CH=CH_2), 136.1 (C-6), 144.3 (Ph), 150.4 (C-2), 158.6 (Ph), 163.1 (C-4); *m*/*z* FAB 570 (M).

4.1.2. Preparation of 5-allyl-3′-*O*-*tert*-butyldimethylsilyl-2′-deoxy-5′-*O*-dimethoxytrityluridine (4). Compound **3** (0.490 g, 0.86 mmol) was dissolved in anhydrous pyridine (30 mL) in a darkened flask. $AgNO_3$ (0.165 g, 0.97 mmol) was added and the mixture was stirred for 5 min. TBDMSCl (0.145 g, 0.96 mmol) was added and the reaction mixture was stirred overnight, concentrated under reduced pressure and coevaporated with toluene. The residue was dissolved in ethyl acetate (50 mL), washed with a saturated aqueous

solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (1–5% CH_3OH and 1% pyridine in CH_2Cl_2) to give the product as a white foam (0.495, 86%) (Found C, 66.96; H, 7.09; N, 3.84%; $C_{39}H_{48}N_2O_7Si\ H_2O$ requires C, 66.64; H, 7.16; N, 3.98%); mp = 60–64 °C; R_f 0.60 (5% CH_3OH in CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.02–0.16 (6H, m, $Si(CH_3)_2$), 0.81–0.97 (9H, m, $C(CH_3)_3$), 2.17–2.39 (2H, m, H-2′), 2.60–2.88 (2H, m, 5-CH_2), 3.28–3.48 (2H, m, H-5′), 3.82 (6H, s, OCH_3), 4.00 (1H, m, H-4′), 4.52 (1H, m, H-3′), 4.80–4.86 (2H, m, CH=CH_2), 5.67 (1H, m, CH=CH_2), 6.38 (1H, t, J = 6.7 Hz, H-1′), 6.82 (4H, m, Ph), 7.16–7.51 (9H, m, Ph), 7.55 (1H, s, H-6), 8.98 (1H, s, NH); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.7 ($Si(CH_3)_2$), 17.9 ($C(CH_3)_3$), 25.7 (C(CH_3)$_3$), 30.6 (C-2′) 41.3 (5-CH_2), 55.2 (OCH_3), 62.8 (C-5′), 72.1 (C-3′), 84.8 (C-1′), 86.7 (Ph), 87.4 (C-4′), 113.2 (Ph), 113.48 (C-5), 116.6 (CH=CH_2), 127.1, 127.7, 127.8, 127.9, 128.1, 128.2, 129.0, 129.1, 130.0, 134.4, 135.4 (Ph), 135.5 (CH=CH_2), 136.1 (C-6), 144.3 (Ph), 150.1 (C-2), 158.6 (Ph), 163.0 (C-4); m/z FAB 684 (M).

4.1.3. Preparation of 5-allyl-3′-*O*-*tert*-butyldimethylsilyl-2′-deoxyuridine (5). Compound **4** (0.450 g, 0.66 mmol) was dissolved in a mixture of CH_3OH and CH_2Cl_2 (2:3 v/v, 50 mL) and the solution was stirred at 0 °C. A solution of *p*-toluenesulfonic acid monohydrate (0.155 g, 0.82 mmol) in a mixture of CH_3OH and CH_2Cl_2 (2:3 v/v, 5 mL) was added over 5 min. The reaction mixture was stirred for 30 min and quenched by the addition of saturated aqueous ammonia (0.5 mL). The mixture was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (3×50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (1–3% CH_3OH in CH_2Cl_2) to give the product as a white foam (0.220 g, 88%); R_f 0.22 (5% CH_3OH in CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.01–0.13 (6H, m, $Si(CH_3)_2$), 0.83–0.96 (9H, m, $C(CH_3)_3$), 2.19–2.41 (2H, m, H-2′), 3.06–3.09 (2H, m, 5-CH_2), 3.72–3.76 (2H, m, H-5′), 3.92 (1H, m, H-4′), 4.50 (1H, m, H-3′), 5.11–5.18 (2H, m, CH=CH_2), 5.85 (1H, m, CH=CH_2), 6.15 (1H, t, J = 6.7 Hz, H-1′), 7.34 (1H, s, H-6), 9.01 (1H, s, NH); ^{13}C NMR ($CHCl_3$) δ −4.9, −4.7 $Si(CH_3)_2$), 18.0 ($C(CH_3)_3$), 25.7 (C(CH_3)$_3$), 30.5 (C-2′), 40.4 (5-CH_2), 62.0 (C-5′), 71.6 (C-3′), 87.2 (C-1′), 87.6 (C-4′), 113.5 (C-5), 117.6 (CH=CH_2), 134.2 (CH=CH_2), 137.6 (C-6), 150.2 (C-2), 163.1 (C-4); HiRes MALDI FT-MS m/z (M + Na) found/calcd 405.1828/405.1822.

4.1.4. Preparation of 5-allyl-5′-*O*-*tert*-butyldimethylsilyl-2′-deoxyuridine (6). 5-Allyl-2′-deoxyuridine **2**[19] (0.979 g, 3.65 mmol) was coevaporated with anhydrous pyridine and redissolved in anhydrous pyridine (36 mL) in a darkened flask. $AgNO_3$ (0.503 g, 2.96 mmol) was added and the mixture was stirred for 5 min. TBDMSCl (0.235 g, 1.56 mmol) was added and the reaction mixture was stirred for 2 h. Another portion of TBDMSCl (0.339 g, 2.25 mmol) was added in 3 parts during 3 h, and the reaction was stirred for 5 h and quenched by the addition of CH_3OH (1 mL). The reaction mixture was concentrated under reduced pressure and coevaporated with toluene. The residue was dissolved in CH_2Cl_2 (80 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by dry column chromatography (2–4% CH_3OH in CH_2Cl_2) to give the product as white foam (0.597 g, 42%) (Found C, 55.96; H, 8.02; N, 7.19%; $C_{18}H_{30}N_2O_5Si\cdot 1/4H_2O$ requires C, 55.86; H, 7.94; N, 7.23%); R_f 0.48 (10% CH_3OH in CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.07–0.10 (6H, m, $Si(CH_3)_2$), 0.91 (9H, s, $C(CH_3)_3$), 2.08 (1H, m, H-2′), 2.40 (1H, m, H-2″), 3.05–3.07 (2H, m, 5-CH_2), 3.81–3.83 (2H, m, H-5′), 4.04 (1H, m, H-4′), 4.40 (1H, m, H-3′), 5.06–5.12 (2H, m, CH=CH_2), 5.86 (1H, m, CH=CH_2), 6.34 (1H, m, H-1′), 7.42 (1H, s, H-6), 9.12 (1H, s, NH); ^{13}C NMR ($CDCl_3$) δ −5.3, −5.1 ($Si(CH_3)_2$), 18.5 ($C(CH_3)_3$), 26.1 (C(CH_3)$_3$), 31.1 (C-2′), 41.1 (5-CH_2), 63.8 (C-5′), 72.7 (C-3′), 85.3 (C-1′), 87.2 (C-4′), 113.5 (C-5), 116.5 (CH=CH_2), 134.7 (CH=CH_2), 136.2 (C-6), 150.5 (C-2), 163.2 (C-4); HiRes MALDI FT-MS m/z (M + Na) found/calcd 405.1836/405.1816.

4.1.5. Preparation of 5-allyl-5′-*O*-(*tert*-butyldimethylsilyl)uridine-3′-*O*-(*N*,*N*-diisopropyl)-(2-cyanoethyl)phosphoramidite (7). Compound **6** (0.152 g, 0.40 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL) and a 0.5 M solution of 4,5-dicyanoimidazole (0.55 mL, 0.28 mmol) in CH_3CN was added. 2-Cyanoethyl-*N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite (0.126 g, 0.42 mmol) was added dropwise over 5 min and the reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL). The combined aqueous phases were extracted with CH_2Cl_2 (30 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by dry column chromatography (50–60% ethyl acetate and 1% triethylamine in petrol ether) to give the product as a colourless oil and an epimeric mixture (0.173 g, 75%); R_f 0.36, 0.49 (75% ethyl acetate in petrol ether); ^1H NMR ($CDCl_3$) δ 0.10–0.11 (6H, m, $Si(CH_3)_2$), 0.88–0.98 (9H, m, $C(CH_3)_3$), 1.17–1.22 (12H, m, CH(CH_3)), 2.01–2.11 (1H, m, H-2′), 2.39–2.55 (1H, m, H-2″), 2.61–2.66 (2H, m, CH_2CN), 3.06–3.08 (2H, m, 5-CH_2), 3.56–3.91 (6H, m, H-5′, CH_2OP, 2×CH(CH_3)), 4.09–4.18 (1H, m, H-4′), 4.48–4.54 (1H, m, H-3′), 5.06–5.13 (2H, m, CH=CH_2), 5.80–5.91 (1H, m, CH=CH_2), 6.30–6.34 (1H, m, H-1′), 7.41, 7.45 (1H, 2 s, H-6), 8.27 (1H, br s, NH); ^{31}P NMR ($CDCl_3$) δ 149.45, 149.89; m/z FAB 583 (M + H).

4.1.6. Preparation of 2′-*O*-allyl-3-*N*-benzoyl-3′,5′-*O*,*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)uridine (10). Compound **9**[27] (0.496 g, 0.840 mmol) and allylethylcarbonate[34] (0.351 g, 2.70 mmol) was dissolved in anhydrous THF (4 mL). A solution of tris(dibenzylidenacetone)dipalladium(0) (0.012 g, 0.013 mmol, 1.5 mol%) and bis(diphenylphosphino)butane (0.038 g, 0.09 mmol, 10 mol%) in anhydrous THF (1 mL) was added. The reaction mixture was stirred at reflux for 45 min and then concentrated under reduced pressure. The residue was purified by column chromatography (4–50% ethyl acetate in petrol ether) to give the product as a white foam (0.487 g, 92%) (found: C, 59.19; H, 7.42; N, 4.43% $C_{31}H_{46}N_2O_8Si_2$ requires: C, 59.02; H, 7.35; N, 4.44%); R_f 0.71 (75% ethyl acetate in petrol ether); ^1H NMR ($CDCl_3$) δ 0.85–1.26 (28H, m, $SiCH(CH_3)_2$), 3.92 (1H, s, H-4′), 4.00 (1H, d, J = 14.0 Hz,

H-5′), 4.21–4.33 (5H, m, H-2′, H-3′, H-5″, 2′-OCH$_2$), 5.15 (1H, dd, J=1.5, 12.4 Hz, CH=CH_2), 5.31 (1H, dd, J=1.5, 17 Hz, CH=CH_2), 5.79 (1H, d, J=8.2 Hz, H-5), 5.76 (1H, s, H-1′), 5.87 (1H, m, CH=CH$_2$), 7.48–7.95 (m, 5H, Ph), 8.04 (1H, d, J=8.2 Hz, H-6); ^{13}C NMR ($CDCl_3$) δ 12.4, 12.8, 13.1, 13.4 (SiCH(CH$_3$)$_2$), 16.7, 16.8, 17.0, 17.1, 17.3, 17.3, 17.4, 17.5, 17.9 (SiCH(CH$_3$)$_2$), 59.4 (C-5′), 67.9 (C-3′), 71.2 (2′-OCH$_2$), 81.1 (C-4′), 82.0 (C-2′), 89.2 (C-1′), 101.45 (C-5), 117.4 (CH=CH$_2$), 129.2, 130.5, 131.3, 134.1 (Ph), 135.2 (CH=CH$_2$), 139.2 (C-6), 148.9 (C-2), 162.2 (C-4), 168.7 (C=O); m/z FAB 631 (M+H).

4.1.7. Preparation of 2′-*O*-allyluridine (11). Compound **10** (2.40 g, 3.80 mmol) was dissolved in THF (10 mL) and the solution was stirred at room temperature. A 1 M solution of TBAF in THF (8.6 mL, 8.6 mmol) was added over 5 min and the mixture was stirred for 30 min. A mixture of pyridine, CH_3OH and water (3:1:1 v/v, 10 mL) was added and the combined mixture was poured on 13 g amberlite IR-120® in pyridine, CH_3OH and water (3:1:1 v/v, 60 mL). The suspension was stirred for 30 min and filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in CH_3OH (50 mL) and added 25% aqueous ammonia (10 mL). The reaction mixture was stirred for 1 h 30 min, concentrated under reduced pressure and coevaporated with anhydrous ethanol. The residue was purified by dry column chromatography (0–10% CH_3OH in CH_2Cl_2) to give the product as a hygroscopic white foam (1.030 g, 95%); R_f 0.55 (10% CH_3OH in CH_2Cl_2); ^{1}H NMR (CD_3OD) δ 3.71–3.89 (2H, m, H-5′), 3.90–4.02 (2H, m, H-2′, H-4′), 4.20–4.24 (3H, m, H-3′, 2′-OCH$_2$), 5.13–5.34 (2H, m, CH=CH_2), 5.68 (1H, d, J=7.9 Hz, H-5), 5.87–5.98 (1H, m, CH=CH$_2$), 5.95 (1H, d, J=3.8 Hz, H-1′), 8.07 (1H, d, J=7.9 Hz, H-6); ^{13}C NMR (CD_3OD) δ 61.7 (C-5′), 70.0 (C-3′), 72.4 (2′-OCH$_2$), 82.5 (C-4′), 86.2 (C-2′), 89.2 (C-1′), 102.5 (C-5), 117.9 (CH=CH$_2$), 135.7 (CH=CH$_2$), 142.5 (C-6), 152.2 (C-2), 166.2 (C-4); HiRes MALDI FT-MS m/z (M+Na) found/calcd 307.0898/307.0901.

4.1.8. Preparation of 2′-*O*-allyl-5′-*O*-(*tert*-butyldimethylsilyl)uridine (12). Compound **11** (0.312 g, 1.10 mmol) was dissolved in anhydrous pyridine (9 mL). TBDMSCl (0.213 g, 1.41 mmol) and $AgNO_3$ (0.740 g, 4.36 mmol) were added, and the reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of CH_3OH (1 mL) and the mixture was concentrated under reduced pressure and coevaporated with toluene. The residue was dissolved in ethyl acetate (75 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL). The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by dry column chromatography (0–6% CH_3OH in CH_2Cl_2) to give the product as a white foam (0.344 g, 79%) (Found C, 54.61; H, 7.70; N, 6.81%; $C_{18}H_{30}N_2O_6Si$ requires C, 54.25; H, 7.59; N, 7.03%); R_f 0.67 (10% CH_3OH in ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.12 (6H, s, Si(CH$_3$)$_2$), 0.93 (9H s, C(CH$_3$)$_3$), 2.64 (1H, d, J=7.9 Hz, 3′-OH), 3.84–3.92 (2H, m, H-5′), 4.01–4.07 (2H, m, 2′-OCH$_2$), 4.20–4.24 (2H, m, H-2′, H-4′), 4.40 (1H, m, H-3′), 5.23–5.33 (2H, m, CH=CH_2), 5.67 (1H, d, J=8.3 Hz, H-5), 5.89 (1H, m, CH=CH$_2$), 5.98 (1H, s, H-1′), 8.06 (1H, d, J=8.3 Hz, H-6), 9.07 (1H, s, NH); ^{13}C NMR ($CDCl_3$) δ −5.6 (Si(CH$_3$)$_2$), 18.4 (C(CH$_3$)$_3$), 25.9 (C(CH$_3$)$_3$), 61.3 (C-5′), 67.9 (C-3′), 71.4 (2′-OCH$_2$), 81.5 (C-4′), 84.6 (C-2′), 87.3 (C-1′), 102.0 (C-5), 118.7 (CH=CH$_2$), 133.3 (CH=CH$_2$), 140.0 (C-6), 150.1 (C-2), 163.3 (C-4); HiRes MALDI FT-MS m/z (M+Na) found/calcd 421.1750/421.1765.

4.1.9. Preparation of 2′-*O*-allyl-5′-*O*-(*tert*-butyldimethylsilyl)uridine-3′-*O*-(*N*,*N*-diisopropyl)-(2-cyanoethyl)phosphoramidite (13). Compound **12** (0.123 g, 0.31 mmol) was dissolved in anhydrous CH_2Cl_2 (1.5 mL) and stirred at 0 °C. *N*,*N*-Diisopropylethylamine (0.30 mL, 0.227 g, 1.76 mmol) was added and chloro-*N*,*N*-diisopropylamino-(2-cyanoethyl)phosphine (0.20 g, 0.85 mmol) was added. The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 5 h. The reaction mixture was cooled to 0 °C and another portion of chloro-*N*,*N*-diisopropylamino-(2-cyanoethyl)phosphine (0.20 g, 0.85 mmol) was added. The mixture was stirred at room temperature for 1.5 h and then quenched by the addition of water (1 mL). The mixture was diluted with ethyl acetate (10 mL) and washed with a 5% aqueous solution of $NaHCO_3$ (2× 25 mL) and brine (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (0.5% triethylamine and 50% ethyl acetate in petrol ether) to give the product as yellow foam and an epimeric mixture (0.120 g, 65%); R_f 0.36 (75% ethyl acetate in petrol ether); ^{1}H NMR ($CDCl_3$) δ 0.10–0.13 (6H, m, Si(CH$_3$)$_2$), 0.94–0.97 (9H, m, C(CH$_3$)$_3$), 1.11–1.23 (12H, m, CH(CH_3)$_2$), 2.59–2.66 (2H, m, CH$_2$CN), 3.59–3.70 (4H, m, CH$_2$OP, CH(CH$_3$)$_2$), 3.70–3.84 (2H, m, H-5′), 3.84–4.01 (2H, m, 2′-OCH$_2$), 4.17–4.32 (3H, m, H-2′, H-3′, H-4′), 5.16–5.33 (2H, m, CH=CH_2), 5.64–5.68 (1H, m, H-5), 5.85–6.92 (1H, m, CH=CH$_2$), 6.02–6.06 (1H, m, H-1′), 7.94–7.98 (2H, m, H-6); ^{31}P NMR ($CDCl_3$) δ 150.91, 150.97; m/z FAB 599 (M+H).

4.1.10. Preparation of 3-*N*-benzoyl-1-(3′,5′-*O*,*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-β-D-arabinofuranosyl) uracil (15). Compound **14**[29] (5.33 g, 11.0 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL), stirred at 0 °C and added triethylamine (7.63 mL, 54.8 mmol). TMSCl (4.17 mL, 32.9 mmol) was added over 5 min and the reaction mixture was stirred at room temperature for 2 h. The mixture was cooled to 0 °C and added a 1.0 M aqueous solution of $NaHCO_3$ (100 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was redissolved in anhydrous pyridine (50 mL) and stirred at 0 °C. *N*,*N*-diisopropylethylamin (5.62 mL, 32.9 mmol) was added and the mixture was stirred for 10 min. Benzoyl chloride (3.81 mL, 32.9 mmol) was added and the reaction mixture was stirred at room temperature for 17 h. The reaction mixture was cooled to 0 °C and a 1.0 M aqueous solution of $NaHCO_3$ (100mL) was added. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and coevaporated with toluene (3× 10 mL). The residue was redissolved in CH_2Cl_2 (100 mL) and stirred at 0 °C. A solution of *p*-toluenesulfonic acid (4.72 g, 27.4 mmol) in THF (50 mL) was added and the reaction mixture was stirred for 10 min. Triethylamine (3.05 mL, 21.9 mmol) was added and the mixture was stirred for 15 min. A 1.0 M aqueous solution of $NaHCO_3$ (100mL) was added, and the organic phase was separated,

dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (5–40% ethyl acetate in petrol ether) to give the product as a white foam (5.21 g, 81%); mp = 50–53 °C; ^{1}H NMR ($CDCl_3$) δ 0.97–1.13 (28H, m, $CH(CH_3)_2$), 3.31 (1H, d, J = 4.6 Hz, 2′-OH), 3.73 (1H, m, H-4′), 4.05 (1H, dd, J = 2.5, 13.5 Hz, H-5′), 4.12 (1H, dd, J = 1.4, 13.5 Hz, H-5′), 4.16 (1H, t, J = 8.6 Hz, H-3′), 4.42 (1H, m, H-2′), 5.75 (1H, d, J = 8.2 Hz, H-5), 6.03 (1H, d, J = 6.2 Hz, H-1′), 7.80 (1H, d, J = 8.2 Hz, H-6), 7.93–7.42 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 12.2, 12.8, 12.9, 13.3 ($CH(CH_3)_2$), 16.7, 16.8, 16.9, 17.1, 17.2, 17.3, 17.4 ($CH(CH_3)_2$), 60.0 (C-5′), 72.4 (C-3′), 75.4 (C-2′), 80.7 (C-4′), 101.3 (C-5), 128.3, 130.3, 131.3, 134.9 (Ph), 140.2 (C-6), 149.9 (C-2), 162.1 (C-4), 168.5 (C=O).

4.1.11. Preparation of 1-(2′-*O*-allyl-β-D-arabinofuranosyl)uracil (17). Compound **15** (5.21 g, 8.82 mmol) was dissolved in anhydrous THF (35 mL) and added allylethylcarbonate[34] (1.51 mL, 13.2 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.121 g, 0.132 mmol) and 1,4-bis(diphenylphosphino)butane (0.376 g, 0.88 mmol). The reaction mixture was stirred at reflux for 3 h and then concentrated under reduced pressure. The crude compound **16** was dissolved in THF (50 mL) and a 1.0 M solution of TBAF in THF (19.4 mL, 19.4 mmol) was added over 5 min. The reaction mixture was stirred for 15 min and then concentrated under reduced pressure. The residue was dissolved in CH_3OH (35 mL) and the solution was stirred at 0 °C. NH_3(g) was bubbled through the solution for 45 min. The mixture was concentrated under reduced pressure and the residue was dissolved in a mixture of pyridine, CH_3OH and water (3:1:1 v/v, 80 mL). The mixture was stirred with Dowex® (50 W×2) for 2 h and the resin was removed by filtration. The filtrate was concentrated under reduced pressure and coevaporated with toluene. The residue was purified by column chromatography (0–7% CH_3OH in CH_2Cl_2) to give the product as white solid (1.90 g, 76%); mp = 167–168 °C; ^{1}H NMR (CD_3OD) δ 3.34–3.83 (2H, m, H-5′), 3.87 (1H, m, H-4′), 3.97 (1H, m, 2′-OCH_2), 4.10 (1H, m, H-2′), 4.15 (1H, m, 2′-OCH_2), 4.20 (1H, t, J = 4.8 Hz, H-4′), 5.11–5.26 (2H, m, CH=CH_2), 5.69 (1H, d, J = 8.2 Hz, H-5), 5.97 (1H, m, CH=CH_2), 6.26 (1H, d, J = 5.2 Hz, H-1′), 7.85 (1H, d, J = 8.2 Hz, H-6); ^{13}C NMR (CD_3OD) δ 61.8 (C-5′), 72.6 (C-3′), 74.9 (2′-OCH_2), 84.6 (C-2′), 85.1 (C-4′), 85.7 (C-1′), 101.3 (C-5), 117.2 (CH=CH_2), 135.2 (CH=CH_2), 144.1 (C-6), 152.2 (C-2), 166.2 (C-4).

4.1.12. Preparation of 1-(2′-*O*-allyl-3′,5′-*O*,*O*-bis(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl)uracil (18). Compound **17** (0.200 g, 0.70 mmol) was dissolved in anhydrous DMF (7 mL) and added imidazole (0.480 g, 7.04 mmol) and TBDMSCl (0.530 g, 3.52 mmol). The reaction mixture was stirred for 24 h at room temperature, concentrated under reduced pressure and coevaporated with xylene (2.5 mL). The residue was dissolved in CH_2Cl_2 (20 mL), washed with water (2×20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (0–2% CH_3OH in CH_2Cl_2) to give the product as a colourless oil (0.298 g, 83%); ^{1}H NMR ($CDCl_3$) δ 0.09–0.13 (12H, m, $Si(CH_3)_2$), 0.87–0.93 (18H, m, $C(CH_3)_3$), 3.74–4.01 (6H, m, 2′-OCH_2, H-2′, H-4′, H-5′), 4.29 (1H, t, J = 5.2 Hz, H-3′), 5.11–5.20 (2H, m, CH=CH_2), 5.65–5.81 (2H, m, CH=CH_2, H-5), 6.26 (1H, J = 5.3 Hz, H-1′), 7.65 (1H, d, J = 8.4 Hz, H-6), 8.91 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, −4.9, −4.5 ($Si(CH_3)_2$), 17.9, 18.4 ($C(CH_3)_3$), 25.5, 25.6, 25.9 ($C(CH_3)_3$), 61.0 (C-5′), 72.3 (C-3′), 73.6 (2′-OCH_2), 83.2, 83.7, 83.9 (C-1′, C-2′, C-3′), 101.2 (C-5), 117.6 (CH=CH_2), 133.3 (CH=CH_2), 141.9 (C-6), 150.3 (C-2), 163.2 (C-4); *m/z* MALDI (M+Na) 535.

4.1.13. Preparation of 1-(2′-*O*-allyl-3′-*O*-(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl)uracil (19). Compound **18** (0.701 g, 1.37 mmol) was dissolved in 80% aqueous acetic acid (20 mL) and the reaction mixture was stirred at 60 °C for 2 h 30 min. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (0–2% CH_3OH in CH_2Cl_2) to give the product as a white foam (0.399 g, 73%); mp = 131–132 °C; ^{1}H NMR ($CDCl_3$) δ 0.11–0.16 (6H, m, $Si(CH_3)_2$), 0.87–0.94 (9H, m $C(CH_3)_3$), 2.23 (1H, m, 5′-OH), 3.78–3.98 (6H, m, 2′-OCH_2), 4.24 (1H, t, J = 3.8 Hz, H-3′), 5.15–5.21 (2H, m, CH=CH_2), 5.71 (1H, d, J = 8.2 Hz, H-5), 5.75 (1H, m, CH=CH_2), 6.27 (1H, d, J = 4.6 Hz, H-1′), 7.62 (1H, d, J = 8.2 Hz, H-6), 8.71 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.6 ($Si(CH_3)_2$), 17.9 ($C(CH_3)_3$), 25.6 ($C(CH_3)_3$), 61.4 (C-5′), 72.3 (C-3′), 75.1 (2′-OCH_2), 83.3, 84.3, 84.4 (C-1′, C-2′, C-4′), 101.2 (C-5), 118.3 (CH=CH_2), 132.9 (CH=CH_2), 142.0 (C-6), 150.2 (C-2), 163.0 (C-4); HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 421.1751/421.1765.

4.1.14. Preparation of (5-allyl-3′-*O*-*tert*-butyldimethylsilyl-2′-deoxyuridin-5′-yl) (2′-*O*-allyl-5′-*O*-*tert*-butyldimethylsilyluridin-3′-yl) 2-cyanoethylphosphate (20). Compound **13** (0.103 g, 0.17 mmol) and compound **5** (0.073 g, 0.19 mmol) were coevaporated with anhydrous CH_2Cl_2 and dissolved in anhydrous CH_2Cl_2 (6 mL). A 0.45 M solution of 1*H*-tetrazole in CH_3CN (1.9 mL, 0.86 mmol) was added and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of CH_3OH (1 mL) and the mixture was concentrated under reduced pressure. The residue (crude phosphite, R_f 0.41 (75% ethyl acetate in petrolether)) was dissolved in a mixture of CH_2Cl_2 and CH_3CN (3:1 v/v, 8 mL) and cooled to 0 °C. A 3 M solution of *t*-BuOOH in toluene (0.3 mL, 0.9 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C and for 2 h at room temperature. The reaction was quenched by the addition of CH_3OH (1 mL) and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (50% ethyl acetate in petrol ether and 10% CH_3OH in CH_2Cl_2) to give the product as a white foam (0.156 g, 100%); R_f 0.27 (75% ethyl acetate in petrol ether); ^{1}H NMR (CD_3CN) δ 0.10–0.12 (12H, m, $Si(CH_3)_2$), 0.81–0.92 (18H, m, $C(CH_3)_3$), 2.18–2.26 (2H, m, T2-H-2′), 2.78–2.82 (4H, m, 5-CH_2, CH_2CN), 3.83–4.43 (12H, m, U1-H-5′, U1-H-4′, U1-H-2′, U1-2′-OCH_2, T2-H-5′, T2-H-4′, T2-H-3′, CH_2OP), 4.87–4.92 (1H, m, U1-H-3′), 5.01–5.29 (4H, m, 2×CH=CH_2), 5.63–5.67 (1H, m, H-5), 5.78–5.94 (2H, m, 2×CH=CH_2), 5.99–6.02 (1H, m, U1-H-1′), 6.15–6.21 (1H, m, T2-H-1′), 7.31 (½H, s, T2-H-6), 7.38 (½H, s, T2-H-6), 7.72–7.75 (1H, m, H-6), 8.91–8.95 (2H, br s, 2×NH); ^{31}P NMR (CD_3CN) δ −1.74, −1.49; *m/z* ESI 918 (M+Na), 896 (M+H).

4.1.15. Preparation of allyl (2′-*O*-allyl-3′-*O*-(*tert*-butyldimethylsilyl)arabinouridin-5′-yl) (5′-*O*-*tert*-butyldimethylsilylthymidin-3′-yl) phosphate (21). Compound **19** (0.081 g, 0.20 mmol) was coevaporated with anhydrous CH_3CN and dissolved in anhydrous CH_3CN (3 mL). A 0.45 M solution of 1*H*-tetrazole in CH_3CN (0.68 mL, 0.30 mmol) was added and the mixture for stirred for 10 min. A solution of **1** (0.252 g, 0.46 mmol) in anhydrous CH_3CN (3 mL) was added and the reaction mixture was stirred for 2 h. The reaction was quenched by the addition of CH_3OH (0.5 mL) and the reaction mixture was concentrated under reduced pressure and coevaporated with CH_2Cl_2. The residue was dissolved in anhydrous CH_2Cl_2 (4 mL) and cooled to 0 °C. A 3 M solution of *t*-BuOOH in toluene (0.14 mL, 0.41 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of CH_3OH (1 mL) and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (0–2% CH_3OH in CH_2Cl_2) to give the product as a white foam and an epimeric mixture (0.148 g, 85%); mp = 70–71 °C; ^{1}H NMR ($CDCl_3$) δ 0.08–0.13 (12H, m, $Si(CH_3)_2$), 0.90–0.92 (18H, m, $C(CH_3)_3$), 1.90–1.94 (3H, br s, T1-CH_3), 2.00–2.06 (1H, m, T1-H-2′), 2.52–2.58 (1H, m, T1-H-2′), 3.90–4.28 (10H, m, U2-2′-OCH_2, U2-H-5′, U2-H-4′, U2-H-3′, U2-H-2′, T1-H-5′, T1-H-4′), 4.56-4.61 (2H, m, CH_2OP), 4.98-5.02 (1H, m, T1-H-3′), 5.14-5.21 (2H, m, U2-CH=CH_2), 5.29–5.43 (2H, m, T1-CH=CH_2), 5.68–5.80 (2H, m, U2-C*H*=CH_2, U2-H-5), 5.95–6.01 (1H, m, T1-C*H*=CH_2), 6.28–6.32 (1H, m, U2-H-1′), 6.33–6.39 (1H, m, T1-H-1′), 7.48–7.52 (1H, m, T1-H-6), 7.61–7.69 (1H, m, U2-H-6), 9.53–9.69 (2H, m, 2×NH); ^{31}P NMR ($CDCl_3$) δ −0.59; HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 879.3420/879.3404.

4.1.16. Preparation of (2′-*O*-allyl-3′-*O*-(*tert*-butyldimethylsilyl)arabinouridin-5′-yl) (2′-*O*-allyl-5′-*O*-*tert*-butyldimethylsilyluridin-3′-yl) 2-cyanoethylphosphate (22). Compound **13** (0.140 g, 0.23 mmol) and compound **19** (0.111 g, 0.28 mmol) were coevaporated twice with anhydrous CH_3CN and redissolved in anhydrous CH_3CN (7 mL). A 0.45 M solution of 1*H*-tetrazole in CH_3CN (2.6 mL, 1.17 mmol) was added and the reaction mixture was stirred for 2 h. The reaction was quenched by the addition of CH_3OH (0.5 mL) and the mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and CH_3CN (1:1 v/v, 16 mL) and stirred at 0 °C. A 3 M solution of *t*-BuOOH in toluene (0.38 mL, 1.14 mmol) was added and the reaction mixture was stirred at room temperature for 90 min. The reaction was quenched by the addition of CH_3OH (0.5 mL) and the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate) and precipitated twice from a mixture of ethyl acetate and petrol ether to give the product as a white powder and an epimeric mixture (0.181 g, 78%); R_f 0.27 (75% ethyl acetate in petrol ether); ^{1}H NMR (DMSO-d_6) δ 0.08–0.12 (12H, m, $Si(CH_3)_2$), 0.86–0.90 (18H, m, $C(CH_3)_3$), 2.92–2.96 (2H, m, CH_2CN), 3.77–4.28 (15H, m, U1-H-5′, U1-H-4′, U1-H-2′, U2-H-5′, U2-H-4′, U2-H-3′, U2-H-2′, CH_2OP, U1-2′-OCH_2, U2-2′-OCH_2), 4.82–4.86 (1H, m, U1-H-3′), 5.09–5.25 (4H, m, 2×C*H*=CH_2), 5.59–5.68 (2H, m, 2×H-5), 5.70–5.90 (2H, m, 2×C*H*=CH_2), 5.92–5.97 (1H, m, U1-H-1′), 6.21–6.23 (1H, m, U2-H-1′), 7.56–7.72 (2H, m, 2×H-6), 11.41–11.47 (2H, m, 2×NH); ^{31}P NMR (DMSO-d_6) δ −1.12; HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 934.3442/934.3462.

4.1.17. Preparation of (5-allyl-2′-deoxy-3′-*O*-*tert*-butyldimethylsilyluridin-5′-yl) (5-allyl-2′-deoxy-5′-*O*-*tert*-butyldimethylsilyluridin-3′-yl) 2-cyanoethylphosphate (23). Compound **7** (0.156 g, 0.268 mmol) and compound **5** (0.111 g, 0.290 mmol) were coevaporated twice with anhydrous CH_3CN and dissolved in anhydrous CH_3CN (3 mL). A 0.45 M solution of 1*H*-tetrazole in CH_3CN (3.0 mL, 1.35 mmol) was added and the reaction mixture was stirred for 30 min. The reaction was quenched by the addition of CH_3OH (0.6 mL) and the mixture was concentrated under reduced pressure. The residue (crude phosphite, R_f 0.23 (75% ethyl acetate in petrol ether)) was dissolved in anhydrous CH_3CN (3 mL) and a 3 M solution of *t*-BuOOH in toluene (0.45 mL, 1.35 mmol) was added. The reaction mixture was stirred for 1.5 h and added another portion of the 3 M solution of *t*-BuOOH in toluene (0.23 mL, 0.69 mmol). The reaction mixture was stirred for 30 min and the reaction was quenched by the addition of CH_3OH (0.5 mL). The mixture was concentrated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (50 mL), washed with a saturated aqueous solution of $NaHCO_3$ (25 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by dry column chromatography (50–0% petrol ether in ethyl acetate) to give the product as a white foam and an epimeric mixture (0.142 g, 60%); (Found C, 53.01; H, 7.32; N, 7.42%; $C_{39}H_{62}N_5O_{12}PSi_2$ requires C, 53.23; H, 7.10; N, 7.96%); R_f 0.36 (75% ethyl acetate in petrolether); ^{1}H NMR ($CDCl_3$) δ 0.10–0.11 (12H, m, $Si(CH_3)_2$), 0.89–0.91 (18H, m, $C(CH_3)_3$), 2.08–2.68 (4H, m, T1-H-2′, T2-H-2′), 2.75–2.80 (2H, m, CH_2CN), 3.00–3.08 (4H, T1-5-CH_2, T2-5-CH_2), 3.80–4.03 (4H, m, T2-H-5′, T2-H-4′, T1-H-4′), 4.20–4.30 (5H, m, T1-H-5′, T2-H-3′, CH_2OP), 4.41–4.45 (1H, m, T1-H-3′), 5.04–5.17 (4H, m, 2×CH=CH_2), 5.85–5.89 (2H, m, 2×C*H*=CH_2), 6.10–6.17 (1H, m, T1-H-1′), 6.27–6.32 (1H, m, T2-H-1′), 7.20–7.22 (1H, m, H-6), 7.39–7.41 (1H, m, H-6), 9.00–9.13 (2H, m, 2×NH); ^{31}P NMR ($CDCl_3$) δ −1.58, −1.44; HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 902.3581/902.3563.

4.1.18. Preparation of allyl (5-allyl-2′-deoxy-3′-*O*-*tert*-butyldimethylsilyluridin-5′-yl) (5′-*O*-*tert*-butyldimethylsilylthymidin-3′-yl) phosphate (24). Compound **5** (0.188 g, 0.49 mmol) and compound **1** (0.520 g, 0.96 mmol) were coevaporated twice with anhydrous CH_3CN (10 mL) and dissolved in anhydrous CH_3CN (25 mL). A 0.45 M solution of 1*H*-tetrazole in CH_3CN (5.3 mL, 2.38 mmol) was added over 5 min and the reaction mixture was stirred for 1.5 h at room temperature. A 3 M solution of *t*-BuOOH in toluene (0.82 mL, 2.46 mmol) was added, and the mixture was stirred for another 1.5 h. The reaction was quenched by the addition of CH_3OH (0.25 mL), and the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2×20 mL) and brine (20 mL). The aqueous phase was extracted with ethyl acetate (30 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated under

reduced pressure. The residue was purified by column chromatography (20–70% ethyl acetate in petrol ether) to give the product as a white foam and an epimeric mixture (0.266 g, 64%); mp = 74–76 °C; R_f 0.34 (75% ethyl acetate in petrol ether); ^{1}H NMR ($CDCl_3$) δ 0.01–0.12 (12H, m, $Si(CH_3)_2$), 0.83–0.92 (18H, m, $C(CH_3)_3$), 1.90–1.94 (3H, m, CH_3), 2.08–2.19 (1H, m, T1-H-2′), 2.21–2.29 (2H, m, T2-H-2′), 2.50–2.58 (1H, m, T1-H-2″), 3.08–3.11 (2H, m, T2-5-CH_2), 3.85–3.92 (T1-H-5′), 4.01–4.03 (1H, m, T2-H-4′), 4.20–4.29 (3H, m, T2-H-5′, T1-H-4′), 4.41–4.44 (1H, m, T2-H-3′), 4.55–4.60 (2H, m, CH_2OP), 5.00–5.04 (1H, T1-H-3′), 5.09–5.17 (2H, m, T2-CH=C*H*$_2$), 5.28–5.41 (2H, m, T1–CH=C*H*$_2$), 5.84–6.00 (2H, m, 2×C*H*=CH_2), 6.17–6.25 (1H, m, T2-H-1′), 6.32–6.37 (1H, m, T1-H-1′), 7.24–7.28 (1H, m, T2-H-6), 7.46–7.48 (1H, m, T1-H-6), 8.76–8.87 (2H, m, 2×NH); ^{31}P NMR ($CDCl_3$) δ −0.61; HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 863.3454/863.3454.

4.1.19. Preparation of cyclic 5′-*O*,3′-*O*-*bis*-TBDMS protected dUpU containing a 5-to-5 (*E*/*Z*)-2-butenelinker (25). Compound **23** (26 mg, 0.030 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL). Grubbs second-generation catalyst $\mathbf{X}^2$ (1.4 mg, 1.6 μmol) was added and the reaction mixture was stirred at reflux for 22 h. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (2–8% CH_3OH in CH_2Cl_2) to give the product as a white powder and a mixture of diastereomers (6 mg, 23%) as well as starting material **23** (7 mg, 27%); R_f 0.28 (10% CH_3OH in CH_2Cl_2); ^{31}P NMR ($CDCl_3$) δ −2.01 (1), −0.90 (0.13), −0.56 (0.61), 0.02 (0.17); HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 874.3199/874.3250.

4.1.20. Preparation of cyclic 5′-*O*,3′-*O*-bis-TBDMS protected dTpU containing a phosphate-to-5 (*E*/*Z*)-2-butenelinker (26). Compound **24** (0.052 g, 0.062 mmol) was dissolved in anhydrous CH_2Cl_2 (6 mL). Grubbs second-generation catalyst $\mathbf{X}^2$ (2.8 mg, 3.2 μmol, 5.2 mol%) was added and the reaction mixture was stirred at reflux for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (10–0% petrol ether in ethyl acetate) to give the product as a white foam and an epimeric mixture (29 mg, 58%); R_f 0.29 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.10–0.13 (12H, m, $Si(CH_3)_2$), 0.89–0.94 (18H, m, $C(CH_3)_3$), 1.90–1.94 (3H, m, T1-CH_3), 2.06–2.30 (3H, m, T2-H-2′, T1-H-2′), 2.50–2.60 (1H, m, T1-H-2″), 3.10–3.14 (2H, m, T2-5-CH_2), 3.80–3.96 (2H, m, T1-H-5′), 3.98–4.49 (5H, m, T1-H-4′, T2-H-5′, T2-H-4′, T2-H-3′), 4.51–4.90 (2H, m, CH_2OP), 5.01–5.05 (1H, m, T1-H-3′), 5.84–5.89 (1H, m, CH=C*H*CH_2OP), 5.91–5.98 (1H, m, C*H*=$CHCH_2OP$), 6.36–6.42 (2H, m, T1-H-1′, T2-H-1′), 7.37–7.51 (2H, m, T1-H-6, T2-H-6), 9.02–9.20 (2H, m, NH); ^{31}P NMR ($CDCl_3$) δ −0.65, 2.01. HiRes MALDI FT−MS *m/z* (M+Na) found/calcd 835.3148/835.3141; IR (KBr) ν cm^{-1}: 3441, 3065, 2954, 2930, 2857, 1694, 1471, 1276, 1100, 1006, 987, 837, 780.

4.1.21. Analytical formation of Tp-5-(4-amino-2-butenyl)-2′-deoxyuridine (27). Compound **26** (2 mg) was dissolved in 32% aqueous NH_3 (1 mL) for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure to give the product as a white foam; ^{1}H NMR (DMSO-d_6) δ 1.78 (3H, s, CH_3), 1.91–2.18 (3H, m, T1-H-2′, T2-H-2′), 2.24–2.33 (1H, m, T1-H-2″), 2.92–3.09 (2H, m, T2-5-CH_2), 3.40–3.43 (2H, m, CH_2N), 3.51–3.59 (2H, m, T1-H-5′), 3.75–4.31 (5H, m, T2-H-5′, T1-H-4′, T2-H-4′, T2-H-3′), 4.60–4.70 (1H, m, T1-H-3′), 5.20–5.32 (2H, m, 2×OH), 5.69–5.78 (1H, m, CH=C*H*CH_2N), 5.89–5.97 (1H, m, C*H*=$CHCH_2N$), 6.14–6.18 (1H, m, T1-H-1′), 6.25 (1H, t, J=7.4 Hz, T2-H-1′), 7.68 (1H, s, T2-H-6), 7.70 (1H, s, T1-H-6); ^{31}P NMR (DMSO-d_6) δ −0.86; MALDI-MS *m/z*: 601.27 (MH^+), 623.19 (MNa^+).

4.1.22. Preparation of cyclic 5′-*O*,3′-*O*-bis-TBDMS protected dTpU containing a phosphate-to-5 butanelinker (28). Compound **24** (0.255 g, 0.303 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) and Grubbs second-generation catalyst $\mathbf{X}^2$ (14.0 mg, 16 μmol, 5.4 mol%) was added. The reaction mixture was stirred at reflux for 3.5 h and then bubbled with hydrogen for 5 min. The mixture was placed in an autoclave at 1000 psi hydrogen at 50 °C overnight. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (20–0% petrol ether in ethyl acetate) to give the product as a white foam and an epimeric mixture (0.156 g, 63.0%); R_f 0.29 (1% CH_3OH in ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.10–0.13 (12H, m, $Si(CH_3)_2$), 0.89–0.93 (18H, m, $C(CH_3)_3$), 1.55–1.85 (4H, m, $CH_2CH_2CH_2CH_2OP$), 1.92–1.94 (3H, m, CH_3), 2.10–2.58 (6H, m, T1-H-2′, T2-H-2′, T2-5-CH_2), 3.85–4.01 (4H, m, T1-H-5′, CH_2OP), 4.09–4.44 (3H, m, T2-H-4′, T2-H3′, T1-H-4′), 4.45–4.60 (2H, m, T2-H-5′), 4.95–5.05 (1H, m, T1-H-3′), 6.29–6.40 (2H, m, T2-H-1′, T1-H-1′), 7.39–7.52 (2H, m, T1-H-6, T2-H-6), 9.13–9.24 (2H, m, 2×NH); ^{31}P NMR ($CDCl_3$) δ −0.81, 1.29; HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 837.3336/837.3298.

4.1.23. Preparation of cyclic dTpU containing a phosphate-to-5 butanelinker (29). Compound **28** (0.145 g, 0.178 mmol) was dissolved in a 90% aqueous solution of trifluoroacetic acid (5 mL) and stirred for 3 h. The mixture was concentrated under reduced pressure and coevaporated with 99.9% CH_3CH_2OH (3×5 mL) and with CH_3OH (5 mL) to give the product as a white powder and an epimeric mixture (0.104 g, 100%); ^{1}H NMR (CD_3OD) δ 1.56–1.75 (4H, m, $CH_2CH_2CH_2CH_2OP$), 1.77–1.80 (3H, s, CH_3), 2.08–2.50 (6H, m, T1-H-2′, T2-H-2′, T2-5-CH_2), 3.69–3.73 (2H, m, T1-H-5′), 3.90–4.42 (7H, m, T1-H-4′, T2-H-5′, T2-H-4′, T2-H-3′, $POCH_2$), 4.99–5.02 (1H, m, T1-H-3′), 6.18–6.28 (2H, m, T1-H-1′, T2-H-1′), 7.40 (½H, s, T2-H-6), 7.50 (½H, s, T2-H-6), 7.69–7.70 (1H, m, T1-H-6); ^{31}P NMR (CD_3OD) δ −1.05, 0.01 (^{1}H and ^{31}P NMR data from DMSO-d_6 has been published in Ref. 9); HiRes MALDI FT-MS *m/z* (M+Na) found/calcd 609.1584/609, 1568; IR (KBr) ν cm^{-1}: 3435, 1690, 1472, 1277, 1022, 784.

4.1.24. Analytical formation of Tp-5-(4-aminobutanyl)-2′-deoxyuridine (30). Compound **29** (2 mg) was dissolved in 32% aqueous NH_3 (1 mL) for 5 days at 55 °C. The reaction mixture was concentrated under reduced pressure to give the product as a white foam; ^{1}H NMR (DMSO-d_6) δ 1.51–1.56 (4H, m, $CH_2CH_2CH_2CH_2N$), 1.78 (3H, s, CH_3), 2.03–2.10 (2H, m, T2-H-2′), 2.11–2.19 (2H, m, T2-5-CH_2), 2.23-2.28 (2H, m, T1-H-2′), 2.81–2.84 (2H, m, CH_2N), 3.58–3.62 (2H, m, T1-H-5′), 3.81–3.88 (2H, m, T2-H-5′), 3.94–3.96 (2H, m, T1-H-4′, T2-H-4′), 4.30–4.32 (1H, m, T2-H-3′), 4.63–4.67 (1H, m, T1-H-3′), 5.31 (1H, br, OH),

6.16 (1H, t, $J=6.7$ Hz, T1-H-1′), 6.26 (1H, t, $J=7.0$ Hz, T2-H-1′), 7.70 (1H, s, T1-H-6), 7.73 (1H, s, T2-H-6), 8.2–9.2 (3H, br, NH_3); ^{31}P NMR (DMSO-d_6) δ −0.82; MALDI-MS *m/z*: 603 (M^+), 625 (MNa^+); IR (KBr) ν cm^{-1}: 3400, 2255, 2128, 1684, 1469, 1277, 1203, 1026, 825, 763.

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Electrochemical reductive cleavage of carbon–halogen bonds in 5-bromo-1,3-dichloro-2-iodobenzene

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Abstract—The electrochemical reduction of carbon–halogen bonds in 5-bromo-1,3-dichloro-2-iodobenzene follows quadratic activation–driving force relationship except in one of the carbon–chlorine bonds. The variation of the transfer coefficient with the electrode potential has been estimated using the voltammetric data coupled with the convolution analysis. The standard potentials pertaining to the reduction of carbon–halogen bonds are evaluated using the Marcus theory of outer sphere electron transfer.

1. Introduction

Electrochemical single electron transfer reactions constitute a frontier area of research[1] and the kinetics of these reactions can be analyzed using the Marcus–Hush theory of outer sphere electron transfer assuming the validity of the Born–Oppenheimer approximation. Electron transfer to an organic molecule (RX) is often accompanied by bond cleavage leading to a radical ($R^{\bullet}$) and an anion (X^{-}) occurring either in a stepwise manner (reaction 1) or a single elementary step (reaction 2).

$$RX + e^{-} \rightleftharpoons RX^{\cdot -} \quad (E^{0}_{RX/RX^{\cdot -}}) \tag{1a}$$

$$RX^{\cdot -} \rightarrow R^{\cdot} + X^{-} \tag{1b}$$

$$RX + e^{-} \rightarrow R^{\cdot} + X^{-} \quad (E^{0}_{RX/R^{\cdot}+X^{-}}) \tag{2}$$

Application of general electrochemical techniques yields the transfer coefficient and the forward electron transfer rate constant for the above reactions, but not the information about the standard potential (E^{0}) vis-à-vis the standard rate constant; since the dissociative electron transfer reactions are completely irreversible, E^{0} values can not be obtained directly (for example, by cyclic voltammetry). However, the kinetic analysis of homogeneous redox catalysis of the electrochemical reduction leads to the determination of E^{0}.[2]

An elegant method for the estimation of standard potentials of irreversible systems obeying a quadratic activation–driving force relationship was demonstrated in the dissociative reduction of perbenzoates.[3] The above methodology, making use of linear variation of transfer coefficient (α) with the electrode potential (E), was adopted in the electrochemical reduction of several organic[4–6] and biologically relevant molecules.[7] However, studies in this direction on the stepwise reductive cleavage reactions involving rapid decomposition of the anion radicals (especially aromatic compounds) are limited.

In this communication, we report the standard potentials of the irreversible reduction of aromatic carbon–halogen bonds in 5-bromo-1,3-dichloro-2-iodobenzene using the quadratic activation–driving force relationship. Convolution potential sweep voltammetry is the main tool for investigating the reaction kinetics, since, in contrast to homogeneous redox catalysis, the convolution approach allows one to obtain extensive data on the logarithmic electron transfer rate constant ($\ln k_{ET}$) versus electrode potential (E) variation. It has to be emphasized here that the present approach fails for systems involving linear variation of $\ln k_{ET}$ with E (Butler–Volmer kinetics)—an example of which also is demonstrated in the present study.

2. Experimental

The voltammetric studies were carried out in a single compartment electrochemical cell thermostated at 298 K, using the Bio Analytical Systems (BAS) 100A Electrochemical workstation. The working electrode was a glassy

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carbon disc (BAS) of 3 mm diameter while platinum foil (2 cm^2) served as the counter electrode. The working electrode was polished with the alumina slurry (BAS) and ultrasonically rinsed prior to use. The electrochemical pretreatment was carried out in the background solution using several cycles at 0.05–1 V s^{-1} in a wide potential range. Tetra *n*-butyl ammonium bromide (nBu_4NBr) (Fluka) was the supporting electrolyte and used as received. *N*,*N*′-dimethyl formamide (DMF) was initially distilled from anhydrous copper sulfate, then the distillate was again distilled from calcium hydride under reduced pressure and stored over 4 Å molecular sieves. Silver/silver ion (1 mM) electrode (BAS) was used as the quasi-reference electrode which was subsequently calibrated with the ferrocene/ferrocenium couple under identical conditions of solvent and supporting electrolyte. The background subtracted voltammograms were analyzed by the convolution approach, the experimental and computational details of which have been described earlier.[8] NMR spectra were recorded on Bruker Avance 400 spectrometer. UV–Vis spectrum was obtained with the Ocean Optics UV/Vis spectrometer.

5-Bromo-1,3-dichloro-2-iodobenzene was synthesized by the following procedure: 2,6-dichloroaniline was brominated by passing the vapours of bromine into a solution of 2,6-dichloroaniline in hydrochloric acid. The solid 4-bromo-2,6-dichloroaniline was filtered and purified by column chromatography (silica gel). 4-Bromo-2,6-dichloroaniline was then diazotized in hydrochloric acid (6 M) using aqueous sodium nitrite (6 M) and the resulting solution was slowly added to aqueous potassium iodide (5 M). When no gas was evolved, the crude product was filtered, washed with aqueous sodium hydroxide, subsequently with sodium metabisulphite and finally with water. The residue was purified by column chromatography (silica gel) using hexane as the eluent to give 5-bromo-1,3-dichloro-2-iodobenzene as white solid: Mp 67.8–68.7 °C (literature:[9] 67.5–68.2 °C); ^1H NMR (400 MHz, $CDCl_3$, TMS as internal standard) δ 7.48 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.41, 122.36, 129.89, 141.33; UV–Vis ($CHCl_3$) broad band centered at 300 nm. The compound was crystallized in hexane (colorless crystals) for the electrochemical studies and the crystal structure confirms the identity of the compound[†].

3. Results and discussion

Halobenzenes (RX) undergo irreversible electron transfers at the electrode surface and are capable of hosting transitorily the incoming electron in their π^* orbitals leading to the radical anions ($RX^{\cdot -}$) (reaction 1a). The radical anions readily undergo decomposition with a first order rate constant greater than 10^4 s^{-1} to neutral radicals ($R^{\cdot}$) and halide ions (X^-) (reaction 1b).[10] The dissociation of the radical anion may be viewed as an intramolecular dissociative single-electron transfer from the π^* orbital to the σ^* orbital of the carbon–halogen bond.[11] Interestingly, the neutral radicals are easier to reduce than the parent halobenzenes and immediately undergo a second electron transfer to form R^-. However, the characteristic features of the reduction wave of halobenzene are solely governed by the kinetics of the first electron transfer. R^- abstracts a proton either from the solvent or the supporting electrolyte to give the hydrocarbon RH and it was observed that several halobenzenes and other aromatic halides upon electrolysis yielded 100% of RH.[10] A recent investigation, involving in situ electrochemical-NMR spectroscopy,[12] has revealed that the aryl anion abstracts a proton preferably from the solvent rather than the supporting electrolyte. It is worth mentioning here that the hydrocarbon RH is reducible and, in fact, a second wave is observed in some cases before the background discharge.[10] However, in most cases, the reduction wave of RH is suppressed by the background discharge current of the supporting electrolyte.

Figure 1 shows the cyclic voltammogram pertaining to the reduction of 5-bromo-1,3-dichloro-2-iodobenzene at the glassy carbon electrode in DMF containing 0.1 M nBu_4NBr as the supporting electrolyte. The reduction waves a, b, c and d represent, respectively, the two-electron reduction of carbon–iodine (C–I), carbon–bromine (C–Br) and two carbon–chlorine (C–Cl (1) and C–Cl (2)) bonds. This assignment follows from the fact that the carbon–halogen bonds are susceptible to reduction in the order of: C–I > C–Br > C–Cl > C–F. Each wave represents the hydrogenolysis of a carbon–halogen bond finally leading to the formation of benzene and hence an overall consumption of eight electrons in a single voltammetric cycle. The voltammogram B shows the reduction waves of 1,3-dichlorobenzene which corresponds to the peaks c and d of the voltammogram A. The π^* level of 5-bromo-1,3-dichloro-2-iodobenzene being comparatively lower than the monosubstituted benzene is proved by the fact that the reduction potential of carbon–iodine bond (wave a) is ca. 336 mV more positive than that of iodobenzene. A similar behaviour also arises for the carbon–bromine bond, the reduction potential of which is ca. 486 mV more positive than that of bromobenzene. However, the peak potential of wave d corresponds to that of chlorobenzene.[10] All the waves remain irreversible even at a scan rate of 2000 mV s^{-1}, indicating that the life time of the radical anion is less than 10^{-4} s. The peak currents of the waves a, b, c and d are proportional to the square root of the sweep rate. The transfer coefficient of the reduction of carbon–halogen bond can be calculated from the peak width measurements (Eq. 3) and the values are listed for various carbon–halogen bonds in Table 1.

$$\alpha = \frac{1.856RT}{F}\frac{1}{(E_{P/2} - E_P)} \tag{3}$$

The α values close to or greater than 0.5 are expected for stepwise mechanism. However, this is not an absolute criterion[3] and our systematic study has revealed that the reduction of carbon–iodine bond, for which the α value is less than 0.5, indeed follows a stepwise mechanism.[13]

[†] Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 231991. Copies of the data can 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).

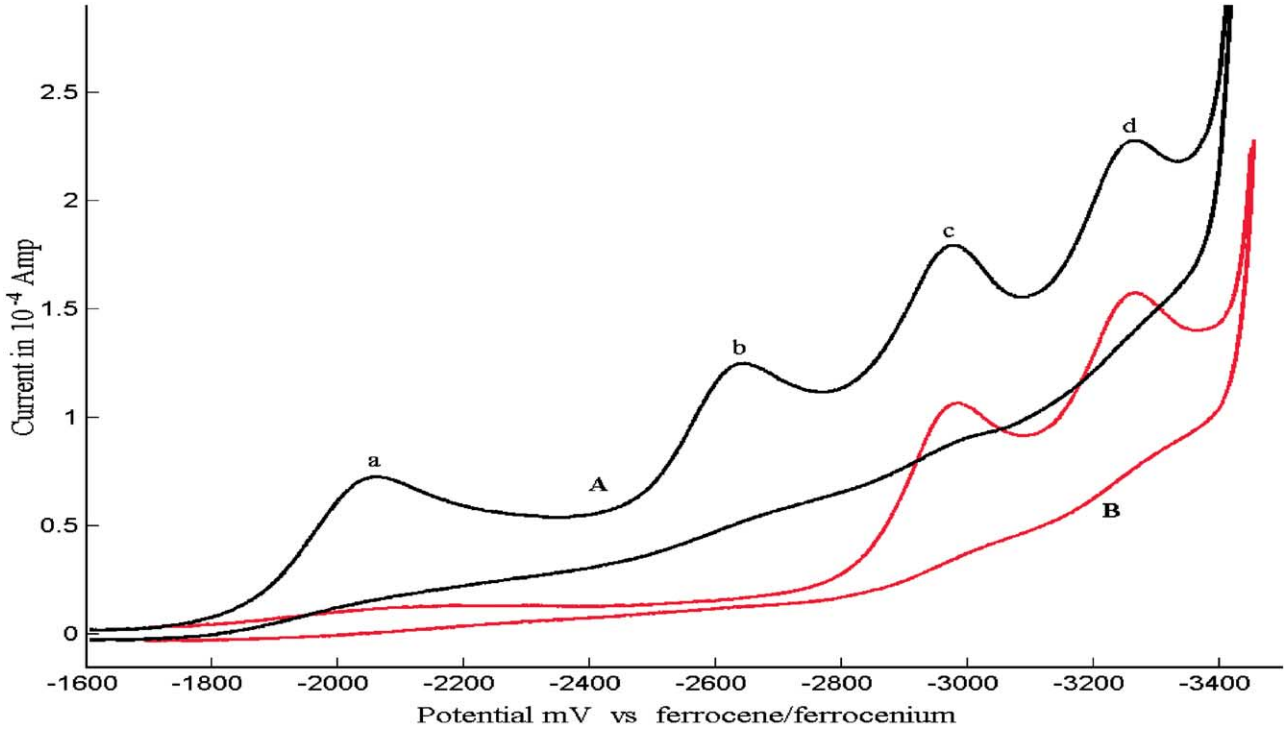

Figure 1. Cyclic voltammograms of (A) 5-bromo-1,3-dichloro-2-iodobenzene and (B) 1,3 dichlorobenzene in DMF/0.1 M nBu$_4$NBr at glassy carbon electrode. Scan rate: 200 mV s^{-1}; temperature: 298 K.

3.1. Convolution analysis

In order to analyze the thermodynamic and kinetic behaviour of the electron transfer, it is essential to deduce the electron transfer rate constant as a function of potential. In this respect, convolution voltammetry is a powerful electrochemical tool since it employs all the data points of the voltammetric wave rather than the peak characteristics alone.[3] The convolution current (I) is related to the actual current (i) through the convolution integral[14] (Eq. 4).

$$I = \frac{1}{\sqrt{\pi}} \int_0^t \frac{i(u)}{(t-u)^{1/2}} \mathrm{d}u \tag{4}$$

The plot between I versus E is sigmoidal in shape with the plateau being reached when the applied potential is sufficiently negative. Under this condition, I reaches its limiting value I_L defined as in Eq. 5

$$I_L = nFAD^{1/2}C_b \tag{5}$$

where D is the diffusion coefficient and C_b, the bulk concentration. Figure 2 shows the convolution potential sweep voltammogram of the reduction of 5-bromo-1,3-dichloro-2-iodobenzene at a scan rate of 200 mV s^{-1}. In the case of closely spaced waves I_L was obtained at a potential at which the minimum occurs in the plot of derivative of the convolution current at the plateau region. The logarithmic analysis of the convolution current in conjunction with the voltammetric current yields the heterogeneous electron transfer rate constant[14] as in Eq. 6.

$$\ln k_{ET} = \ln D^{1/2} - \ln \frac{I_L - I(t)}{i(t)} \tag{6}$$

Figure 3 depicts the variation of $\ln k_{ET}$ with E at various scan rates for the reduction of C–I, C–Br, C–Cl (1) and C–Cl (2) bonds. In the cases of C–I, C–Br and C–Cl (2), the variations are parabolic, obeying the quadratic activation (ΔG^*)–driving force (ΔG^0) relationship (Eq. 7).

$$\Delta G^* = \frac{(\Delta G^0)^2}{16\Delta G_0^*} + \frac{\Delta G^0}{2} + \Delta G_0^* \tag{7}$$

However, in the reduction of C–Cl (1) bond, the variation of $\ln k_{ET}$ with E is linear. In this case the transfer coefficient is constant, conforming to Butler–Volmer kinetics (α obtained from the slope of the plot (Eq. 9) equals that obtained from

Table 1. Electrochemical reduction behaviour of carbon–halogen bonds in 5-bromo-1,3-dichloro-2-iodobenzene

Carbon–halogen bond	Transfer coefficient from peak width measurements	Transfer coefficient from the Eq. 9	E^0_{RX/RX^-} in mV versus SCE	E^0_{RX/RX^-} for halobenzenes in mV versus SCE from Ref. 17
C–I	0.331	—	−1401	−2240 (iodobenzene)
C–Br	0.451	—	−2124	−2440 (bromobenzene)
C–Cl (1)	0.659	0.667	—	—
C–Cl (2)	0.604	—	−2856	−2780 (chlorobenzene)

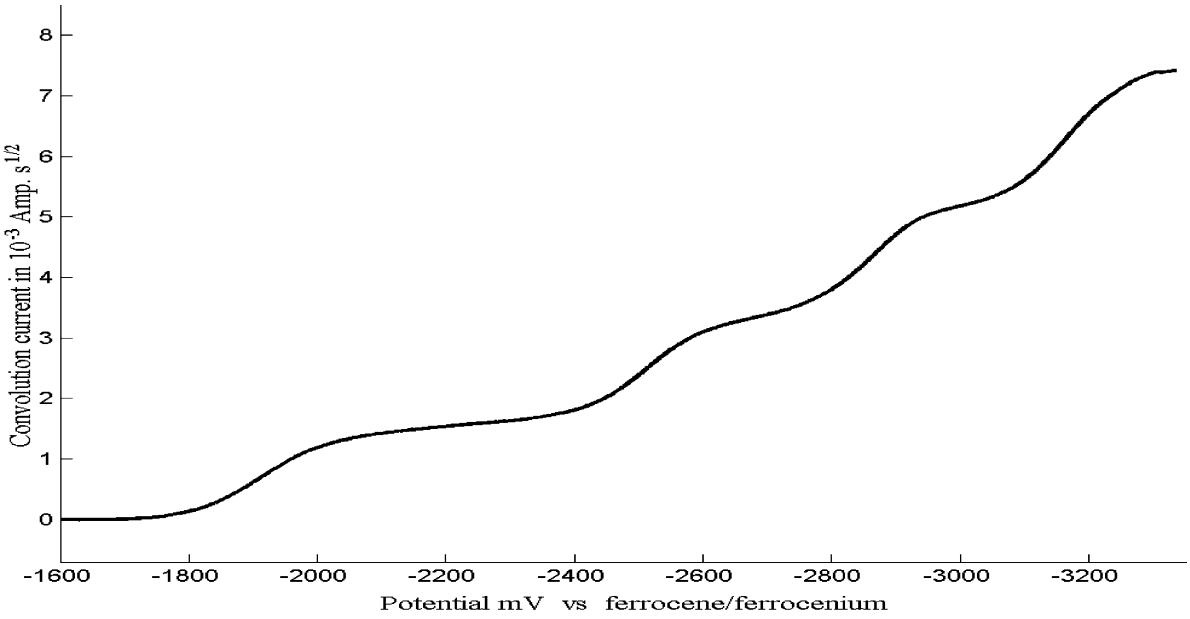

Figure 2. Convolution potential sweep voltammogram of background subtracted voltammetric curve for the reduction of 5-bromo-1,3-dichloro-2-iodobenzene in DMF containing 0.1 M nBu$_4$NBr at the glassy carbon electrode. Scan rate: 200 mV s^{-1}; temperature: 298 K.

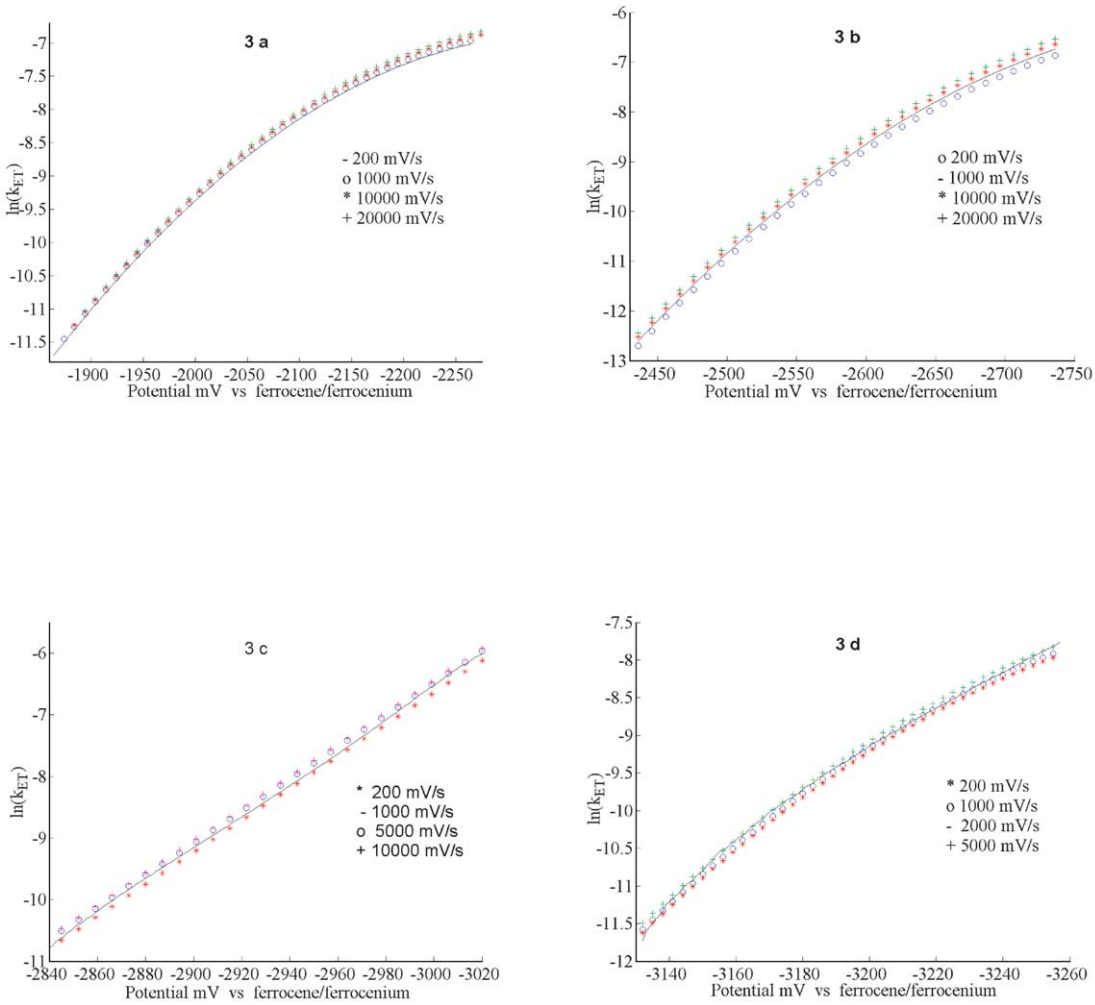

Figure 3. Potential dependence of logarithmic heterogeneous electron transfer rate constant for the reduction of (a) carbon–iodine bond (b) carbon–bromine bond (c) carbon–chlorine (1) bond and d) carbon–chlorine (2) bond at various scan rates.

the peak width measurements (Table 1)). It may be argued that a parabola with a small curvature would also fit the experimental ln k_{ET} versus E plot for the reduction of C–Cl (1) bond. However, this possibility can be excluded, since the ln k_{ET} versus E plot is too linear to be accounted for within the purview of a stepwise mechanism. Furthermore, α is too large to be accounted for by the theory within the framework of a concerted pathway.

3.2. Standard potential

The rate of change of activation energy (ΔG^*) with respect to the driving force (ΔG^0), yields the transfer coefficient as Eq. 8

$$\alpha = \frac{\partial \Delta G^*}{\partial \Delta G^0} = 0.5 + \frac{\Delta G^0}{8\Delta G_0^*} \tag{8}$$

Experimentally α is estimated from the derivative of ln k_{ET} versus E plot using Eq. 9

$$\alpha = -\frac{RT}{F}\frac{\mathrm{d}\ln k_{ET}}{\mathrm{d}E} \tag{9}$$

wherein the symbols R, T and F assume the usual significance. Figure 4 shows the variation of α with E at various scan rates for the reduction of C–I, C–Br and C–Cl (2) bonds. Since the variation of ln k_{ET} with E is parabolic, α varies linearly with E. As implied by Eq. 8, most theoretical models for outer sphere or dissociative electron transfers predict that α should be 0.5 at zero driving force[15,16] ($\Delta G^0 = F(E-E^0) = 0$). From the linear α versus E variation, $E^0_{RX/RX^{\cdot-}}$ of the reduction of respective carbon–halogen bonds can be estimated as the potential at which α becomes 0.5.[4] Table 1 shows $E^0_{RX/RX^{\cdot-}}$ values for the reduction of C–I, C–Br and C–Cl (2) bonds obtained using the above methodology. Table 1 also provides $E^0_{RX/RX^{\cdot-}}$ values for the reduction of iodobenzene, bromobenzene and chlorobenzene for comparison.[10,17] The standard potentials of the reduction of bromobenzene and chlorobenzene were determined through the kinetic analysis of homogeneous redox catalysis of the electrochemical reduction by Saveant et al.[10] and that of the reduction of iodobenzene was obtained in an approximate way using the standard free energy of anion radical cleavage.[17]

The standard potentials of the reduction of C–I and C–Br are 839 and 316 mV more positive than those for the reduction of iodobenzene and bromobenzene, respectively (Table 1). This is consistent with the fact that the energy of the π* orbital of the ring increases with the elimination of each halogen, viz. lowest at the first wave and highest at the fourth wave, which is reflected in the standard potentials of the reduction of respective carbon–halogen bonds. Even though α is substantially lower in the reduction of C–I, the energy of the π* orbital of the ring is low enough to trap the unpaired electron before it

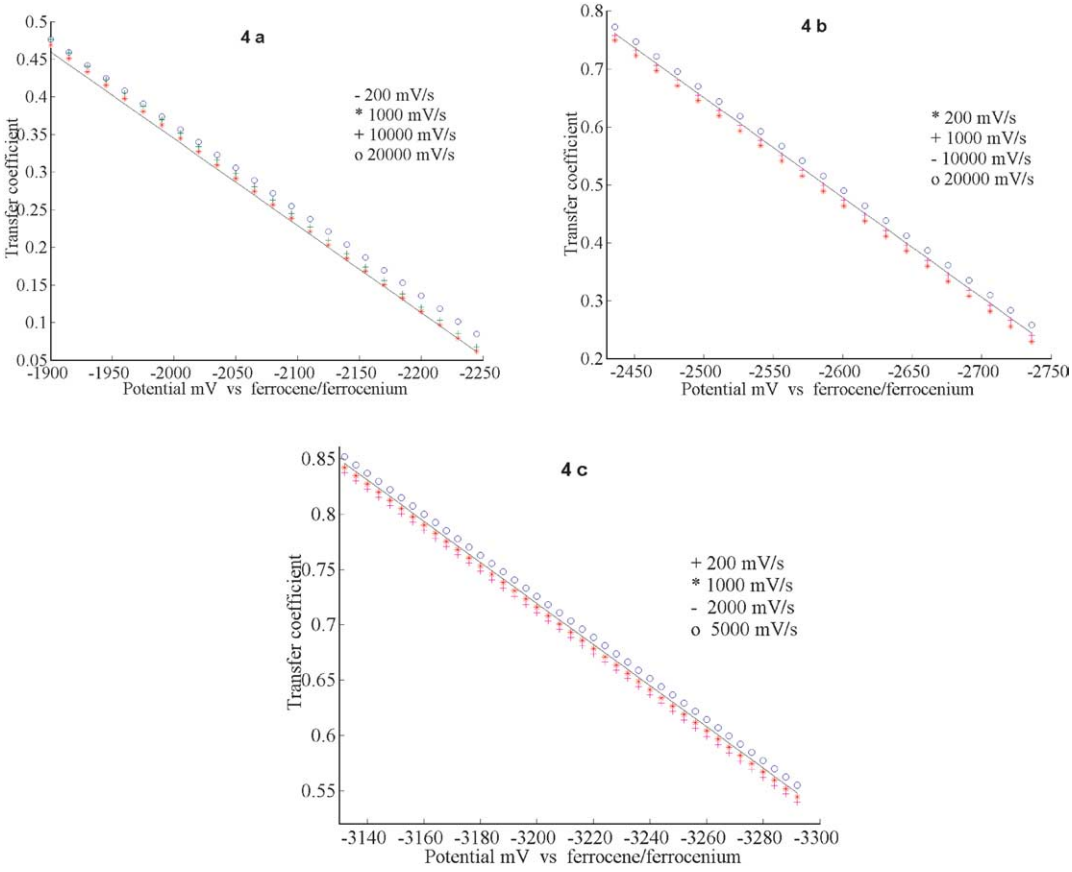

Figure 4. Variation of apparent transfer coefficient with electrode potential at various scan rates for the reduction of (a) carbon–iodine bond (b) carbon–bromine bond and (c) carbon–chlorine (2) bond.

dissociatively reduces the C–I bond in a successive step.[13] A difference between the $E^0_{RX/RX^{\cdot-}}$ for the reduction of C–Cl (2) and that for the reduction of chlorobenzene may be attributed to the different supporting electrolyte (nBu$_4$NI) and working electrode (mercury) employed in the earlier study.[10] Further, in our estimation of standard potentials, double layer corrections have not been applied; however it has been demonstrated[18] that the standard potential calculations carried out incorporating the double layer effects amounts to a maximum difference of only 0.06–0.07 V. This fact is particularly significant, since good experimental data are obtained from the glassy carbon electrode—the double layer properties of which are unknown.

4. Summary

The electrochemical reduction of 5-bromo-1,3-dichloro-2-iodobenzene results in four irreversible voltammetric waves consuming eight electrons in a single cycle. The reduction of C–I, C–Br and C–Cl (2) bonds lead to parabolic $\ln K_{ET}$ versus E plots obeying quadratic activation–driving force relationship. The analysis employing the Marcus theory of outer sphere electron transfer in conjunction with the convolution approach yields standard potentials of the reduction of carbon–halogen bonds in 5-bromo-1,3-dichloro-2-iodobenzene except in one of the carbon–chlorine bonds wherein the reduction follows Butler–Volmer kinetics.

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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.2004.09.020

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Photoinduced proton exchange between molecular switches

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Abstract—The identification of strategies to establish communication between independent molecules is an essential requirement for the development of operating principles to manipulate information at the molecular level. In this context, we have devised a strategy to exchange signals between pairs of complementary molecular switches. It is based on the photoinduced ring closing of a merocyanine to produce a spiropyran with the concomitant release of a proton. The liberated proton is captured by either one of two pyridine derivatives with the formation of their conjugate acids. This transformation induces a significant increase in chemical shift for the resonances of the pyridyl protons and, in one instance, also a pronounced color change. The overall process is fully reversible and the pair of communicating molecules reverts to the original state in the dark. Relying on this mechanism, an optical input is transduced into a detectable spectroscopic output after the controlled intermolecular exchange of protons. A simple analysis of the signal transduction operated by the communicating molecular switches reveals that a binary digit is passed unaltered from the input to the output even although the nature of the signal carrying the information changes at each step. Furthermore, the different nature of input and output implies that the state of the ensemble of molecules can be probed non-destructively at any point in time. The timescales of the switching steps, however, are seriously limited by the slow reaction kinetics. The photoinduced transformation occurs within minutes, but the thermal reaction reverts the switch state only after several hours.

1. Introduction

The identification of experimental strategies to reproduce AND, NOT and OR operations with fluorescent compounds[1] has stimulated the development of chemical systems for digital processing.[2] The operating principles of these molecular logic gates are based on the interplay between chemical, electrical or optical stimulations and absorbance, luminescence or redox outputs. Generally, electron, energy or proton transfer processes and supramolecular events are invoked to transduce the input stimulations into detectable output changes. Relying on these mechanisms and on collections of relatively simple organic molecules in solution, diverse logic operations have been reproduced successfully.[3–24] Some of them can even replicate the signal transduction of complex digital circuits composed of several AND, NOT and OR gates.[25] The chemical counterparts of these circuits, however, are single molecular switches.[26] They combine the functions of multiple logic gates into individual molecular skeletons. This approach to digital processing with molecules is extremely ingenious and fascinating but, at the present stage of development, lacks the modularity of conventional digital circuits. It is not yet possible to connect the molecular equivalents of AND, NOT and OR gates and build multimolecular logic circuits with desired configurations. This severe limitation will be overcome only after the identification of viable strategies to establish communication between independent molecular switches.

In search for efficient protocols to exchange signals between molecular switches, we have identified a mechanism for intermolecular communication based on photon transfer.[17b,d] Our approach is based on the ability of one of the two states of a photochromic switch[27] to absorb the light emitted by a compatible fluorophore. Under these conditions, the optical inputs addressing the photochromic component modulate the emission intensity of the fluorescence component. Relying on these operating principles, we have reproduced the functions of complex logic circuits with multimolecular ensembles of fluorescent and photochromic compounds. In alternative to this mechanism, we have devised a strategy to exchange signals between molecular switches in the form of protons.[17c,f] We have demonstrated that a photoacid can transfer a proton to either a chromogenic or an electroactive base upon illumination. The photoinduced protonation of the base triggers the release of an optical or electrical output. Overall, optical inputs modulate color or electrical current after the chemical communication established between pairs of compatible molecular switches. We have demonstrated that these processes can be exploited to

Keywords: Logic gates; Molecular switches; Photochromism; Proton transfer; Spiropyrans.
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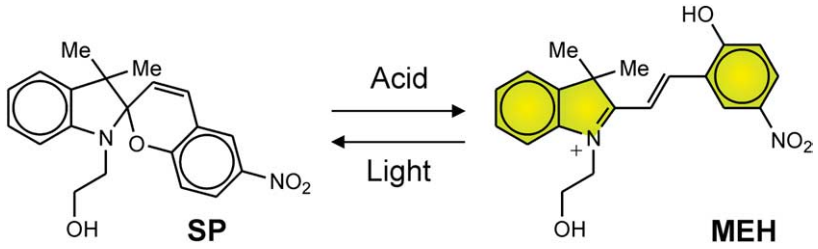

Figure 1. The reversible interconversion of the spiropyran **SP** and the protonated merocyanine **MEH**.

reproduce the memory effects characteristic of sequential logic circuits. In this article, we report a nuclear magnetic resonance (NMR) spectroscopic investigation of the photo-induced exchange of protons between a photochromic spiropyran[28] and either one of two pyridine-based switches. In addition, we assess the timescales of these reversible processes by visible absorption spectroscopy and offer an alternative analysis of the signal transduction associated with these chemical systems.

2. Results and discussion

2.1. Design

Our design is based on the established properties of the spiropyran **SP** (Fig. 1).[17a,g] In acetonitrile, this compound switches to the protonated merocyanine **MEH** upon addition of acid. The process is accompanied by the appearance of a yellow-green color, since **MEH** has an absorption band centered at 401 nm. The irradiation of **MEH** with light of wavelengths falling in its visible absorption band induces the release of a proton and the formation of the colorless **SP**. If a species able to capture the released proton is present in the same solution (Fig. 2) then 'chemical' communication, in the form of proton transfer, is established under illumination. Indeed, the photoacid **MEH** can send a signal to the base after the application of an optical input. The protonated form of the base can then release a detectable output, for example, a color change. Overall, the optical input addressing **MEH** is transduced into an output signal as a result of intermolecular communication established between two complementary molecular switches.

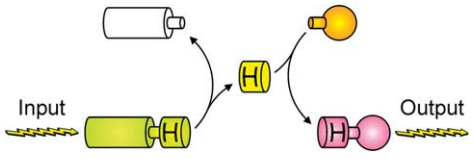

Figure 2. Transduction of an input stimulation into a detectable output after the transfer of a proton from one molecular switch to another.

2.2. Influence of acidification on the ^{1}H NMR spectra of two pyridyl switches

The ^{1}H NMR spectrum (a in Fig. 3) of the azopyridine **AZ** shows five sets of signals between 6.5 and 9.0 ppm. In addition, a singlet for the 6 equivalent methyl protons is observed at 3.12 ppm. Irradiation at a frequency corresponding to this singlet results in nuclear Overhauser enhancements (NOE) of +6 and −2% for the resonances at 6.88 and 7.90 ppm associated with the two pairs of phenylene protons (Fig. S1). The absolute values the NOEs suggest that the protons resonating at 6.88 ppm are closer to the methyl groups than those appearing at 7.90 ppm. Thus, we can assign the doublet at 6.88 ppm to the pair of protons H^6 and that at 7.90 ppm to the pair of protons H^3. The same experiment reveals NOEs of −1 and −4% for the two doublets at 7.67 and 8.66 ppm. These two doublets integrate for one proton each and, one the basis of the NOE values, can be assigned to the pyridyl protons H^4 and H^1, respectively. A correlated spectroscopy (COSY) experiment shows cross peaks between the doublet for H^1 and the set of signals at 7.39 ppm (Fig. S2), which can be assigned to the pyridyl protons H^5. Similarly, cross peaks between the doublet for H^4 and the set of signals at 7.90 ppm indicate that the resonances of the pyridyl proton H^2 overlap those of the phenylene protons H^3.

The addition of increasing amounts of CF_3CO_2H to a CD_3CN solution of **AZ** alters significantly the chemical shifts of the pyridyl protons (b–e in Fig. 3). The largest change is observed for the doublet of the proton H^4, which shifts by ca. +0.41 ppm after the addition of 6 equiv of CF_3CO_2H.[29] These observations suggest that the acidification results in the protonation of the pyridyl nitrogen atom with the formation of the azopyridinium **AZH**. Consistently, the change in chemical shift for the phenylene (H^3 and H^6) and methyl protons is negligible, indicating that the appended dimethylamino group remains in a deprotonated form under these conditions.

The ^{1}H NMR spectrum (a in Fig. 4) of the 4,4′-pyridylpyridinium cation **BI** shows singlets for the two methylene protons H^{12} and for the five phenyl protons H^{11} at 5.74 and 7.44 ppm, respectively. Irradiation at a frequency corresponding to the singlet for the methylene protons results in a NOE of +14% for each of the two doublets at 7.72 and 8.28 ppm (Fig. S3). The equal NOE values for both resonances suggest that the distance between the methylene protons H^{12} and those associated with the two doublets are very similar. Thus, these signals must correspond to the pairs of pyridinium and pyridyl protons in the β-positions relative to the nitrogen atoms. Consistently, no cross peaks between these two doublets can be observed in the COSY (Fig. S4). Comparison of their chemical shifts with those of the 4,4′-bipyridine and 1,1′-dibenzyl-4,4′-bipyridinium protons suggests that the doublet at 7.72 ppm corresponds to the pair of pyridyl protons H^{10} and that at 8.28 ppm can be assigned to the pair of pyridinium protons H^9. The remaining multiplet at 8.81 ppm integrates for four protons and must be associated with the two pairs of

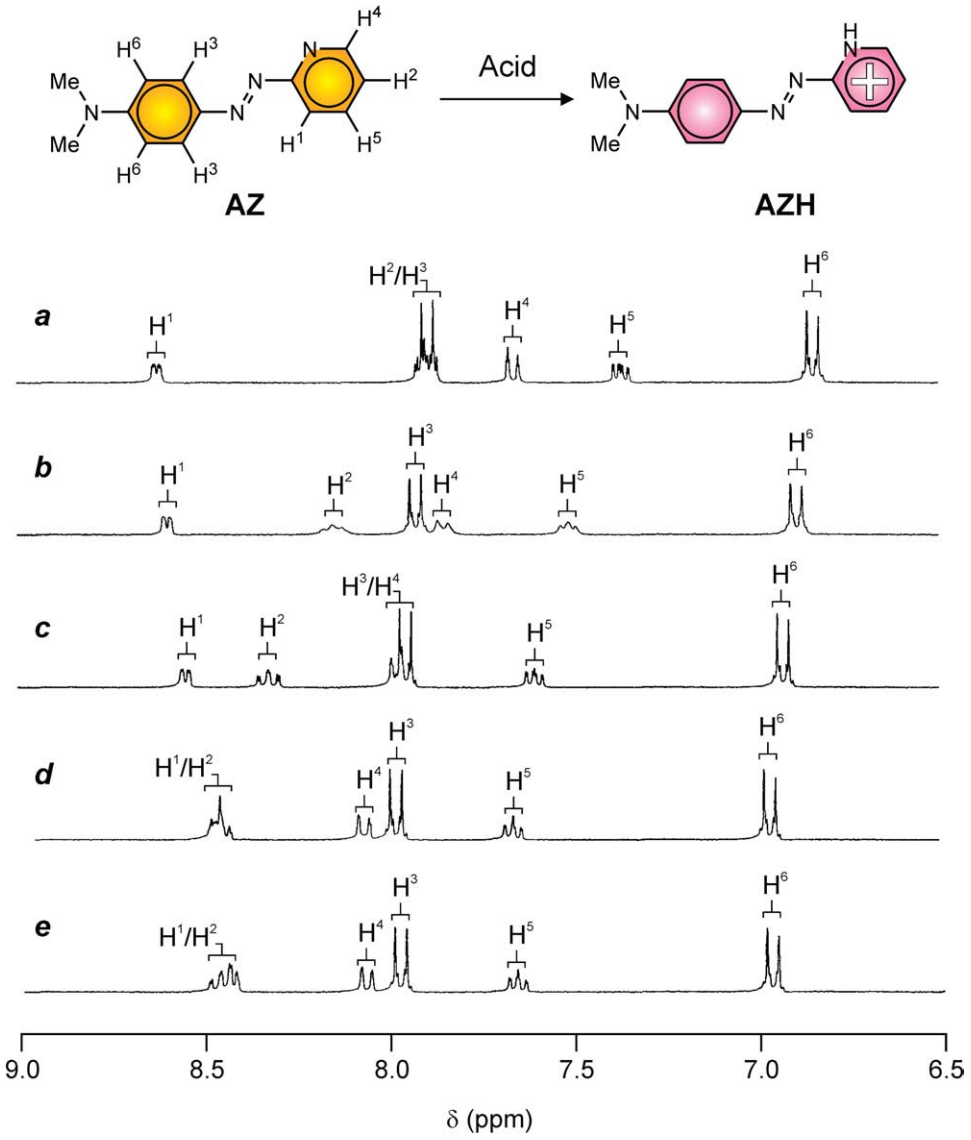

Figure 3. Partial ^{1}H NMR spectra of **AZ** (5×10^{-3} M, CD_3CN, 25 °C) before (a) and after the addition of 1 equiv (b), 2 equiv (c), 4 equiv (d) and 6 equiv (e) of CF_3CO_2H.

4,4′-pyridylpyridinium protons H^7 and H^8. In fact, the same NOE experiment revealed a change of 16% for this set of signals as a result of the close proximity of the pair of protons H^7 to the irradiated methylene protons H^{12}.

The addition of increasing amounts of CF_3CO_2H to a CD_3CN solution of **BI** induces a significant change in the chemical shift for the pair of pyridyl protons H^{10} (b–d in Fig. 4). Their doublet moves from 7.72 to 8.28 ppm after the addition of 10 equiv of CF_3CO_2H. These observations suggest that the acidification results in the protonation of the pyridyl nitrogen atom with the formation of the 4,4′-bipyridinium dication **BIH**.[29]

2.3. Influence of light on the ^{1}H NMR spectra of two pyridyl switches in the presence of a photoacid

The pyridyl nitrogen atoms of **AZ** and **BI** capture protons when exposed to acid (Figs. 3 and 4). Thus, either one of these two bases can be employed in combination with the photoacid **MEH** to implement the operating principles illustrated in Figure 2. Under the influence of an optical input, **MEH** can transfer a proton to the pyridyl nitrogen atom of either **AZ** or **BI**. The formation of the conjugate acids **AZH** and **BIH** produces a detectable output in the form of a large change in chemical shift for the pyridyl protons H^4 and H^{10}, respectively. The concomitant transformation of **MEH** into **SP** can be followed by ^{1}H NMR spectroscopy, since the spectra of **SP** and **MEH** (a and b in Fig. 5) differ dramatically.[17g]

The addition of CF_3CO_2H to an acetonitrile solution of **SP** is followed by the gradual formation of **MEH**, if the solution is maintained in the dark. The process is relatively slow and has a second-order rate constant of only $(54\pm2)\times10^{-5}\ M^{-1}\ s^{-1}$.[17g] For example, ca. 11 d are required for the quantitative conversion of **SP** into **MEH** in the presence of 10 equiv of CF_3CO_2H (a and b in Fig. 5). By contrast, the interconversion of **AZ** and **AZH** in the presence of acid is relatively fast and averaged signals can only be observed in the ^{1}H NMR spectra (b–e in Fig. 3) at ambient temperature. Thus, the ^{1}H NMR spectrum (a in Fig. 6), recorded

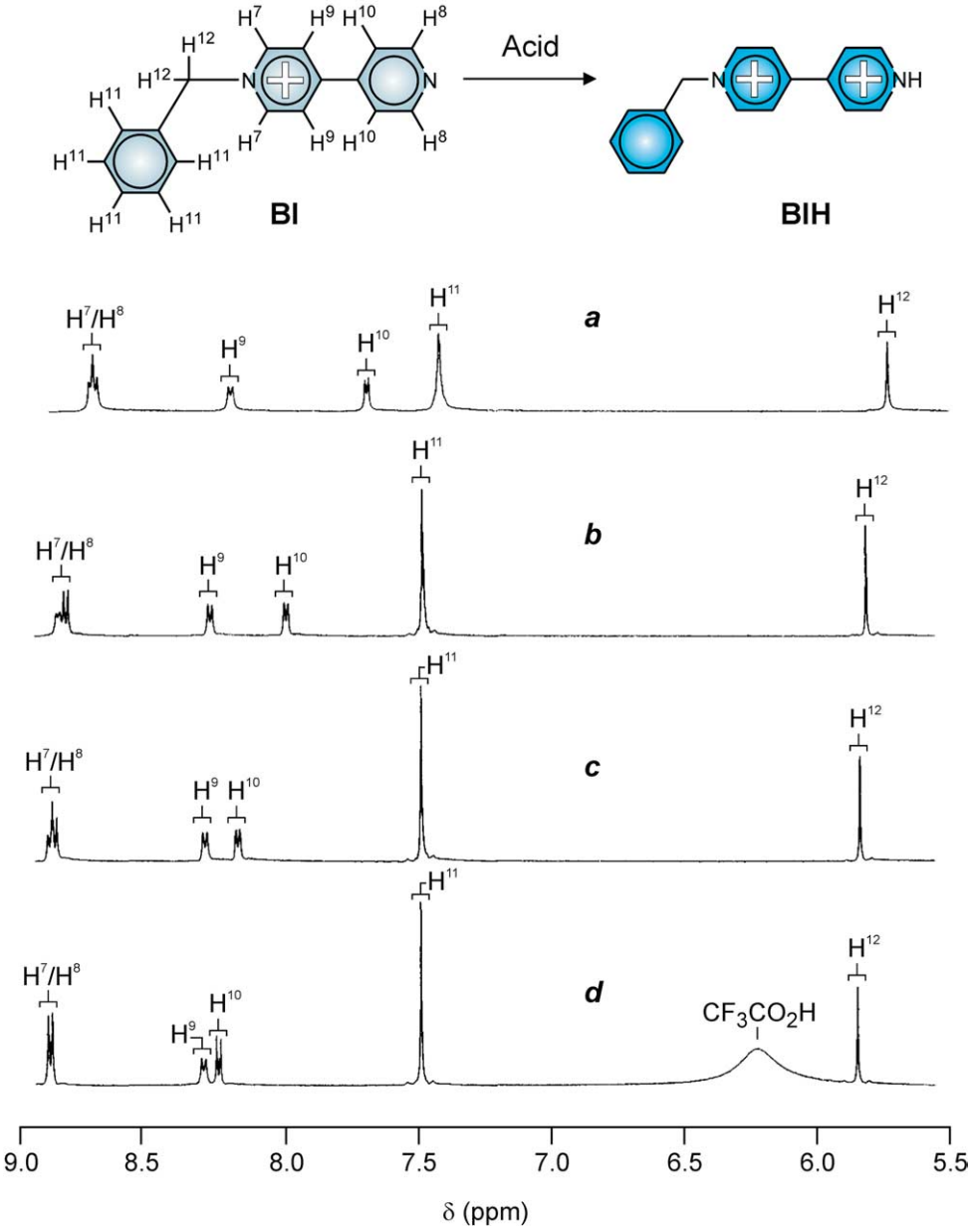

Figure 4. Partial ^{1}H NMR spectra (5×10^{-3} M, CD_3CN, 25 °C) of **BI** before (a) and after the addition of 2 equiv (b), 5 equiv (c) and 10 equiv (d) of CF_3CO_2H.

immediately after mixing equimolar amounts of **SP**, **AZ** and CF_3CO_2H in CD_3CN, reveals averaged resonances for **AZ** and **AZH**, the characteristic signals of **SP** but not those of **MEH**. In particular, a comparison with the ^{1}H NMR spectrum of **AZ** (a in Fig. 3) shows a shift of ca. +0.22 ppm for the doublet associated with pyridyl proton H^4. This chemical shift change corresponds to a ratio between **AZ** and **AZH** of ca. 57:43.[30] Upon storage in the dark, **SP** switches gradually to **MEH**, reducing the concentration of acid available in solution. As a result, **AZH** is converted into **AZ** and the chemical shift of the pyridyl proton H^4 decreases. A stationary state is reached in ca. 4 d. The ^{1}H NMR spectrum (b in Fig. 6), recorded at this point, shows the characteristic resonances of **SP** and **MEH** and a chemical shift of 7.79 ppm for the pyridyl proton H^4. This value corresponds to a ratio between **AZ** and **AZH** of ca. 76:24. Upon exposure of the solution to ambient light, **MEH** switches to **SP** releasing a proton. This transformation induces the protonation of **AZ** and the formation of **AZH**. Consistently, the chemical shift of the pyridyl proton H^4 increases to a stationary value of 7.87 ppm after ca. 8 h. This value corresponds to a ratio between **AZ** and **AZH** of ca. 61:39.

The reversible interconversion of **BI** and **BIH** in the presence of acid is also relatively fast. As a result, averaged signals are observed in the ^{1}H NMR spectra (b–d in Fig. 4) at ambient temperature. Thus, the ^{1}H NMR spectrum (a in Fig. 7), recorded immediately after mixing equimolar amounts of **SP**, **BI** and CF_3CO_2H, reveals a chemical shift of 8.02 ppm for the pyridyl protons H^{10}. This value is 0.30 ppm higher than that of the same protons in the ^{1}H NMR spectrum of **BI** (a in Fig. 4). This significant change corresponds to a ratio between **BI** and **BIH** of ca. 53:47.[30] In addition to the averaged signals of **BI** and **BIH**, the characteristic resonances of **SP** can also be observed in the

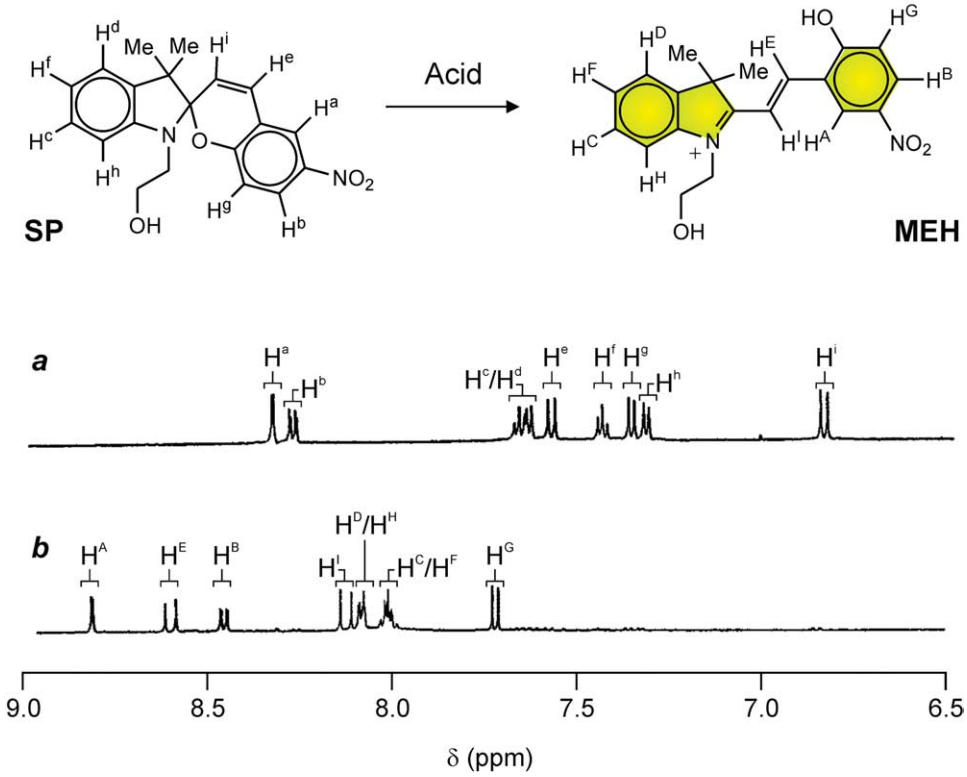

Figure 5. Partial ^{1}H NMR spectra (5×10^{-3} M, CD_3CN, 25 °C) of **SP** before (a) and after (b) the addition of CF_3CO_2H (10 equiv) and storage in the dark for 11 d.

initial ^{1}H NMR spectrum (a in Fig. 7). Upon storage in the dark, **SP** switches gradually to **MEH** reducing the concentration of acid available in solution and inducing the transformation of **BIH** into **BI**. A stationary state is reached after ca. 6 d. Under these conditions, the resonances of both **SP** and **MEH** are clearly visible in the ^{1}H NMR spectrum (b in Fig. 7). Furthermore, the chemical shift for the pyridyl protons H^{10} is now 7.82 ppm. This value corresponds to a ratio between **BI** and **BIH** of ca. 84:16. Upon exposure of the solution to ambient light, **MEH** switches to **SP** releasing a proton, which induces the transformation of **BI** back to **BIH** and a decrease in the chemical shift of the pyridyl protons H^{10}. A stationary state is reached after ca. 2 h. The ^{1}H NMR spectrum recorded at this point shows a chemical shift of 7.98 ppm for the probe protons H^{10}, indicating a ratio between **BI** and **BIH** of ca. 60:40.

2.4. Influence of light on the visible absorption spectra of two pyridyl switches in the presence of a photoacid

The visible absorption spectrum (a in Fig. 8) of **AZ** shows a band centered at 423 nm in acetonitrile.[17c] This band fades upon addition of increasing amounts of CF_3CO_2H.

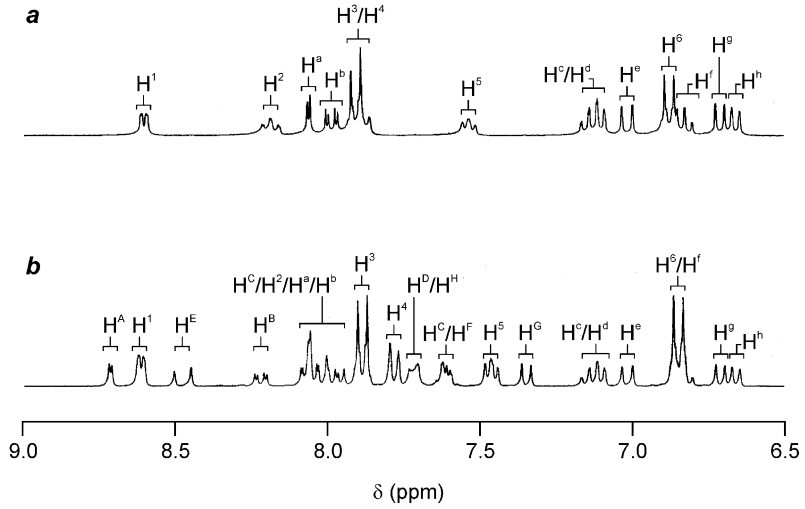

Figure 6. Partial ^{1}H NMR spectra (1.5×10^{-2} M, CD_3CN, 25 °C) recorded immediately after mixing equimolar amounts of **SP**, **AZ** and CF_3CO_2H (a) and after the subsequent storage in the dark for 4 d (b).

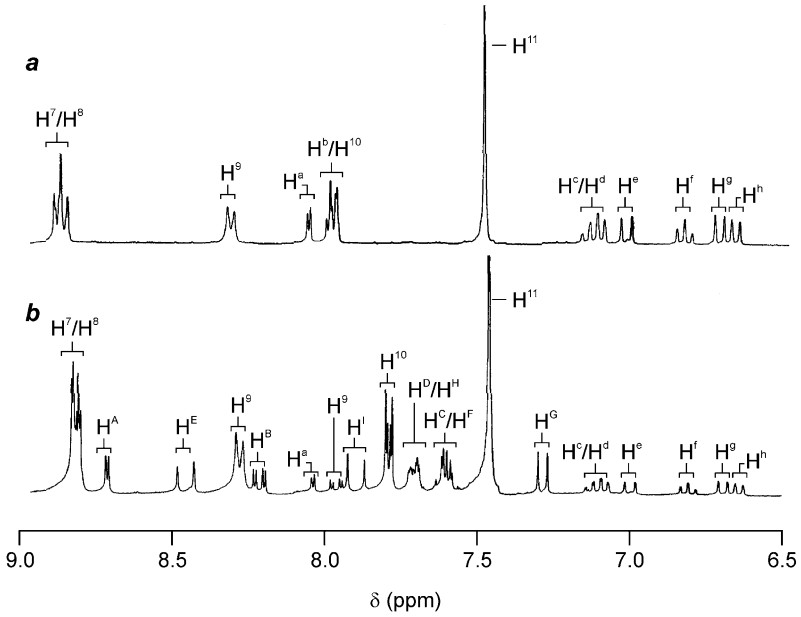

Figure 7. Partial ^{1}H NMR spectra (1.5×10^{-2} M, CD_3CN, 25 °C) recorded immediately after mixing equimolar solution of **SP**, **BI** and CF_3CO_2H (a) and after the subsequent storage in the dark for 6 d (b).

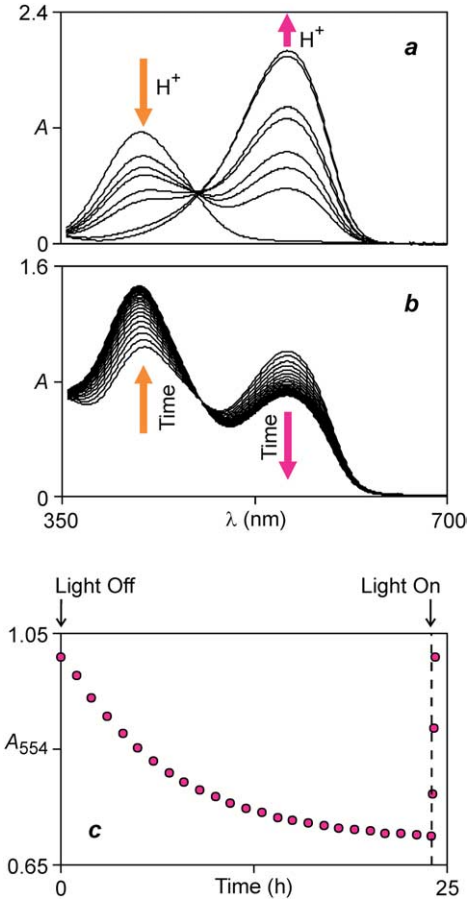

Figure 8. (a) Absorption spectra recorded before and after the addition of increasing amounts of CF_3CO_2H (0.5–13 equiv) to **AZ** (1×10^{-4} M, MeCN, 25 °C). (b) Evolution of the absorption spectrum from the photostationary state to the thermal equilibrium of a solution prepared by mixing equimolar amounts of **SP**, **AZ** and CF_3CO_2H (1×10^{-4} M, MeCN, 25 °C). (c) Time dependence of the absorbance at 554 nm during storage in the dark and the subsequent visible irradiation.

Concomitantly, a new band corresponding to **AZH** grows at 554 nm. As a result, the transformation of **AZ** into **AZH** is accompanied by a change in color from orange to purple. In the presence of **SP** and **MEH**, the interconversion of **AZ** and **AZH** can be followed by monitoring the absorbance of either one of these two visible bands. Indeed, the evolution of the absorption spectrum (b in Fig. 8) from the photostationary state to the thermal equilibrium of a solution prepared by mixing equimolar amounts of **SP**, **AZ** and CF_3CO_2H shows an absorbance increase at 423 nm with a concomitant absorbance decrease at 554 nm. These changes indicate that **AZH** switches gradually to **AZ** in the dark and are a consequence of the thermal interconversion of **SP** into **MEH**. The time dependence (c in Fig. 8) of the absorbance at 554 nm reveals the transition from the photostationary state to the thermal equilibrium to require ca. 24 h. This absorbance decay corresponds to an increase in the ratio between **AZ** and **AZH** from ca. 57:43 to 70:30.[31] The photostationary absorbance value is fully restored after visible irradiation for ca. 15 min (c in Fig. 8). The photoinduced absorbance enhancement indicates that **AZ** switches back to **AZH**, as the photoacid **MEH** reverts to **SP** releasing a proton.

The base **BI** and its conjugate acid **BIH** do not absorb in the visible region. In the presence of **SP**, however, their interconversion can be monitored by probing the absorbance for the characteristic visible band of **MEH**. Indeed, the evolution of the absorption spectrum (a in Fig. 9) from the photostationary state to the thermal equilibrium of a solution prepared by mixing equimolar amounts of **SP**, **BI** and CF_3CO_2H shows an absorbance increase at 401 nm. Under these conditions, **SP** switches gradually to **MEH** and encourages the concomitant transformation of **BIH** into **BI**. The process requires ca. 24 h to reach thermal equilibrium (b in Fig. 9). Under visible irradiation, however, **MEH** reverts to **SP** releasing its proton and promoting the reconversion of **BI** into **BIH**. The photostationary state is

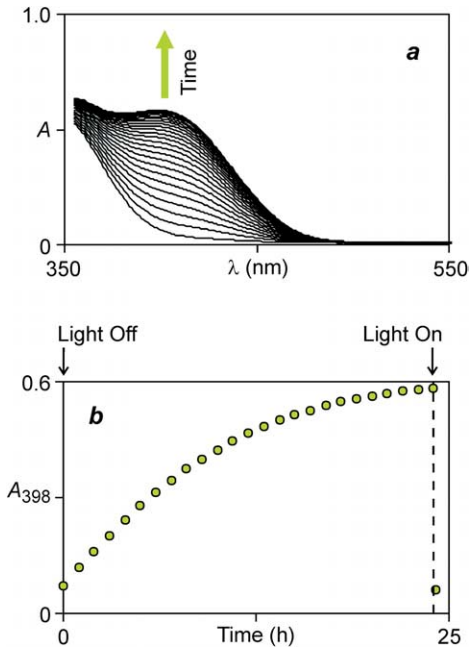

Figure 9. (a) Evolution of the absorption spectrum from the photostationary state to the thermal equilibrium of a solution prepared by mixing equimolar amounts of **SP**, **BI** and CF_3CO_2H (1×10^{-4} M, MeCN, 25 °C). (b) Time dependence of the absorbance at 401 nm during storage in the dark and the subsequent visible irradiation.

restored in ca. 15 min (b in Fig. 9). The ratio between **SP** and **MEH** at the photostationary state and at the thermal equilibrium can be estimated to be 96:4 and 64:36.[32]

2.5. Analysis of the signal transduction operated by the two pairs of communicating switches

In the presence of CF_3CO_2H, **SP** switches to **MEH** (Fig. 1) consuming some of the H^+ available in solution. Upon visible irradiation, **MEH** reverts to **SP** releasing back the captured H^+. Thus, the concentration of H^+ (chemical output) switches to a high value as the light (optical input) is turned on (a in Fig. 10). It returns to a low value when the light is turned off. Under a positive logic convention, we can assign a binary 0 to the off and low states of input (**I**) and output (**O**) and a binary 1 to their on and high states. A glance at the corresponding truth table (c in Fig. 10) reveals that this particular molecular switch transfers unaltered the binary value encoded in the optical input to the chemical output. It is important to stress, however, that the timescales of the switching steps are seriously limited by the relatively slow reaction kinetics. In particular, the thermal transformation of **SP** into **MEH** has a small second-order rate constant[17g] and requires several hours to occur. Similarly,

a

Light	H^+
Off	Low
On	High

b

H^+	δ
Low	Low
High	High

c

I	*O*
0	*0*
1	*1*

Figure 10. Signal transductions operated by **SP/MEH** (a) and either **AZ/AZH** or **BI/BIH** (b) and equivalent truth table (c).

the photoinduced interconversion of **MEH** into **SP** has a modest quantum yield and occurs within several minutes.

The concentration of H^+ controls the interconversion of **AZ** and **BI** into the corresponding conjugate acids (Figs. 3 and 4). Both transformations induce significant changes in the chemical shifts (δ) of probe protons. Thus, the chemical shift (spectroscopic output) switches to a high value when the concentration of H^+ (chemical input) is high (b in Fig. 10). It reverts to a low value when the concentration of H^+ is low. Once more, we can assign a binary 0 to the low values of input (**I**) and output (**O**) and a binary 1 to their high values, under a positive logic convention. Again, the corresponding truth table (c in Fig. 10) shows that a binary digit is passed unaltered from the chemical input to the spectroscopic output.[33]

When the molecular switch **SP/MEH** is operated together with either **AZ/AZH** or **BI/BIH**, the concentration of H^+ becomes a common signal to both systems. Indeed, the binary digit encoded in the optical input addressing **SP/MEH** (a in Fig. 10) is communicated chemically to either **AZ/AZH** or **BI/BIH** and passed to the final spectroscopic output (b in Fig. 10). Thus, a binary value travels unaltered through a sequence of two communicating molecular switches, while the nature of the signal carrying the information is converted from light, to H^+ and finally to chemical shift.

It is worth stressing that the communication between **SP/MEH** and **AZ/AZH** can also be monitored by following the absorbance changes at 554 nm. At this particular wavelength, neither **SP** nor **MEH** absorb. Thus, the state of the photochromic component **SP/MEH** can be probed optically, but non-destructively, through its chromogenic partner **AZ/AZH**. In fact, the need to read the state of a photochromic switch without altering it has been one of the major limitations in the development of optical memories based on this class of compounds.[27] It follows that our protocol for signal transduction might also contribute to the identification of viable solutions to this challenging problem.

3. Conclusions

We have identified a mechanism to establish communication between pairs of molecular switches. It is based on the reversible interconversion of a spiropyran and a protonated merocyanine in the presence of acid and under the influence of visible light. In the dark, the spiropyran switches to the merocyanine consuming H^+. Under illumination, the process is fully reversed with the liberation of H^+. The capture and release of H^+ can be exploited to regulate the interconversion of either one of two pyridyl switches. Their protonation produces the corresponding conjugate acids and induces a significant enhancement in the chemical shift of the pyridyl protons. Thus, an optical input can modulate a chemical shift output on the basis of intermolecular proton exchange. Furthermore, these processes can be monitored by visible absorption spectroscopy, following the absorbance changes associated with the bands of the protonated form of one of the two communicating switches. These analyses indicate that the transition from

the photostationary state to the thermal equilibrium requires approximately one day in acetonitrile at submillimolar concentrations. The opposite and photoinduced transformation, instead, is considerably faster and the photostationary state is restored within minutes. The timescales of both processes are certainly not compatible with any practical computing scheme. These results, however, demonstrate that relatively simple reactions can be coupled, with a judicious choice of compatible molecular components, to transduce incoming optical inputs in well-defined spectroscopic outputs. Methods to reduce the switching times by several orders of magnitude now need to be identified. Under these conditions, our strategy might be employed to exchange effectively signals between collections of molecules operating in solution.

4. Experimental procedures

4.1. General methods

Chemicals were purchased from commercial sources. Acetonitrile (MeCN) was distilled over calcium hydride (CaH_2). The spiropyran **SP** and the 4,4′-pyridylpyridinum cation **BI** were prepared according to literature procedures.[17f,g] ^{1}H NMR spectra were recorded with a Bruker Avance 400 (400 MHz) using quartz tubes (diameter = 5 mm). Absorption spectra were recorded with a Varian Cary 100 Bio using quartz cells (path length = 5 mm). The cells were irradiated with a Cole-Parmer Fiber Optic Illuminator 9745-00 coupled to a band pass filter (360–650 nm).

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Supplementary data

Difference nuclear Overhauser enhancement (NOE) and ^{1}H–^{1}H correlated spectroscopy (COSY) spectra of **AZ** and **BI**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.09.065

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29. Analyses of the chemical shift changes with the concentration of CF_3CO_2H indicate the limiting values ($\Delta\delta_L$) to be 0.51 and 0.65 ppm for **AZ** and **BI**, respectively.
30. The **AZ/AZH** and **BI/BIH** ratios were determined from the molar fractions (χ) of **AZH** and **BIH**, respectively. The χ values are equal to the ratios between the observed ($\Delta\delta_O$) and limiting ($\Delta\delta_L$) chemical shift changes of the probe protons. The values of $\Delta\delta_L$ are quoted in Ref. 29.
31. The ratios were calculated from the absorbance values at 554 nm, considering molar extinction coefficients for **AZ** and **AZH** of ca. 600 and 46,000 $M^{-1}\,cm^{-1}$, respectively, at this wavelength. The molar extinction coefficient of **AZH** was determined by non-linear curve fitting of the absorbance profile at 554 nm (a in Fig. 8) of a solution of AZ treated with increasing amounts of CF_3CO_2H.
32. The ratios were calculated from the absorbance values at 401 nm, considering molar extinction coefficients for **SP** and **MEH** of ca. 200 and 32,000 $M^{-1}\,cm^{-1}$, respectively, at this wavelength (Ref. 17g).
33. The spectroscopic output (chemical shift) chosen to illustrate the signal transduction mechanism requires a rather cumbersome detection protocol (^1H NMR spectroscopy). However, these operating principles are not limited to chemical shift measurements and can be easily extended to more practical electrical or optical detection methods. In fact, the signal transduction associated with the combination of **SP/MEH** and **AZ/AZH** results in an optical output, which can be monitored with simple transmission absorption measurements.

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Stepwise and one-pot cross-coupling–heteroannulation approaches toward 2-substituted C5-, C6-, and C7-nitroindoles☆

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Abstract—A general and efficient synthesis of 2-substituted C5-, C6-, and C7-nitroindoles has been established. Starting from commercially available 2-amino nitrophenols, C5-, C6-, and C7-nitroindoles were synthesized via the stepwise Pd-catalyzed cross-coupling of nitro 2-trifloxyanilides with 1-alkynes followed by the *t*-BuOK-mediated heteroannulation. A Pd-catalyzed one-pot coupling–heteroannulation procedure was carried out by using nitro 2-trifluoroacetamidoaryl triflates.

1. Introduction

Nitroindoles are known to be biologically active[1] and serve as the useful precursors to a variety of nitrogen-substituted indole derivatives, which exhibit diverse regulatory activities on bio-macromolecules. Selected examples are given in Figure 1, including SDZ-216525 (a 5-HT_7 selective agonist),[2] Delavirdine (a non-nucleoside reverse

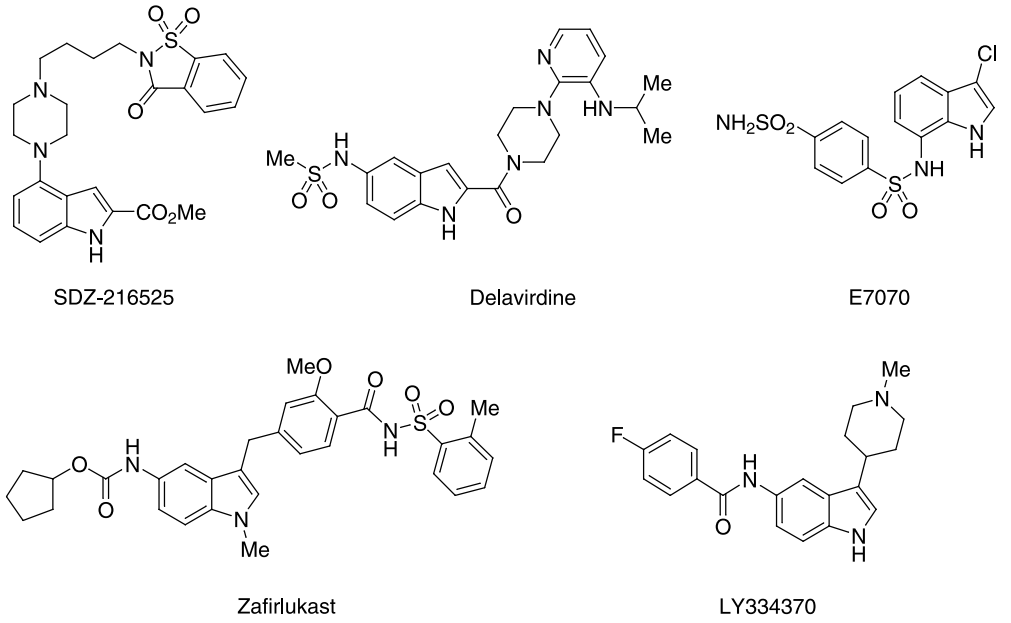

Figure 1. Selected bioactive indoles possessing a nitrogen-based substituent.

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Keywords: Cross-coupling; Heteroannulation; Nitroindoles; Aryl triflates; 2-Aminophenols.
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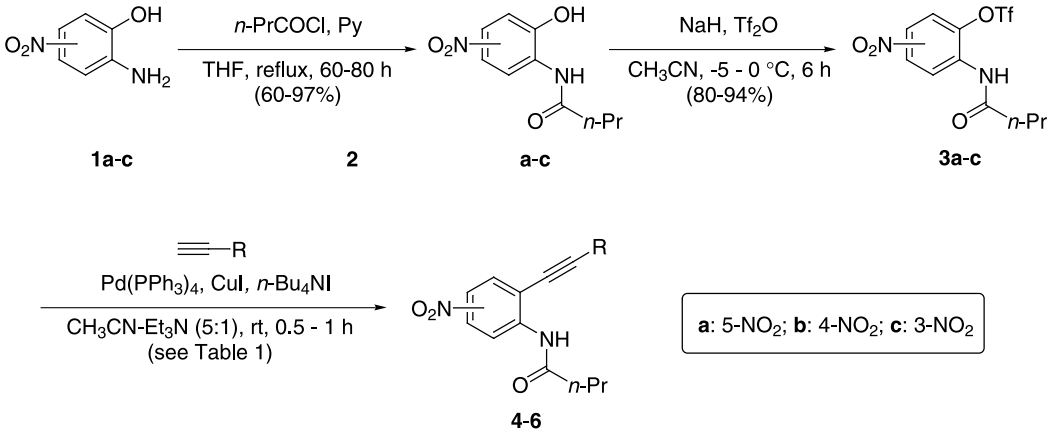


Scheme 1. Synthesis of 2-alkynylanilines **4**–**6**.

transcriptase inhibitor approved for HIV therapy),[3] Zafirlukast (an LTD_4 antagonist),[4] LY334370 (a selective 5-HT_{1F} receptor agonist),[5] and E7070 (an anticancer agent thought to affect the progression of the cell cycle in the G1 phase with inhibition of expression of cyclin E and phosphorylation of cdk2).[6] Direct nitration of indoles is a straightforward method for synthesis of nitroindoles,[1,7] but it suffers from non-selectivity in some cases.[1] A number of methodologies[8] have been used to form nitroindoles. These cover the Fischer indole synthesis,[9] the Bergman indole synthesis,[10] and various nucleophilic/electrophilic cyclization approaches by using the nitro-containing substrates.[11] However, low yields and/or formation of mixtures of nitroindoles were reported.[9e,f,11c–e]

The metal-catalyzed cross-coupling reactions have emerged as the most powerful methods for carbon–carbon bond formation in recent years and they have been used for heterocycle synthesis.[12] Among the metal-catalyzed indole syntheses,[8] the cross-coupling and heteroannulation procedures enjoy wide applications. 2-Haloanilines and derivatives are the common substrates, which are transformed into 2-alkynylanilines via Pd(0)–Cu(I)-catalyzed Sonogashira cross-coupling with 1-alkynes[13] followed by metal-catalyzed,[13–19] or base-[20–22] and iodonium(I)-mediated[23] heteroannulation. Alternatively, 2-alkynylanilines undergo aminopalladation–reductive elimination with aryl/vinyl iodides and triflates to form highly functionalized indoles.[24,25] Moreover, 2-iodoanilines react with internal alkynes via Pd-catalyzed annulation to afford 2,3-disubstituted indoles (Larock indole synthesis).[14,26] There are two reports on synthesis of C5- and C7-nitroindoles through the cross-coupling and heteroannulation procedures.[17f,20h,k] In both cases, 2-iodo nitroanilines were used as the starting materials, which were synthesized from nitroanilines by using bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) as the iodinating agent.[17f] The nitro-containing 2-alkynylanilines cyclized to nitroindoles via CuI- and *t*-BuOK-mediated heteroannulation, respectively.[17f,20h,k] We report here on a general and efficient synthesis of 2-substituted C5-, C6-, and C7-nitroindoles starting from commercially available 2-amino nitrophenols.[20j]

2. Results and discussion

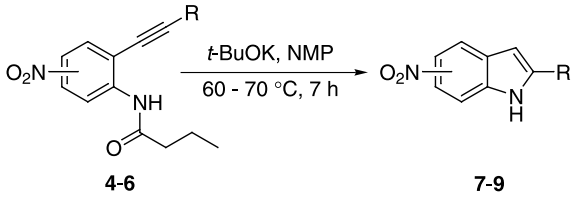
2-Iodoanilines could be prepared from 4-substituted anilines by using IPy_2BF_4 as the iodinating agent.[17f] However, the C4 substituent is necessary for directing the iodination at C2.[27] Alternatively, the oxygen-substituted 2-iodoanilines could be prepared from protected aminophenols by directed *ortho*-lithiation followed by trapping with I_2.[20g] We used the nitro 2-trifloxyanilides **3** to substitute 2-iodoanilines in the metal-catalyzed indole synthesis. Before our work,[20i,j] a 2-trifloxyanilide was used for the Pd-catalyzed cross-coupling with alkynylstannanes to provide 2-alkynylanilides.[15g] The Pd(0)–Cu(I)-catalyzed Sonogashira cross-coupling of 2-trifloxyanilides with 1-alkynes was virtually unknown. We found a remarkable additive effect on the cross-coupling of 2-trifloxyanilides with 1-alkynes and high yields of 2-alkynylanilides were obtained in the presence of 1.5 equiv of *n*-Bu_4NI.[20i] As shown in Scheme 1, three nitro 2-trifloxyanilides **3a**–**c** were readily prepared from 2-amino-5-nitrophenol (**1a**), 2-amino-4-nitrophenol (**1b**), and 2-amino-3-nitrophenol (**1c**) via selective N-acylation[28] followed by formation of triflates from **2a**–**c**. The butyryl anilides were selected for their relatively good solubility in common organic solvents compared with the acetamides. Cross-coupling of **3a**–**c** with 1-alkynes took place at room temperature in CH_3CN–Et_3N (5:1) with 1.5 equiv of *n*-Bu_4NI as the additive to give the 2-alkynyl nitroanilides **4**–**6** in excellent yields. The results are summarized in Table 1.

Table 1. Cross-coupling of aryl triflates **3** with 1-alkynes[a]

Entry	Aryl triflate	R	Yield (%)
1	**3a**: 5-NO_2	Ph	**4a**: 95
2	**3a**: 5-NO_2	*n*-Pr	**4b**: 95
3	**3b**: 4-NO_2	Ph	**5a**: 96
4	**3b**: 4-NO_2	*n*-Pr	**5b**: 90
5	**3c**: 3-NO_2	Ph	**6a**: 90
6	**3c**: 3-NO_2	*n*-Pr	**6b**: 91

[a] Carried out with 10 mol% $Pd(PPh_3)_4$, 30 mol% CuI, and 150 mol% *n*-Bu_4NI.

Table 2. Synthesis of nitroindoles **7–9** via *t*-BuOK-mediated heteroannulation[a]



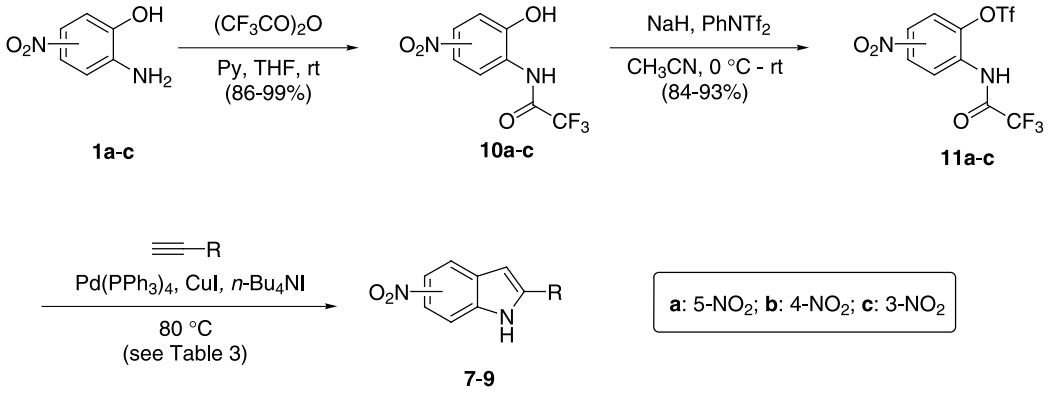
4-6 **7-9**

Entry	Nitroindoles	R	Yield (%)
1	5-NO_2	Ph	**7a**: 85
2	5-NO_2	*n*-Pr	**7b**: 84
3	6-NO_2	Ph	**8a**: 84
4	6-NO_2	*n*-Pr	**8b**: 86
5	7-NO_2	Ph	**9a**: 76
6	7-NO_2	*n*-Pr	**9b**: 72

[a] 1.2 equiv of *t*-BuOK were used.

Heteroannulation of 2-alkynyl nitroanilides **4–6** was carried out in NMP with 1.2 equiv of *t*-BuOK at 60–70 °C for 7 h to furnish 2-substituted C5-, C6-, and C7-nitroindoles **7–9** in 72–86% yields (Table 2). In Knochel's nitroindole synthesis, a unprotected 2-alkynylaniline was used.[20h] We found that the *N*-acyl group, the position of nitro group, and the nature of R in **4–6** did not affect the efficiency of the base-mediated heteroannulation.[29] Nitroindoles **7–9** are all crystalline compounds; the C6-nitroindole **8b** was analyzed by X-ray crystallography, showing a flat nitroindole skeleton.[30]

Next, we examined a one-pot cross-coupling and heteroannulation procedure toward nitroindoles **7–9** as shown in Scheme 2. A Cu(I)-catalyzed one-pot synthesis of indoles from 2-iodotrifluoroacetanilide and 1-alkynes was recently reported.[17h] In our nitroindole synthesis, the trifluoroacetamidoaryl triflates **11a–c** were prepared in good yields by selective N-acylation of **1a–c** followed by triflate formation from **10a–c** and $PhNTf_2$. The one-pot cross-coupling and heteroannulation of **10a–c** with various 1-alkynes was investigated and the results are given in Table 3. We observed solvent effect on the one-pot reactions and used three solvent combinations, A (DMF–Et_3N=5:1), B (CH_3CN–Et_3N=5:1), and C (DMF–TMG=5:1). For formation of C5- and C6-nitroindoles **7** and **8** (entries 1–10, Table 3), solvents A and B could be used and the product yields are comparable to those given in Table 2. However, the one-pot reaction times were significantly prolonged than the stepwise protocol. Under the one-pot reaction conditions, some functional groups such as OH, CN, and Cl remained intact and protection of OH was not required. Formation of C7-nitroindoles **9** by the one-pot procedure was somewhat problematic. After screening on catalyst precursor, solvent, and base, three C7-nitroindoles **9a–c** could be obtained albeit in lower yields (entries 11–13,



Scheme 2. One-pot synthesis of nitroindoles **7–9**.

Table 3. One-pot synthesis of nitroindoles via Pd-catalyzed coupling and heteroannulation[a]

Entry	Nitroindoles	R	*t* (h)	Yield (%)
1	5-NO_2	Ph	41	**7a**: 85
2	5-NO_2	*n*-Pr	24	**7b**: 90
3[b]	5-NO_2	$(CH_2)_2OH$	42	**7c**: 68
4	5-NO_2	$(CH_2)_3CN$	25	**7d**: 75
5[b]	5-NO_2	$(CH_2)_3Cl$	24	**7e**: 45
6[b]	6-NO_2	Ph	17	**8a**: 88
7	6-NO_2	*n*-Pr	21	**8b**: 84
8	6-NO_2	$(CH_2)_2OH$	19	**8c**: 69
9	6-NO_2	$(CH_2)_3CN$	8	**8d**: 73
10[b]	6-NO_2	$(CH_2)_3Cl$	20	**8e**: 66
11[c–e]	7-NO_2	Ph	3.5	**9a**: 52
12[c,d]	7-NO_2	*n*-Pr	7.5	**9b**: 39
13[d]	7-NO_2	$(CH_2)_2OH$	12	**9c**: 48

[a] Carried out in solvent A (DMF–Et_3N=5:1) with 10 mol% $Pd(PPh_3)_4$, 30 mol% CuI, and 150 mol% *n*-Bu_4NI.
[b] Carried out in solvent B (CH_3CN–Et_3N=5:1).
[c] Carried out in solvent C (DMF–TMG=5:1).
[d] $Pd(PPh_3)_2Cl_2$ was used to replace $Pd(PPh_3)_4$.
[e] Carried out at 100 °C. TMG=1,1,3,3-tetramethylguanidine.

Table 3). Use of $Pd(PPh_3)_2Cl_2$ as the catalyst precursor seems essential along with a stronger base, TMG. Higher reaction temperature (100 °C) was also applied for the formation of **9a**. These results suggest that the *ortho* nitro group in **11c** may form hydrogen bond with the amido moiety, thus interfering the indole ring closure reaction. This type of intramolecular hydrogen bond would be destroyed when a strong base such as *t*-BuOK was used for the heteroannulation. Therefore, no difference was recognized among the stepwise synthesis of C5-, C6-, and C7-nitroindoles.

3. Conclusion

In summary, we have established general and efficient cross-coupling–heteroannulation procedures toward 2-substituted C5-, C6-, and C7-nitroindoles starting from the commercially available 2-amino nitrophenols. Both stepwise and one-pot protocols were examined and the former approach seems much more reliable and tolerant to the position of nitro group on the benzene ring. Nitroindoles can be converted, by hydrogenation over Pd/C, into aminoindoles,[20j] which are useful precursors to a variety of indole derivatives possessing nitrogen-based ring substituents.

4. Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 (300 MHz for ^1H and 75 MHz for ^{13}C, respectively) with $CHCl_3$ or acetone as the internal reference. IR spectra were taken on a FT-IR spectrophotometer. Mass spectra (MS) were measured by the +CI method. Elemental analyses were performed by Zhejiang University and Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. All reactions were carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25-mm E. Merck silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials. Reagents were obtained commercially and used as received. Room temperature is around 20 °C.

4.1. Representative procedure for the acylation of 2-amino nitrophenols 1a–c

4.1.1. *N*-(2′-Hydroxy-5′-nitrophenyl)butyramide (2b). To a solution of 2-amino-4-nitrophenol **1b** (462.0 mg, 3.00 mmol) in dry THF (25 mL) cooled in an ice-water bath was added pyridine (0.30 mL, 3.80 mmol) and butyryl chloride (0.34 mL, 3.30 mmol) through a syringe, respectively. The resultant mixture was stirred for 60 h at refluxing temperature under a nitrogen atmosphere. The reaction was quenched by water and the resultant mixture was extracted with EtOAc (30×3 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% EtOAc in hexane) to give **2b** (650.0 mg, 97%) as a pale yellow crystalline solid; mp 191–192 °C (CH_2Cl_2–hexane); R_f=0.53 (33% EtOAc in hexane); IR (film) 3406, 1646, 1529, 1498, 1343, 1289 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.85 (br s, 1H), 9.24 (br s, 1H), 8.99 (d, J=2.8 Hz, 1H), 8.06 (dd, J=8.9, 2.8 Hz, 1H), 7.20 (d, J=9.0 Hz, 1H), 2.68 (t, J=7.4 Hz, 2H), 1.88 (sextet, J=7.4 Hz, 2H), 1.13 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 172.8, 152.8, 140.2, 126.9, 120.2, 116.3, 115.8, 37.9, 18.4, 12.7; MS (+CI) m/z 225 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.81; H, 5.40; N, 12.31%.

4.1.2. *N*-(2′-Hydroxy-4′-nitrophenyl)butyramide (2a). Prepared in 86% yield from 2-amino-5-nitrophenol **1a**. *Compound* **2a**. A colorless crystalline solid; mp 175–176 °C (CH_2Cl_2–hexane); R_f=0.51 (50% EtOAc in hexane); IR (film) 3409, 1664, 1504, 1421, 1341 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 9.22 (br s, 1H), 8.36 (d, J=8.8 Hz, 1H), 7.94–7.87 (m, 2H), 2.69 (t, J=7.4 Hz, 2H), 1.87 (sextet, J=7.4 Hz, 2H), 1.12 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 172.5, 146.3, 143.2, 133.2, 119.6, 115.4, 110.1, 38.1, 18.3, 12.7; MS (+CI) m/z 225 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.62; H, 5.48; N, 12.38%.

4.1.3. *N*-(2′-Hydroxy-6′-nitrophenyl)butyramide (2c). Prepared in 60% yield from 2-amino-3-nitrophenol **1c** using NaH to replace pyridine as the base (room temperature, 24 h). *Compound* **2c**. A yellow crystalline solid; mp 119–120 °C (CH_2Cl_2–hexane); R_f=0.34 (25% EtOAc in hexane); IR (film) 3395, 3141 (br), 1663, 1540, 1511, 1367 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.09 (br s, 1H), 9.32 (s, 1H), 7.71 (dd, J=8.4, 1.5 Hz, 1H), 7.36 (dd, J=8.2, 1.5 Hz, 1H), 7.24 (t, J=8.3 Hz, 1H), 2.56 (t, J=7.4 Hz, 2H), 1.82 (sextet, J=7.4 Hz, 2H), 1.04 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 151.2, 141.2, 127.1, 126.1, 122.2, 117.9, 39.4, 19.0, 13.5; MS (+CI) m/z 225 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.72; H, 5.45; N, 12.42%.

4.2. Representative procedure for the synthesis of nitroaryl triflates using NaH as the base

4.2.1. *N*-[5′-Nitro-2′-(((trifluoromethane)sulfonyl)oxy)-phenyl]butyramide (3b). To a suspension of NaH (60%, 8.0 mg, 2.03 mmol) in dry MeCN (15 mL) cooled in an ice-water bath under a nitrogen atmosphere was added a solution of **2b** (363.0 mg, 1.62 mmol) in dry MeCN (30 mL) followed by stirring at the same temperature for 20 min. Tf_2O (0.30 mL, 1.78 mmol) was then added dropwise, and the resultant mixture was stirred for 6 h at −5–0 °C. The reaction was quenched by water and the resultant mixture was extracted with EtOAc (30×2 mL). The combined organic layer was washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% EtOAc in hexane) to give **3b** (461.0 mg, 80%) as a white crystalline solid; mp 73–74 °C (CH_2Cl_2–hexane); R_f=0.51 (25% EtOAc in hexane); IR (film) 3271 (br), 2969, 1681, 1542, 1430, 1217 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ

9.30 (d, J=2.7 Hz, 1H), 8.04 (dd, J=9.0, 2.7 Hz, 1H), 7.55–7.47 (br s, 1H), 7.48 (d, J=9.0 Hz, 1H), 2.45 (t, J=7.4 Hz, 2H), 1.79 (sextet, J=7.4 Hz, 2H), 1.03 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 148.6, 141.9, 131.6, 122.1, 119.6, 118.5, 118.3 (q, J_{C-F}=318.4 Hz), 39.4, 18.5, 13.6; MS (+CI) m/z 357 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{11}F_3N_2O_6S$: C, 37.08; H, 3.11; N, 7.86. Found: C, 37.45; H, 3.13; N, 7.77%.

4.2.2. *N*-[4′-Nitro-2′-(((trifluoromethane)sulfonyl)oxy)-phenyl]butyramide (3a). Prepared from **2a** in 87% yield. *Compound* **3a**. A colorless crystalline solid; mp 88–89 °C (EtOAc); R_f=0.45 (25% EtOAc in hexane); IR (film) 3274 (br), 2972, 1690, 1516, 1435, 1350, 1217 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.68 (br s, 1H), 8.68–8.48 (m, 3H), 2.70 (t, J=7.4 Hz, 2H), 1.88 (sextet, J=7.4 Hz, 2H), 1.12 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 142.7, 138.8, 136.8, 123.9, 123.6, 118.3 (q, J_{C-F}=318.4 Hz), 117.4, 38.0, 17.9, 12.7; MS (+CI) m/z 357 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{11}F_3N_2O_6S$: C, 37.08; H, 3.11; N, 7.86. Found: C, 37.40; H, 3.21; N, 7.66%.

4.3. Procedure for the synthesis of nitroaryl triflate using Et_3N as the base

4.3.1. *N*-[6′-Nitro-2′-(((trifluoromethane)sulfonyl)oxy)-phenyl]butyramide (3c). To a solution of **2c** (395.0 mg, 1.76 mmol) and Et_3N (0.30 mL, 2.20 mmol) in dry CH_2Cl_2 (20 mL) cooled in an ice-water bath under a nitrogen atmosphere was added Tf_2O (0.33 mL, 1.93 mmol) dropwise. The resultant mixture was stirred at the same temperature for 7 h. After removal of CH_2Cl_2 under reduced pressure, the residue was dissolved in 25 mL EtOAc and then washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% EtOAc in hexane) to give **3c** (590.0 mg, 94%) as a white crystalline sold; mp 119–119.5 °C (CH_2Cl_2–hexane); R_f=0.40 (25% EtOAc in hexane); IR (film) 3248 (br), 2973, 1676, 1541, 1518, 1425, 1209 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 8.10 (dd, J=8.4, 1.4 Hz, 1H), 7.62 (dd, J=8.4, 1.4 Hz, 1H), 7.48 (t, J=8.4 Hz, 1H), 2.46 (t, J=7.4 Hz, 2H), 1.77 (sextet, J=7.4 Hz, 2H), 1.02 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 145.1, 145.0, 127.5, 126.9, 126.1, 124.9, 118.4 (q, J_{C-F}=318.5 Hz), 38.5, 18.4, 13.6; MS (+CI) m/z 357 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{11}F_3N_2O_6S$: C, 37.08; H, 3.11; N, 7.86. Found: C, 37.16; H, 3.15; N, 8.06%.

4.4. Representative procedure for the cross-coupling of triflates with 1-alkynes

4.4.1. *N*-[(5′-Nitro-2′-phenylethynyl)phenyl]butyramide (5a). To a suspension of triflate **3b** (142.0 mg, 0.40 mmol), $Pd(PPh_3)_4$ (46.0 mg, 4.0×10^{-2} mmol), CuI (23.0 mg, 0.12 mmol), and n-Bu_4NI (222.0 mg, 0.60 mmol) in degassed dry MeCN (5 mL) was added Et_3N (1.0 mL) and phenylacetylene (90 μL, 0.80 mmol), respectively, through a syringe under a nitrogen atmosphere. The resultant mixture was stirred at room temperature for 1 h. The reaction was quenched by saturated aqueous NH_4Cl and the resultant mixture was extracted with EtOAc (20×2 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexane) to give **5a** (126.0 mg, 96%) as a yellow crystalline solid; mp 168–169 °C (CH_2Cl_2–hexane); R_f=0.44 (25% EtOAc in hexane); IR (film) 3290, 2960, 2214, 1665, 1534, 1341 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.36 (d, J=2.2 Hz, 1H), 8.09 (br s, 1H), 7.92 (dd, J=8.5, 2.2 Hz, 1H), 7.62 (d, J=8.5 Hz, 1H), 7.58–7.55 (m, 2H), 7.47–7.40 (m, 3H), 2.47 (t, J=7.4 Hz, 2H), 1.82 (sextet, J=7.4 Hz, 2H), 1.05 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 147.9, 139.5, 132.0, 131.7 (×2), 129.9, 128.8 (×2), 121.2, 118.0, 117.8, 114.3, 100.8, 82.8, 39.8, 18.8, 13.7; MS (+CI) m/z 309 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.75; H, 6.00; N, 9.20%.

4.4.2. *N*-[(4′-Nitro-2′-phenylethynyl)phenyl]butyramide (4a). Prepared from the triflate **3a** and 1-phenylacetylene in 95% yield. *Compound* **4a**. A colorless crystalline solid; mp 149–150 °C (CH_2Cl_2–hexane); R_f=0.54 (25% EtOAc in hexane); IR (film) 3306, 2959, 2212, 1677, 1574, 1506 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J=9.2 Hz, 1H), 8.38 (d, J=2.6 Hz, 1H), 8.25 (br s, 1H), 8.20 (dd, J=8.6, 2.6 Hz, 1H), 7.58–7.55 (m, 2H), 7.47–7.40 (m, 3H), 2.49 (t, J=7.4 Hz, 2H), 1.82 (sextet, J=7.4 Hz, 2H), 1.05 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 143.9, 142.6, 131.6 (×2), 129.7, 128.8 (×2), 127.1, 125.2, 121.2, 118.7, 112.3, 98.5, 82.02, 40.0, 18.8, 13.7; MS (+CI) m/z 309 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.34; H, 5.63; N, 8.87%.

4.4.3. *N*-[(4′-Nitro-2′-(pentyn-1″-yl))phenyl]butyramide (4b). Prepared from the triflate **3a** and 1-pentyne in 95% yield. *Compound* **4b**. A white crystalline solid; mp 87–88 °C (CH_2Cl_2–hexane); R_f=0.59 (25% EtOAc in hexane); IR (film) 3335, 2965, 2228, 1678, 1503, 1345 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, J=9.2 Hz, 1H), 8.23–8.15 (br s, 1H), 8.19 (d, J=2.6 Hz, 1H), 8.09 (dd, J=9.2, 2.6 Hz, 1H), 2.51 (t, J=7.0 Hz, 2H), 2.42 (t, J=7.4 Hz, 2H), 1.81–1.65 (m, 4H), 1.08 (t, J=7.4 Hz, 3H), 1.02 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 144.0, 142.3, 126.9, 124.4, 118.2, 112.9, 100.3, 74.2, 39.9, 21.9, 21.4, 18.7, 13.6, 13.5; MS (+CI) m/z 275 ($M+H^+$, 100). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 66.03; H, 6.73; N, 10.05%.

4.4.4. *N*-[(5′-Nitro-2′-(pentyn-1″-yl))phenyl]butyramide (5b). Prepared from the triflate **3b** and 1-pentyne in 90% yield. *Compound* **5b**. A white crystalline solid; mp 91–92 °C (CH_2Cl_2–hexane); R_f=0.38 (25% EtOAc in hexane); IR (film) 3290, 2962, 2223, 1668, 1529, 1344 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, J=2.2 Hz, 1H), 8.04 (br s, 1H), 7.85 (dd, J=8.5, 2.2 Hz, 1H), 7.47 (d, J=8.5 Hz, 1H), 2.55 (t, J=7.0 Hz, 2H), 2.42 (t, J=7.4 Hz, 2H), 1.82–1.67 (m, 4H), 1.11 (t, J=7.4 Hz, 3H), 1.04 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 147.4, 139.5, 131.9, 118.5, 117.8, 113.9, 102.9, 75.0, 39.8, 21.9, 21.6, 18.8, 13.7, 13.6; MS (+CI) m/z 275 ($M+H^+$, 100). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.48; H, 6.79; N, 9.86%.

4.4.5. *N*-[(6′-Nitro-2′-phenylethynyl)phenyl]butyramide (6a). Prepared from the triflate **3c** and 1-phenylacetylene in 90% yield. *Compound* **6a**. A white crystalline solid; mp 167–168 °C (CH_2Cl_2–hexane); R_f=0.31 (25% EtOAc in hexane); IR (film) 3275, 2923, 2215, 1668, 1509 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.89 (dd, J=8.3, 1.4 Hz, 1H), 7.76 (dd, J=8.3, 1.4 Hz, 1H), 7.53–7.48 (m, 2H), 7.42–7.35 (m, 3H), 7.29 (t, J=8.1 Hz, 1H), 2.44 (t, J=7.4 Hz, 2H), 1.78 (sextet, J=7.4 Hz, 2H), 1.01 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 144.3, 136.7, 131.6 (×2), 131.4, 129.3, 128.6 (×2), 125.3, 124.9, 121.8, 120.9, 97.2, 83.7, 38.9, 18.8, 13.7; MS (+CI) *m/z* 309 ($M+H^+$, 100). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.31; H, 5.91; N, 8.82%.

4.4.6. *N*-[(6′-Nitro-2′-(pentyn-1″-yl))phenyl]butyramide (6b). Prepared from the triflate **3c** and 1-pentyne in 91% yield. *Compound* **6b**. A white crystalline solid; mp 144–145 °C (CH_2Cl_2–hexane); R_f=0.36 (25% EtOAc in hexane); IR (film) 3272, 2961, 2225, 1670, 1511, 1536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.79 (dd, J=8.0, 1.4 Hz, 1H), 7.60 (dd, J=8.0, 1.4 Hz, 1H), 7.20 (t, J=8.0 Hz, 1H), 2.44 (t, J=7.0 Hz, 2H), 2.39 (t, J=7.4 Hz, 2H), 1.83–1.56 (m, 4H), 1.05 (t, J=7.3 Hz, 3H), 1.01 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 144.3, 136.4, 131.0, 124.9, 124.2, 121.0, 99.2, 75.3, 38.7, 21.9, 21.4, 18.7, 13.6, 13.5; MS (+CI) *m/z* 275 ($M+H^+$, 100). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 64.19; H, 6.05; N, 10.50%.

4.5. Representative procedure for the synthesis of trifluoroacetanilides 10a–c

4.5.1. *N*-(2′-Hydroxy-5′-nitrophenyl)trifluoroacetamide (10b). To a solution of 2-amino-4-nitrophenol **1b** (3.124 g, 20 mmol) in dry THF (83 mL) and pyridine (2.4 mL, 29.95 mmol) cooled in an ice-water bath was added dropwise a solution of trifluoroacetic anhydride (3.1 mL, 22 mmol) in dry THF (7 mL). The resultant mixture was stirred for 16 h at room temperature under a nitrogen atmosphere. The reaction was quenched by adding water (10 mL) and brine (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (20×2 mL). The combined organic layer was washed with 5% HCl (15 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc in hexane) to give **10b** (5.000 g, 99%) as a yellow crystalline solid; mp 188–189 °C (EtOAc–hexane); R_f=0.30 (50% EtOAc in hexane); IR (KBr): 3386, 3188 (br), 1696 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 11.20–10.30 (br s, 1H), 9.90–9.55 (br s, 1H), 9.02 (d, J=2.7 Hz, 1H), 8.22 (dd, J=9.1, 2.8 Hz, 1H), 7.34 (d, J=9.0 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 153.7, 146.6, 140.0, 123.4, 122.4, 118.0, 115.4 (q, J_{C-F}=287.1 Hz), 114.9; MS (+CI) *m/z* 251 ($M+H^+$,100). Anal. Calcd for $C_8H_5F_3N_2O_4$: C, 38.41; H, 2.01; N, 11.20. Found: C, 38.32; H, 1.88; N, 11.00%.

4.5.2. *N*-(2′-Hydroxy-4′-nitrophenyl)trifluoroacetamide (10a). Prepared in 99% yield from 2-amino-5-nitrophenol **1a** after reaction at room temperature for 4 h. *Compound* **10a**. As a yellow crystalline solid; mp 164–165 °C (EtOAc–hexane); R_f=0.32 (25% EtOAc in hexane); IR (KBr) 3374, 3222 (br), 1697 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.60–9.35 (br s, 2H), 8.40 (d, J=8.7 Hz, 1H), 8.02–7.90 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 154.7 (q, J_{C-F}=45.3 Hz), 147.7, 145.1, 129.7, 121.5, 115.6 (q, J_{C-F}=271.7 Hz), 115.2, 109.7; MS (+CI) *m/z* 251 ($M+H^+$, 100). Anal. Calcd for $C_8H_5F_3N_2O_4$: C, 38.41; H, 2.01; N, 11.20. Found: C, 38.15; H, 1.94; N, 11.39%.

4.5.3. *N*-(2′-Hydroxy-6′-nitrophenyl)trifluoroacetamide (10c). Prepared in 86% yield from 2-amino-3-nitrophenol **1c** after reaction at room temperature for 9 h. *Compound* **10c**. As a yellow crystalline solid; mp 136–137 °C (EtOAc–hexane); R_f=0.41 (50% EtOAc in hexane); IR (KBr) 3310 (br), 1729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.04 (br s, 1H), 8.05–7.75 (br s, 1H), 7.85 (dd, J=7.8, 2.1 Hz, 1H), 7.47–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 153.4 (q, J_{C-F}=43.5 Hz), 146.4, 146.0, 128.5, 120.7, 115.3, 115.5 (q, J_{C-F}=286.8 Hz), 115.0; MS (+CI) *m/z* 251 ($M+H^+$, 100). Anal. Calcd for $C_8H_5F_3N_2O_4$: C, 38.41; H, 2.01; N, 11.20. Found: C, 38.41; H, 1.85; N, 10.80%.

4.6. Representative procedure for the synthesis of nitroaryl triflates 11a–c

4.6.1. *N*-[5′-Nitro-2′-(((trifluoromethane)sulfonyl)oxy)-phenyl]trifluoroacetamide (11b). To a suspension of NaH (0.54 g, 13.5 mmol) in dry THF (80 mL) cooled in an ice-water bath was added dropwise a solution of **10b** (2.25 g, 9.0 mmol) and $PhNTf_2$ (4.82 g, 13.5 mmol) in dry THF (20 mL). The resultant mixture was stirred for 19 h at room temperature under a nitrogen atmosphere. The reaction was quenched by water (25 mL) and brine (25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (45 mL×5) and brine (35 mL), dried over anhydrous Na_2SO_4, evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 25% EtOAc in hexane) to give **11b** (3.20 g, 93%) as a yellow crystalline solid; mp 88–89 °C (EtOAc–hexane); R_f=0.54 (25% EtOAc in hexane); IR (KBr) 3292 (br), 1717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, J=2.7 Hz, 1H), 8.28 (br s, 1H), 8.24 (dd, J=9.3, 3.0 Hz, 1H), 7.62 (d, J=9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (q, J_{C-F}=39.4 Hz), 148.0, 143.8, 129.4, 123.7, 123.2, 120.1, 119.2 (q, J_{C-F}=320.9 Hz), 115.8 (q, J_{C-F}=288.4 Hz); MS (+CI) *m/z* 383 ($M+H^+$, 100). Anal. Calcd for $C_9H_4F_6N_2O_6S$: C, 28.28; H, 1.05; N, 7.33. Found: C, 28.39; H, 0.89; N, 6.65%.

4.6.2. *N*-[4′-Nitro-2′-(((trifluoromethane)sulfonyl)oxy)-phenyl]trifluoroacetamide (11a). Prepared from **10a** in 84% yield after reaction at room temperature for 4 h. *Compound* **11a**. As a yellow crystalline solid; mp 66–67 °C (EtOAc–hexane); R_f=0.38 (25% EtOAc in hexane); IR (KBr) 3284, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, J=9.3 Hz, 1H), 8.46–8.32 (br s, 1H), 8.38 (dd, J=9.0, 2.7 Hz, 1H), 8.31 (d, J=2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8 (q, J_{C-F}=45.1 Hz), 145.4, 138.3, 134.1, 125.4, 123.5, 119.1 (q, J=320.2 Hz), 118.8, 117.2 (q, J=288.1 Hz); MS (+CI) *m/z* 383 ($M+H^+$, 100). Anal. Calcd for $C_9H_4F_6N_2O_6S$: C, 28.28; H, 1.05; N, 7.33. Found: C, 28.53; H, 0.98; N, 6.86%.

4.6.3. *N*-[6′-Nitro-2′-(((trifluoromethane)sulfonyl)oxy)-phenyl]trifluoroacetamide (11c). Prepared from **10c** in 88% yield after reaction at room temperature for 24 h. *Compound* **11c**. As a yellow crystalline solid; mp 108.5–109.5 °C; R_f=0.37 (25% EtOAc in hexane); IR (KBr) 3255, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.10 (br s, 1H), 8.22 (dd, J=8.2, 1.3 Hz, 1H), 7.75 (dd, J=8.4, 1.5 Hz, 1H), 7.66 (t, J=8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1 (q, J_{C-F}=43.2 Hz), 145.6, 145.3, 129.8, 129.1, 126.1, 123.6, 119.1 (q, J_{C-F}=320.6 Hz), 115.9 (q, J_{C-F}=288.2 Hz); MS (+CI) m/z 383 ($M+H^+$, 100). Anal. Calcd for $C_9H_4F_6N_2O_6S$: C, 28.28; H, 1.05; N, 7.33. Found: C, 28.34; H, 0.96; N, 7.25%.

4.7. Representative procedure for the *t*-BuOK-promoted heteroannualtion toward nitroindoles

4.7.1. 6-Nitro-2-phenylindole (8a). A mixture of **5a** (60.0 mg, 0.19 mmol), *t*-BuOK (25.0 mg, 0.22 mmol) in dry NMP (2.0 mL) was heated at 60–70 °C for 7 h under a nitrogen atmosphere. After cooling to room temperature, water (2 mL) and EtOAc (50 mL) were added to the reaction mixture, respectively. The separated aqueous layer was extracted with EtOAc (20×3 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 30% EtOAc in hexane) to give **8a** (37.0 mg, 84%) as a yellow crystalline solid; mp 211–212 °C (CH_2Cl_2–hexane); R_f=0.61 (33% EtOAc in hexane); IR (KBr) 3322, 2923, 1298 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 11.61 (br s, 1H), 8.51 (d, J=2.0 Hz, 1H), 8.12–8.06 (m, 3H), 7.88 (d, J=8.8 Hz, 1H), 7.70–7.63 (m, 2H), 7.61–7.54 (m, 1H), 7.25 (dd, J=2.0, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 144.0, 142.5, 135.5, 133.9, 131.0, 128.9 (×2), 128.6, 125.5 (×2), 119.9, 114.7, 107.5, 99.7; MS (+CI) m/z 239 ($M+H^+$, 100). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.40; H, 4.11; N, 11.64%.

Other results are listed in Table 2.

4.8. Representative procedure for the Pd-catalyzed one-pot cross-coupling and heteroannulation toward nitroindoles

4.8.1. 6-Nitro-2-propylindole (8b). A mixture of **11b** (115.0 mg, 0.3 mmol), *n*-Bu_4NI (169.6 mg, 0.45 mmol), $Pd(PPh_3)_4$ (11.1 mg, 0.03 mmol), CuI (17.14 mg, 0.09 mmol), and 1-pentyne (40.8 mg, 60 μL, 0.6 mmol) in degassed DMF (5 mL) containing Et_3N (1 mL) was heated at ca. 80 °C for 21 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous NH_4Cl (10 mL) and brine (15 mL). The organic layer was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, MeOH–CH_2Cl_2–hexane=1:40:30) to give **8b** (51.7 mg, 84%, entry 7, Table 3) as a yellow crystalline solid;[30] mp 94–95 °C (CH_2Cl_2–hexane); R_f=0.54 (33% EtOAc in hexane); IR (film) 3367, 2962, 1302 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.98 (br s, 1H), 8.42 (d, J=2.0 Hz, 1H), 8.04 (dd, J=8.8, 2.2 Hz, 1H), 7.73 (d, J=8.8 Hz, 1H), 6.55 (d, J=0.5 Hz, 1H), 2.98 (t, J=7.5 Hz, 2H), 1.94 (sextet, J=7.5 Hz, 2H), 1.13 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 141.5, 119.3, 118.6, 114.8, 114.0, 107.3, 106.7, 99.8, 29.9, 21.7, 12.8; MS (+CI) m/z 205 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.74; H, 6.08; N, 14.13%.

Other results are summarized in Table 3.

4.8.2. 5-Nitro-2-phenylindole (7a). A yellow crystalline solid; mp 190–191 °C (CH_2Cl_2–hexane); R_f=0.37 (25% EtOAc in hexane); IR (film) 3344, 1329 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 11.52 (br s, 1H), 8.69 (d, J=2.2 Hz, 1H), 8.26 (dd, J=8.9, 2.2 Hz, 1H), 8.05–8.00 (m, 2H), 7.76–7.60 (m, 3H), 7.56–7.50 (m, 1H), 7.28 (s, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 141.3, 139.8, 130.9, 128.6 (×2), 128.2, 128.1, 128.0, 125.0 (×2), 116.6, 116.5, 110.8, 100.4; MS (+CI) m/z 239 ($M+H^+$, 100). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.32; H, 4.11; N, 11.73%.

4.8.3. 5-Nitro-2-propylindole (7b). A yellow crystalline solid; mp 125–126 °C (CH_2Cl_2–hexane); R_f=0.34 (50% EtOAc in hexane); IR (KBr) 3325, 1314 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.86 (br s, 1H), 8.57 (d, J=2.1 Hz, 1H), 8.11 (dd, J=9.0, 2.1 Hz, 1H), 7.58 (d, J=9.0 Hz, 1H), 6.56 (d, J=0.7 Hz, 1H), 2.92 (t, J=7.4 Hz, 2H), 1.90 (sextet, J=7.5 Hz, 2H), 1.12 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 143.6, 140.6, 138.9, 127.6, 115.4, 115.2, 109.8, 100.4, 28.1, 21.4, 12.5; MS (+CI) m/z 205 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.74; H, 5.85; N, 13.46%.

4.8.4. 5-Nitro-2-(2′-hydroxyethyl)indole (7c). A crystalline solid; mp 114–115 °C (EtOAc–hexane); R_f=0.29 (67% EtOAc in hexane); IR (KBr) 3469, 3185 (br), 1512, 1471, 1337 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.85 (br s, 1H), 8.60 (d, J=2.2 Hz, 1H), 8.11 (dd, J=9.0, 2.3 Hz, 1H), 7.75 (d, J=8.9 Hz, 1H), 6.67 (d, J=0.9 Hz, 1H), 4.22 (t, J=5.3 Hz, 1H), 4.07 (q, J=6.3 Hz, 2H), 3.18 (t, J=6.2 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 142.0, 141.1, 139.3, 127.9, 115.8, 115.6, 110.5, 101.5, 60.8, 31.4; MS (+CI) m/z 207 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.25; H, 5.00; N, 13.75%.

4.8.5. 5-Nitro-2-(3′-cyanopropyl)indole (7d). A crystalline solid; mp 125.5–126 °C (EtOAc–hexane); R_f=0.41 (50% EtOAc in hexane); IR (KBr) 3321, 2250, 1471, 1334 cm^{-1}; ^1H MNR (300 MHz, acetone-d_6): δ 10.9 (br s, 1H), 8.59 (d, J=2.1 Hz, 1H), 8.11 (dd, J=8.7, 2.4 Hz, 1H), 8.60 (d, J=8.7 Hz, 1H), 6.70 (s, 1H), 3.16 (t, J=7.5 Hz, 2H), 2.72 (t, J=7.2 Hz, 2H), 2.33–2.22 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 142.0, 141.5, 138.5, 128.1, 119.2, 116.1, 116.0, 110.6, 101.5, 26.7, 24.7, 15.8; MS (+CI) m/z 230 ($M+H^+$, 100). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.75; H, 4.89; N, 18.37%.

4.8.6. 5-Nitro-2-(3′-chloropropyl)indole (7e). A crystalline solid; mp 107–107.5 °C (EtOAc–hexane); R_f=0.34 (25% EtOAc in hexane); IR (KBr): 3336, 1323 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 10.86 (br s, 1H), 8.59 (d, J=1.8 Hz, 1H), 8.11 (dd, J=8.7, 2.1 Hz, 1H), 7.61 (d, J=

8.7 Hz, 1H), 6.68 (s, 1H), 3.84 (t, J=6.3 Hz, 2H), 3.17 (t, J=7.8 Hz, 2H), 2.44–2.35 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 142.2, 140.8, 139.2, 127.7, 115.7, 115.6, 110.2, 101.0, 43.2, 30.8, 24.2; MS (+CI) m/z 239 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.28; H, 4.71; N, 11.76%.

4.8.7. 6-Nitro-2-(2′-hydroxyethyl)indole (8c). A crystalline solid; mp 141–142 °C (EtOAc–hexane); R_f=0.28 (50% EtOAc in hexane); IR (KBr) 3490, 3275 (br), 1501, 1316, 1051 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.90 (br s, 1H), 8.47 (d, J=2.1 Hz, 1H), 8.03 (dd, J=8.4, 2.1 Hz, 1H), 7.73 (d, J=9.0 Hz, 1H), 6.60 (d, J=2.4 Hz, 1H), 4.25 (br s, 1H), 4.08 (br t, J=6.0 Hz, 2H), 3.21 (t, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 145.3, 142.1, 134.2, 133.7, 118.8, 114.1, 107.2, 100.7, 60.7, 31.6; MS (+CI) m/z 207 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.29; H, 4.77; N, 13.37%.

4.8.8. 6-Nitro-2-(3′-cyanopropyl)indole (8d). A crystalline solid; mp 117–118 °C (EtOAc–hexane); R_f=0.47 (50% EtOAc in hexane); IR (KBr) 3326, 2254, 1499, 1308 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.99 (br s, 1H), 8.41 (d, J=1.8 Hz, 1H), 8.18 (dd, J=8.7, 2.4 Hz, 1H), 7.75 (d, J=8.7 Hz, 1H), 6.63 (d, J=3.0 Hz, 1H), 3.19 (t, J=7.8 Hz, 2H), 2.72 (t, J=8.4 Hz, 2H), 2.35–2.27 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 145.9, 142.8, 134.6, 133.6, 131.6, 119.1, 114.3, 107.1, 100.6, 26.9, 24.7, 15.9; MS (+CI) m/z 230 ($M+H^+$, 100). Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.72; H, 4.85; N, 18.46%.

4.8.9. 6-Nitro-2-(3′-chloropropyl)indole (8e). A white crystalline solid; mp 98–99 °C (EtOAc–hexane); R_f=0.49 (25% EtOAc in hexane); IR (KBr) 3329, 1505, 1337, 1298 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.95 (br s, 1H), 8.42 (d, J=1.2 Hz, 1H), 8.04 (dd, J=8.7, 2.1 Hz, 1H), 7.74 (d, J=8.7 Hz, 1H), 6.60 (d, J=3.0 Hz, 1H), 3.83 (t, J=6.6 Hz, 2H), 3.19 (t, J=7.8 Hz, 2H), 2.45–2.35 (m, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 145.7, 142.0, 134.6, 133.7, 118.1, 114.3, 107.1, 100.4, 44.0, 31.6, 25.2; MS (+CI) m/z 239 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.28; H, 4.51; N, 11.72%.

4.8.10. 7-Nitro-2-phenylindole (9a). A white crystalline solid; mp 142–143 °C (CH_2Cl_2–hexane); R_f=0.74 (25% EtOAc in hexane); IR (film) 3149, 2921, 1338, 1292 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 11.09 (br s, 1H), 8.25 (dd, J=8.1, 0.9 Hz, 1H), 8.18 (dd, J=8.1, 0.9 Hz, 1H), 8.13–8.09 (m, 2H), 7.67–7.55 (m, 3H), 7.40 (t, J=7.9 Hz, 1H), 7.25 (d, J=1.6 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 140.8, 132.9, 130.8, 129.8, 128.9, 128.6 (×2), 128.2, 128.0, 125.8 (×2), 119.1, 118.3, 100.4; MS (+CI) m/z 239 ($M+H^+$, 44), 153 (100). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.36; H, 4.25; N, 12.00%.

4.8.11. 7-Nitro-2-propylindole (9b). A yellow crystalline solid; mp 79–80 °C (CH_2Cl_2–hexane); R_f=0.71 (25% EtOAc in hexane); IR (KBr) 3409, 2956, 1512, 1339 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (br s, 1H), 8.05 (d, J=8.1 Hz, 1H), 7.80 (d, J=7.6 Hz, 1H), 7.13 (t, J=7.9 Hz, 1H), 6.38 (s, 1H), 2.81 (t, J=7.4 Hz, 2H), 1.80 (sextet, J=7.4 Hz, 2H), 1.04 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 132.6, 129.4, 128.4, 127.6, 118.9, 117.9, 100.7, 30.0, 22.2, 13.8; MS (+CI) m/z 205 ($M+H^+$, 100). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.90; H, 6.11; N, 13.75%.

4.8.12. 7-Nitro-2-(2′-hydroxyethyl)indole (9c). A yellow crystalline solid; mp 117–118 °C (EtOAc–hexane); R_f=0.47 (50% EtOAc in hexane); IR (KBr): 3394, 3291 (br), 2923, 1514, 1338 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 11.11 (br s, 1H), 8.19 (d, J=7.8 Hz, 1H), 8.09 (d, J=7.8 Hz, 1H), 7.34 (t, J=7.8 Hz, 1H), 6.67 (d, J=0.9 Hz, 1H), 4.29 (br s, 1H), 4.11 (t, J=6.2 Hz, 2H), 3.26 (t, J=6.4 Hz, 2H); ^{13}C NMR (75 MHz, acetone-d_6) δ 141.7, 132.8, 132.2, 129.1, 127.4, 118.5, 117.2, 101.0, 61.0, 31.0; MS (+CI) m/z 207 ($M+H^+$, 100). Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.39; H, 4.89; N, 13.70%.

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Asymmetric epoxidation of *cis*-1-propenylphosphonic acid (CPPA) catalyzed by chiral tungsten(VI) and molybdenum(VI) complexes

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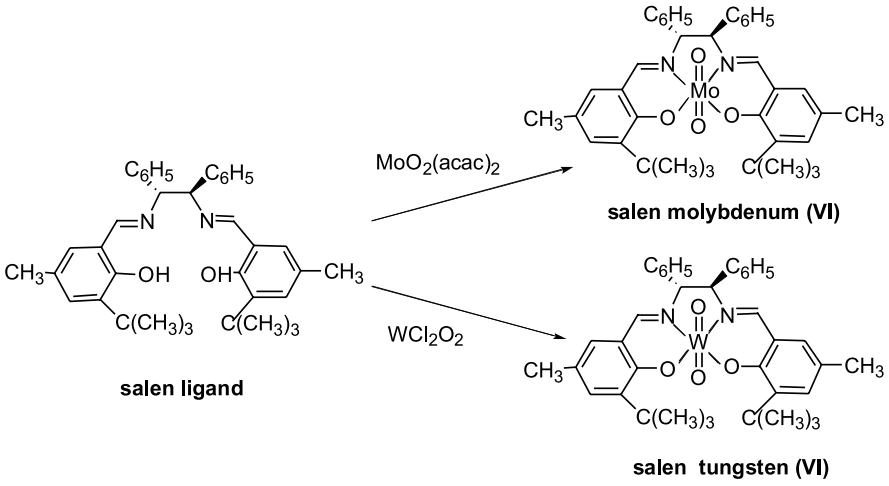
Abstract—In the presence of 5.0 mol% chiral tungsten(VI) and molybdenum(VI) complexes, the catalytic asymmetric epoxidation of *cis*-1-propenylphosphonic acid (CPPA) with 30% aqueous H_2O_2 affording (1*R*,2*S*)-(−)-(1, 2)-epoxypropyl phosphonic acid (fosfomycin) was first described. The enantioselectivities of the tungsten and molybdenum catalysts depend strongly on the ligands, reaction temperature and solvent. In CH_2Cl_2 at 0 °C for 72 h, complex MoO_2[(+)-campy]$_2$ catalyzed the asymmetric epoxidation in a 100% conversion of CPPA with the highest 80% ee. The mechanism of the present epoxidation could be described as direct oxygen transfer occurred on the interface of the biphasic H_2O–nonprotic system.

1. Introduction

(1*R*,2*S*)-(−)-(1,2)-Epoxypropyl phosphonic acid (fosfomycin) is a clinically important drug with wide-spectrum antibiotic activity. It was isolated originally from fermentation broth of *Streptomyces fradiae*[1] and prepared mainly by epoxidation of *cis*-1-propenylphosphonic acid (CPPA) (**1**)[1,2] followed by an optical resolution of the racemic epoxide with chiral amines.[1,3] Although a few of asymmetric synthetic methods were reported for the preparation of fosfomycin,[4] no catalytic asymmetric epoxidation of CPPA has been reported. It is well known that the tungsten and molybdenum derivatives efficiently catalyzed the epoxidation of electron-deficient olefin.[5] Therefore, we were encouraged to explore the asymmetric epoxidation of CPPA catalyzed by chiral salen tungsten(VI) and salen



Scheme 1. Synthesis of chiral salen tungsten(VI) and molybdenum(VI) complexes.

Keywords: *cis*-1-Propenylphosphonic acid; Chiral tungsten and molybdenum complexes; Catalytic asymmetric epoxidation; Enantioselectivity.
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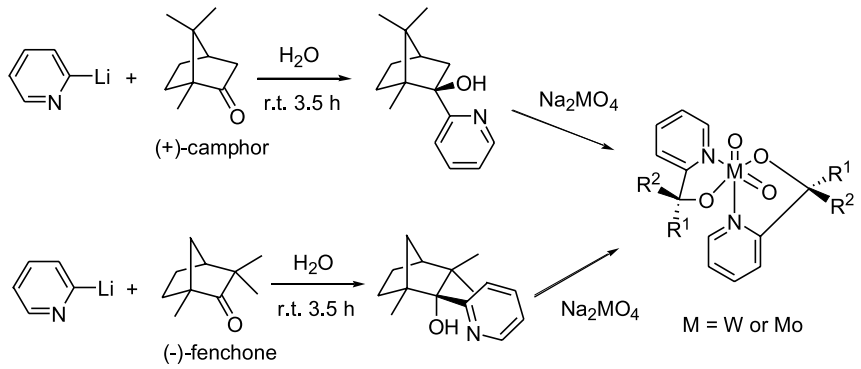


Scheme 2. Synthesis of chiral tungsten(VI) and molybdenum(VI) 2′-pyridinyl alcoholate complexes.

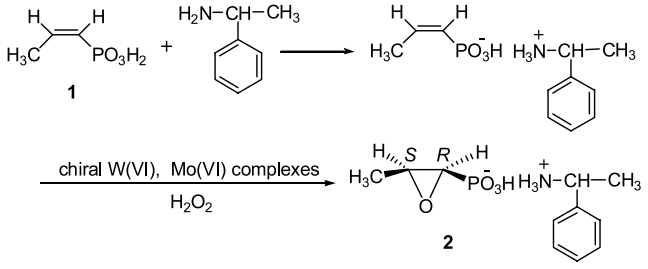
molybdenum(VI) complexes. In this paper, we have reported the catalytic activities and selectivity of several chiral tungsten(VI) and molybdenum(VI) complexes in the asymmetric epoxidation of CPPA.

2. Results and discussion

2.1. Preparation of chiral tungsten(VI) and molybdenum(VI) complexes

Although several salen tungsten(VI) complexes have been prepared,[6] none of those is chiral complex. We first synthesized chiral salen tungsten(VI) and molybdenum(VI) complexes by the reactions of WCl_2O_2, $Mo(acac)_2$ with the ligand shown in Scheme 1.[7]

Chiral tungsten and molybdenum 2′-pyridinyl alcoholate complexes have been also used to catalyze the epoxidation of olefins.[8] We prepared WO_2[(+)-campy]$_2$, MoO_2[(+)-campy]$_2$, WO_2[(−)-fenpy]$_2$ and MoO_2[(−)-fenpy]$_2$ complexes according to the reported methods[8e,f] as shown in Scheme 2.



Scheme 3. Catalytic asymmetric epoxidation of CPPA.

The ligand (+)-campy stands for (1*R*,2*R*,4*R*)-1,7,7-trimethyl-2-(2′-pyridinyl)bicyclo-[2.2.1] heptan-2-ol; the (−)-fenpy stands for (1*R*,2*R*,4*S*)-1,3,3-trimethyl-2-(2′-pyridinyl)bicyclo-[2.2.1] heptan-2-ol.

2.2. Asymmetric epoxidation of *cis*-1-propenylphosphonic acid

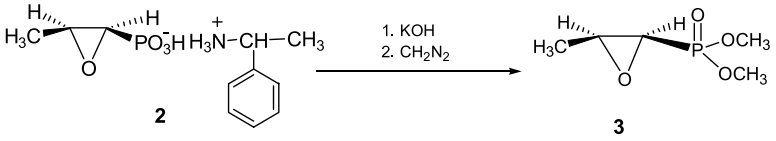
We studied the asymmetric epoxidation of CPPA with 30% aqueous H_2O_2 as oxidant in the presence of catalytic amount of chiral tungsten(VI) and molybdenum(VI) complexes, as shown in Scheme 3.

To a solution of CPPA (0.2 mmol) in ethanol (10 mL) was added racemic α-phenylethylamine (0.2 mmol), then catalyst (0.01 mmol) and H_2O_2 (1.0 mmol, 105 μL of 30% aqueous). The resulting mixture was stirred at 25 °C and the reaction was monitored by ^{1}H NMR. After 24 h, the conversion of CPPA reached 100%, with the ee value of 45%.[10] (Table 1, entry 1). The same reaction in CH_2Cl_2 gave a higher ee value of 69% (Table 1, entry 2). Although salen molybdenum catalyst showed low catalytic activity, it exhibited a similar enantioselectivity as salen tungsten did (Table 1, entries 3 and 4).

Table 1. Asymmetric epoxidation of CPPA at 25 °C[a]

Entry	Catalyst	Solvent	Conv. of CPPA (%)[b]	ee (%) of (1*R*,2*S*)-epoxide[c]
1	Salen W	C_2H_5OH	100	45
2		CH_2Cl_2	100	69
3	Salen Mo	C_2H_5OH	20	46
4		CH_2Cl_2	30	69
5	WO_2[(+)-campy]	C_2H_5OH	100	62
6		CH_2Cl_2	100	74
7	MoO_2[(+)-campy]$_2$	C_2H_5OH	100	63
8		CH_2Cl_2	100	74
9	WO_2[(−)-fenpy]$_2$	C_2H_5OH	100	52
10		CH_2Cl_2	100	71
11	MoO_2[(−)-fenpy]$_2$	C_2H_5OH	100	59
12		CH_2Cl_2	100	72

[a] Reactions were carried out at 25 °C for 24 h using 0.2 mmol of CPPA, 0.2 mmol of α-phenylethylamine, 1.0 mmol H_2O_2 (30% aqueous) and 0.01 mmol of catalyst in 10 mL of solvent.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR with Eu(tfc)$_3$.



Scheme 4. Preparation of the dimethyl ester of the epoxide.

The optical purity of **2** was determined from the corresponding dimethyl ester by ^{1}H NMR analysis with the optically active shift reagent Eu(tfc)$_3$. Its chemical name is tri[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III). The preparation of the dimethyl ester is shown in Scheme 4 and in Section 4.

As shown in Table 1, the enantioselectivities of tungsten and molybdenum catalysts were more dependent on the ligands than on the metals. Tungsten and molybdenum catalysts bearing the same ligand show similar enantioselectivities in either C_2H_5OH or CH_2Cl_2 solvents. For instance, salen tungsten and salen molybdenum (entries 1–4); WO_2[(+)-campy]$_2$ and MoO_2[(+)-campy]$_2$ (entries 5–8); WO_2[(−)-fenpy]$_2$ and MoO_2[(−)-fenpy]$_2$ (entries 9–12) catalyzed the epoxidation of CPPA resulting in almost same ee value. In addition, CH_2Cl_2 is a better solvent for the present catalytic epoxidation. When (+)-campy ligand was employed in CH_2Cl_2 at 25 °C, the highest ee value (74%) was achieved (entries 6 and 8).

Table 2 shows reaction temperature impact on the enantioselectivities in CH_2Cl_2. For all used catalysts, at low temperature (0 °C), catalysts showed the higher ee values than at 50 °C or at 25 °C (Table 1). In the case of MoO_2[(+)-campy]$_2$, the optical yield of the catalytic epoxidation was up to 80% ee.

At 0 °C, we have studied the catalytic asymmetric epoxidation in different solvent. It was found that $CHCl_3$ and toluene were also suitable solvents. In $CHCl_3$ or toluene, WO_2[(+)-campy]$_2$ catalyzed the reaction in a 100% conversion of CPPA with ee values of 78 or 74%, respectively. Similarly, under the same reaction conditions, MoO_2[(−)-campy]$_2$ gave the similar results [100% conversion, 79% ee in $CHCl_3$ and 76% ee in toluene].

2.3. Proposed mechanism: a direct oxygen transfer on biphase interface

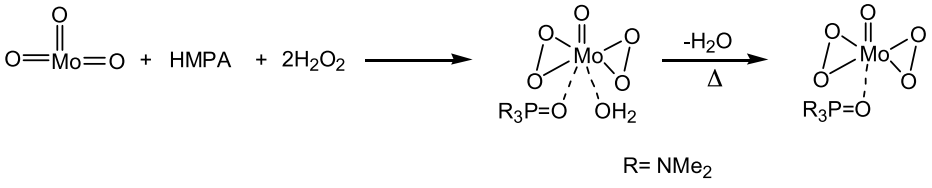
Mimoun type diperoxo complexes, such as $MoO(O_2)_2$-(OPR_3), R=NMe_2 is often used to study on the mechanism of olefin epoxidation catalyzed by tungsten(VI) and molybdenum(VI) complexes. An important characteristic is that every molecule of the complexes possesses two metal-dioxygen rings. Mimoun-type diperoxocomplexes[9] were obtained from the reaction of MoO_3 with H_2O_2 in the presence of ligand, such as HMPA. MoO_3 has three oxo oxygen atoms, among them two have been perhydrolyzed into the two metal-dioxygen ring in the peroxocomplex (Scheme 5). A great number of experiments indicate the last oxo oxygen atom cannot be converted by H_2O_2 into a metal-dioxygen ring.

However, the molecules of above WO_2[(−)-fenpy]$_2$ and MoO_2[(−)-fenpy]$_2$ or salen tungsten(VI) and molybdenum(VI) complexes have only two oxo oxygen atoms (see Schemes 1 and 2) because an oxo oxygen atom has been

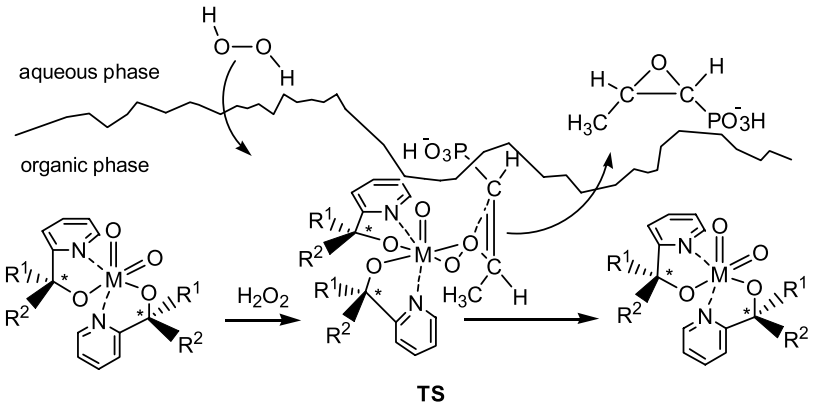
Table 2. Asymmetric epoxidation of CPPA at 0 and 50 °C[a]

Entry	Catalyst	Temperature (°C)	Conv. of CPPA (%)[b]	ee (%) of (1*R*,2*S*)-epoxide[c]
1	Salen W	0	100	74
2		50	100	59
3	Salen Mo	0	24	75
4		50	58	62
5	WO_2[(+)-campy]	0	100	78
6		50	100	67
7	MoO_2[(+)-campy]$_2$	0	100	80
8		50	100	68
9	WO_2[(−)-fenpy]$_2$	0	100	76
10		50	100	63
11	MoO_2[(−)-fenpy]$_2$	0	100	77
12		50	100	64

[a] Reactions were carried out at 0 °C for 72 h, at 50 °C for 1 h by using 0.2 mmol of CPPA, 0.2 mmol of α-phenylethylamine, 1.0 mmol H_2O_2 (30% aqueous) and 0.01 mmol of catalyst in 10 mL CH_2Cl_2.
[b] Determined by ^{1}H NMR.
[c] Determined by ^{1}H NMR using Eu(tfu)$_3$.



Scheme 5. Preparation of Mimoun-type diperoxocomplexes.



Scheme 6. Proposed mechanism for the epoxidation of CPPA in H_2O–nonprotic solvent.

replaced by two oxygen atoms in the ligands. Therefore, they can be only perhydrolyzed into a monoperoxocomplexes with one metal-dioxygen ring.

In recent years, quantum chemical study on epoxidation mechanism has made great progress.[10] The results revealed that a nucleophilic attack of π-electron of the olefin toward the σ* orbital of the peroxo bond maybe involved. This strongly supported the direct oxygen transfer mechanism suggested by Sharpless.[11] Therefore, we consider that the mechanism of the epoxidation of CPPA should be a direct oxygen transfer from the metal-dioxygen ring in the monoperoxocomplexes.

In the epoxidation, 30% aqueous H_2O_2 was used as oxidant. When CH_2Cl_2, $CHCl_3$ and $C_6H_5CH_3$ were used as solvents, the epoxidation was carried out in a biphasic system. H_2O_2 is a molecule with minor polarity and can get into nonprotic solvent such as CH_2Cl_2. Therefore, the chiral tungsten or molybdenum complexes in organic phase can be perhydrolyzed into a monoperoxocomplex (see **TS** in Scheme 6). On the other hand, both methyl group and double bond in CPPA are lipophilic groups, which gets into the organic phase readily. Meanwhile, $-PO_3H^-$ group easily dissolve in H_2O because it is a very strong hydrophilic group. Therefore, the oxygen transfer should occur on the interface of H_2O–nonprotic solvent as shown in Scheme 6. Moreover, the epoxide produced by the epoxidation dissolves easily in water because the three-membered oxygen-containing ring has relatively strong hydrophilic property.

3. Conclusion

CPPA is an α,β-unsaturated acid and an electron-defect olefin. We have developed chiral tungsten(VI) and chiral molybdenum(VI) complexes to catalyze asymmetric epoxidation of CPPA. The ee values depend on the nature of ligands, reaction temperatures and solvents. At 0 °C in CH_2Cl_2, $MoO_2[(+)\text{-campy}]_2$ catalyzed the epoxidation reaction to give the product with the highest ee value of 80%.

4. Experimental

4.1. General

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer as KBr pellets. The NMR spectra were recorded on Bruker AC 300 MHz or AC 500 MHz spectrometer in $CDCl_3$ with TMS as the internal reference. The elemental analyses were performed on a Perkin–Elmer 240C instrument. Optical rotations were determined on a Perkin–Elmer 343 polarimeter.

4.1.1. Preparation of chiral salen tungsten complexes. Under argon atmosphere, salen ligand (50 mg, 0.1 mmol) was dissolved in toluene (5 mL), followed by the addition of WO_2Cl_2 (26 mg, 0.1 mmol) and pyridine (0.014 mL, 0.178 mmol). The resulting mixture was refluxed for 48 h and then cooled to room temperature and washed several times with water. The organic layer was separated and condensed to give a yellow oil. The crude product was purified by flash chromatography (eluent: $CHCl_3$/hexane 2:1) to give a yellow solid in 65% yield.

WO_2 (salen). Mp 161–162 °C. $[\alpha]_D^{25}$ −32.7° (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{38}H_{42}N_2O_4W$: C, 58.92; H, 5.46; N, 3.62. Found: C, 59.02; H, 5.40; N, 3.47%. IR (KBr, cm^{-1}): *ν* (W=O) 880, 928. ^1H NMR 7.93 (s, 1H), 7.84 (s, 1H), 7.39–7.46 (m, 5H), 7.36 (s, 1H), 7.33 (s, 1H), 7.22–7.27 (m, 5H), 6.85 (s, 1H), 6.83 (s, 1H), 6.36 (d, *J*=4.1 Hz, 1H), 4.75 (d, *J*=5.4 Hz, 1H), 2.28 (s, 3H), 2.18 (s, 3H), 1.50 (s, 9H), 1.21 (s, 9H). ^{13}C NMR 166.9, 165.7, 162.7, 157.9, 141.0, 140.1, 138.5, 133.7, 132.5, 129.3 (2C), 129.2 (2C), 128.3 (2C), 128.0 (2C), 122.4, 121.5, 118.1, 80.2, 79.3, 74.7, 35.3, 35.1, 34.7, 32.3 (2C), 29.7 (2C), 29.3 (2C), 20.6, 20.5. ESI-MS: *m/z* 775 (M^++H).

4.1.2. Preparation of chiral salen molybdenum complexes. Under argon atmosphere, salen ligand (50 mg, 0.1 mmol) was dissolved in anhydrous alcohol (5 mL), followed by adding $MoO_2(acac)_2$ (26 mg, 0.1 mmol). The resulting mixture was refluxed for 0.5 h and then was cooled to room temperature. Precipitate was observed when water was added to the reaction mixture. After filtration, the solid was purified by flash chromatography (eluent: $CHCl_3$/hexane 1:1) to give red solid in 86% yield.

MoO_2 (salen). Mp 193–195 °C. $[\alpha]_D^{25}$ −40.6° (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{38}H_{42}N_2O_4Mo$: C, 66.47; H, 6.16; N, 4.08. Found: C, 66.63; H, 6.25; N, 3.84%. IR (KBr,

cm^{-1}): ν (Mo=O) 881, 916. ^1H NMR 7.97 (s, 1H), 7.84 (s, 1H), 7.47–7.53 (m, 5H), 7.41 (s, 1H), 7.38 (s, 1H), 7.25–7.27 (m, 5H), 6.84 (s, 1H), 6.80 (s, 1H), 6.12 (d, $J=4.7$ Hz, 1H), 4.70 (d, $J=5.5$ Hz, 1H), 2.27 (s, 3H), 2.16 (s, 3H), 1.48 (s, 9H), 1.21 (s, 9H). ^{13}C NMR 167.6, 165.7, 161.7, 155.9, 140.0, 139.3, 138.5, 132.7, 131.4, 127.8 (2C), 127.5 (2C), 126.3 (2C), 125.9 (2C), 120.4, 119.3, 116.4, 79.4, 78.5, 73.8, 34.3, 34.0, 33.4, 31.7 (2C), 28.8 (2C), 28.2 (2C), 19.3, 19.1. ESI-MS: m/z 689 ($M^+ + H$).

4.1.3. Asymmetric epoxidation of *cis*-1-propenylphosphonic acid. *cis*-1-Propenylphosphonic acid (25 mg, 0.2 mmol) dissolved in C_2H_5OH or CH_2Cl_2 (10 mL) was added racemic α-phenylethylamine (25 μL, 0.2 mmol) to neutralize the acid. Then catalyst (0.01 mmol) was added to the mixture. After the addition of H_2O_2 (0.105 mL, 1.0 mmol, 30% aqueous), the reaction mixture was stirred for up to 72 h at 0 °C, 24 h at 25 °C or 1 h at 50 °C, respectively. The solvent was removed followed by the addition of water in order to dissolve the epoxide. The mixture was filtered and the filtrate was dried to give the product **2**.

Compound **2**. Mp 83–85 °C. $[\alpha]_D^{25}$ −38.4° (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}NO_4P$: C, 50.96; H, 7.00; N, 5.40. Found: C, 51.05; H, 7.12; N, 5.29%. IR (KBr, cm^{-1}): ν 3168, 2975, 2944, 2848, 2750, 1630, 1537, 1157, 1053, 914, 848, 702, 565. ^1H NMR 7.21–7.16 (d, $J=9.6$ Hz, 1H), 4.30–4.23 (m, 1H), 3.09–3.04 (m, 1H), 2.72–2.63 (dd, $J_1=3.3$ Hz, $J_2=14.7$ Hz, 1H), 1.38–1.36 (d, $J=4.3$ Hz, 3H), 0.92–0.87 (d, $J=5.5$ Hz, 1H). ^{13}C NMR 137.9, 129.3 (2C), 129.2, 126.6 (2C), 54.4, 51.7, 51.0, 19.4, 13.4. ESI-MS: m/z 260 ($M^+ + H$).

4.1.4. Synthesis of the dimethyl ester of fosfomycin. The crude product **2** (25.6 mg, 0.1 mmol) was dissolved in water followed by the addition of KOH (11.2 mg, 0.2 mmol). After stirring for 10 min, CH_2Cl_2 was added. The mixture was separated and the water layer was evaporated to obtained white solid. The solid was then dissolved in CH_3OH (5 mL). Upon the addition of methyl sulphoacid (19.5 mg, 0.2 mmol), much precipitate was produced. Under tempestuously stir, diazomethane in ether was added to the mixture until the yellow color was not disappeared. The precipitate was filtered off and the filtrate was concentrated to give a yellow oil. The crude dimethyl ester was then purified by flash chromatography. ($CHCl_3$/C_2H_5OH 35:1) to obtain colorless oil.

Compound **3**. Anal. Calcd for $C_5H_{11}O_4P$: C, 36.15; H, 6.67. Found: C, 36.27; H, 6.53%. IR (KBr, cm^{-1}): ν 3475, 2960, 1413, 1248, 1034, 834, 786, 562. ^1H NMR 4.00–3.98 (d, $J=5.5$ Hz, 3H), 3.94–3.92 (d, $J=5.4$ Hz, 3H), 3.49–3.36 (m, 1H), 3.17–3.15 (d, $J=6.8$ Hz, 1H), 3.04–3.01 (d, $J=6.8$ Hz, 1H), 1.72–1.70 (d, $J=8.3$ Hz, 3H). ^{13}C NMR 53.2, 52.7, 50.6, 47.8, 13.9. ESI-MS: m/z 167 ($M^+ + H$).

4.1.5. Determination of the ee value of the products. The pure dimethyl ester of fosfomycin **3** (10 mg, 0.06 mmol) was dissolved in $CDCl_3$ (0.5 mL) followed by adding optically active shift reagent $Eu(tfc)_3$ (5.38 mg, 0.006 mmol). The chemical shifts of CH_3O– in levo and dextral dimethyl ester of fosfomycin were different in ^1H NMR and the ee value was determined by calibration.

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Efficient electrocatalytic intramolecular anion radical cyclobutanation reactions

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Abstract—Electrochemically initiated, intramolecular anion radical cyclobutanations of bis(enones) and related substrates are presented. The formation of novel anion radical Diels–Alder adducts in minor amounts is also observed. Total yields of pericyclic products, which include both *cis*- and *trans*-cyclobutanes and a single Diels–Alder adduct, are generally high (51–88%), with electrocatalytic factors in the range of 1.5–5. Mechanistically, strong evidence for the intervention of distonic anion radical intermediates as precursors of both types of pericyclic products is presented. The scope and limitations of these reactions are rather extensively explored and defined, and in particular the tendency, in some cases, for electrogenerated base-catalyzed reactions to compete with these anion radical pericyclic reactions.

1. Introduction

Cyclobutanation reactions of the cation radicals of alkenes with neutral alkenes have by now become rather commonplace and are characterized by impressively high cycloaddition rates and low activation barriers, especially in comparison to the corresponding thermal reactions.[1,2] There have been some recent indications that this extensive body of cation radical cyclobutanation chemistry may have a close counterpart in the domain of anion radical chemistry. Specifically, the reduction of phenyl vinyl sulfone under electrochemical conditions (mercury pool cathode) has been reported to yield *trans*-1,2-bis(phenylsulfonyl)cyclobutane.[3] Subsequently, the cyclodimerizations of a variety vinylpyridines and vinylquinolines under similar conditions have also been established.[4] Still more recently, a few intramolecular anion radical cyclobutanations of tethered bis(enones) have been described from these laboratories.[5,6] These anion radical reactions are of special interest because they represent rare examples of intramolecular anion radical cycloaddition, rather than the more common electrohydrocyclization/dimerization (EHC or EHD).[7,8]

The environmentally benign nature of these electrochemical conversions, inherent in the simplified workup and the consumption of electricity as the sole reagent (in catalytic amounts), further add to their experimental appeal and potential utility. The present paper reports the development of substantially more efficient conditions than those previously reported for carrying out these electrocatalytic intramolecular cycloaddition reactions in high yields, and further extends the scope and defines the limitations of these reactions. In particular, the use of tetraalkylammonium tetrafluoroborates as electrolytes in acetonitrile solution is developed as a particularly efficient method for these cyclobutanations. From a mechanistic viewpoint, experiments are described which strongly support the formulation of the cycloaddition reaction as proceeding in a stepwise fashion, via a distonic anion radical intermediate. Other new mechanistic and theoretical aspects of the reaction are clarified, including the requirement of at least one aroyl group, and the preference for two aroyl moieties.

2. Results and discussion

2.1. Electrolysis of 1a

The cyclobutanations of substrates **1a** and **1g** (Scheme 1) have previously been reported from these laboratories. Using lithium perchlorate (0.1 M) as the electrolyte, the reaction of **1a** was found to afford a total yield of pericyclic products (**2**, **3**) of just 45%, and the ratio of *trans*-**2**/*cis*-**2**/**3** was found to be 2.4:2.0:1. The total yield of pericyclic products obtained from **1g** was even smaller (35%).[5] Consequently, various electrolytes (and other procedural changes) were investigated in the present work in order to determine whether synthetically useful procedures might be developed for carrying out these novel reactions.

Keywords: Anion radical; Cyclobutanation; Catalytic; Electrochemical reduction; Pericyclic; Electrogenerated base.
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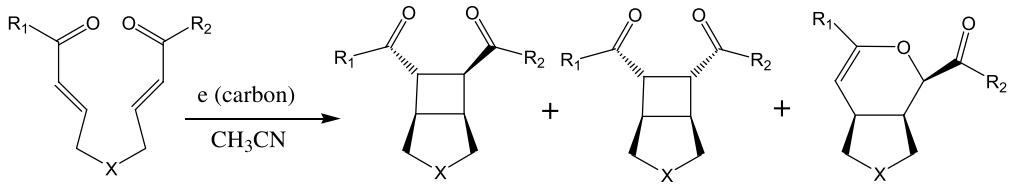


	X	$R_1 = R_2$		X	R_1	R_2
1a	CH_2	Ph	**1f**	CH_2	4-Ph-Ph	4-Ph-Ph
1b	O	Ph	**1g**	CH_2	Ph	CH_3
1c	CH_2	4-Cl-Ph	**1h**	CH_2	CH_3	CH_3
1d	CH_2	3,4-Cl_2-Ph	**1i**	CH_2	Ph	OEt
1e	CH_2	2-Naphthyl	**1j**	CH_2	OEt	OEt

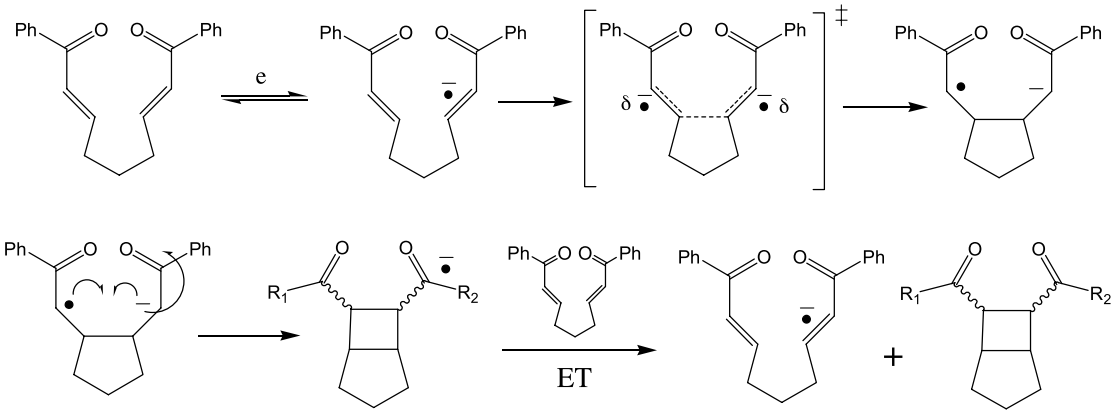
Scheme 1. Pericyclic products in the electrocatalytic, intramolecular anion radical cyclobutanation reactions of various bis(enones).

2.1.1. The anion radical mechanism. The anion radical chain cycloaddition mechanism proposed for these reactions is rather novel and is summarized in Scheme 2. According to this mechanism, reduction of the substrate at the cathode leads to a substrate anion radical, which then cyclizes to a distonic anion radical intermediate. This intermediate cyclizes to the anion radical of the cyclobutane product. The anion radical moiety presumably resides upon one of the benzoyl groups. Finally, exergonic electron transfer (ET) from the product anion radical to a molecule of the neutral substrate occurs, setting up the chain process and affording the neutral cyclobutane product. The distonic anion radical intermediate can also cyclize to a Diels–Alder adduct anion radical, where the anion radical moiety again resides upon a benzoyl moiety.

2.1.2. Tetraalkylammonium tetrafluoroborate electrolytes. The use of tetraalkylammonium tetrafluoroborates as electrolytes was explored on the assumption that ion pairing to the tetraalkylammonium cation should be much looser than with the lithium ion, resulting in a possible increase in reactivity of the anion radical intermediates. In fact, in the case of **1a**, a dramatic increase in yield to 88% was observed under these conditions. As will be noted in Table 1, the yield of the *trans* cyclobutane product (*trans*-**2**) is elevated to 59%. Since the *cis* isomer (obtained in 17% yield) is readily isomerized to the *trans* isomer under acidic or basic conditions, this reaction sequence makes the *trans* isomer available in an overall 71% yield. The novel Diels–Alder product (**3**), obtained in 13% yield, is also of inherent interest in that it represents the first documented instance of an anion radical Diels–Alder reaction. Since complete conversion of **1a** to products is accomplished after a maximum[9] of 21% of the theoretical charge had flowed, the reaction is mildly electrocatalytic, with a catalytic factor of 4.7 (representing a 0.21 F mol^{-1} process).

2.2. Electrolysis of 1b

2.2.1. Effect of electrogenerated bases. The extension of this chemistry to the ethereal substrate **1b** was investigated next. Under conditions similar to the earlier work (using lithium perchlorate as the electrolyte)[5] a total yield of 43% of pericyclic products was isolated, with *trans*-**2b** being the major product. Under both the present and former conditions the catalytic factor was <3. When tetrabutylammonium tetrafluoroborate was used as the electrolyte, pericyclics were isolated in 53% yield. Interestingly, this reaction proceeded somewhat more efficiently in terms of the catalytic factor (10.6) than any of the other reactions, but the yield of pericyclic products was diminished in comparison to the corresponding reduction of substrate **1a** when using the same electrolyte because of a competing reaction of the substrate (Scheme 3). The formation of **4b** implies a base catalyzed deprotonation of **1b**, followed by a Michael type addition of the conjugate base via the alpha carbon of the extended enolate to the beta carbon of the enone moiety. Formation of this product in the reaction using tetrabutylammonium tetrafluoroborate as the electrolyte, and not with any of the other electrolytes, is in



Scheme 2. Proposed mechanism for the anion radical chain cyclobutanation reaction of 1,7-dibenzoyl-1,6-heptadiene.

Table 1. Yields and catalytic factors for the electrocatalytic intramolecular anion radical pericyclic reactions of various bis(enone) substrates (**1**)

Substrate	Procedure[a]	Yield of *trans*-**2**	Yield of *cis*-**2**	Yield of **3**	Total pericyclic yield	Other products	Catalytic factor
1a	A	59%	17%	13%	88%	—	4.7
1b	A	39	11	3	53	**4b**; 11%	10.6
1b	B	21	20	2.0	43	—	1.6
1b	C	21	39	28	88	—	1.8
1c	A	52	11	12	75	**5c**; 5%	5.1
1d	B+C	7	33	16	56	**6d**; 6%	1.3
1d	D	3	0	0	3	**5d**; 17%[b]	7.3
1e	A	29	14	8	51	**5e**; 17%	5.2
1f	C	7	21	25	53	**5f**; 13%, **7f**; 7%	1.9
1f	A	12	0	0	12	**5f**; 17%	1.4
1g	C	0	9	0	9	**7g**; 30%[c]	<1
1g	D	19[d]	0	0	19	—	1.8
1i	B	32[e]	0	0	32	—	<1
1j	D	0	0	0	0	**5j**; 42%	4.5

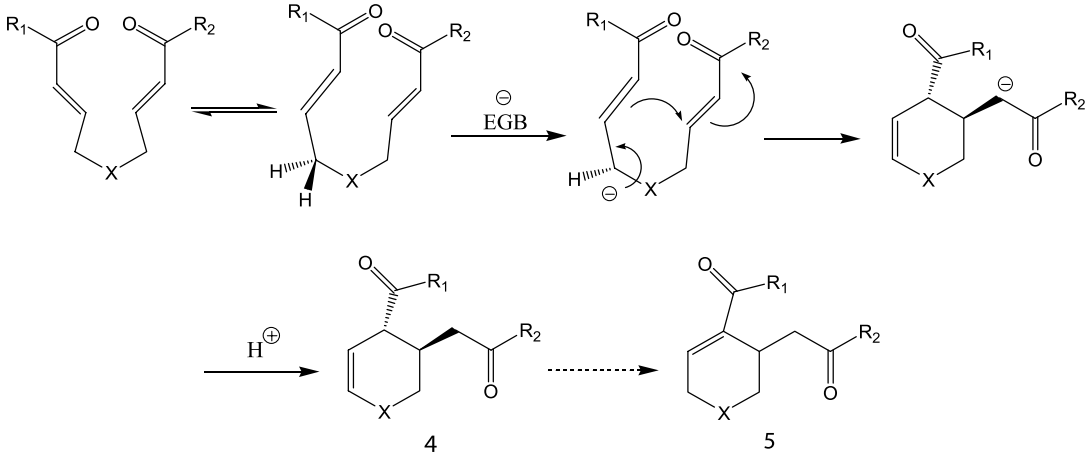
[a] The electrolytes used in the respective procedures were: A=0.1 M tetrabutylammonium tetrafluoroborate; B=0.1 M lithium perchlorate; C=0.1 M magnesium perchlorate; D=0.1 M tetraethylammonium tetrafluoroborate.
[b] Also obtained 35% of an unidentified polymer.
[c] Two isomers.
[d] Both *trans* isomers were observed: 12 and 7% (~2:1 ratio), X-ray of major isomer provided.
[e] Both *trans* isomers were observed: 28 and 4% (7:1 ratio).

agreement with the postulate that the intermediate anionic species are less tightly ion paired under these conditions, and are therefore substantially more reactive (basic). Since a product analogous to **4b** was not observed in the electrochemical reaction of **1a**, it is apparent that the substitution of oxygen for carbon tends to acidify the adjacent C–H bond. A similar competition has been reported in the EHC of butenolides.[10] In the case of substrate **1b**, a product corresponding to the isomerization of the double bond, into conjugation with the carbonyl group, was not observed. However, in several other instances products corresponding to such a structure, **5**,[11] were obtained instead of **4**. The nature of the electrogenerated base (EGB)[12,13] species responsible for the deprotonation is unknown, but likely candidates might be a substrate or product anion radical or a dianionic intermediate produced by further reduction of the proposed distonic anion radical intermediate.

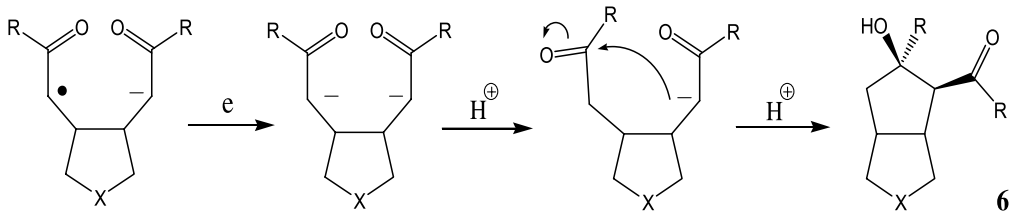
2.2.2. Use of $Mg(ClO_4)_2$ electrolyte. Although the use of tetraalkylammonium tetrafluoroborates as the electrolyte appears to be the more general method of choice for carrying out most of these anion radical cycloadditions with optimal efficiency, in the specific case of **1b** the competing reaction described above tended to lower the yields of the pericyclic products. In view of that, it appeared worthwhile to investigate the effect of using a more strongly ion-pairing counterion than even the lithium ion, that is, the magnesium ion. When the electrochemical reaction was carried out in the presence of magnesium perchlorate as the electrolyte, an 88% yield of pericyclic products was obtained. The increase in the *cis*/*trans* ratio in the cyclobutane product may also reflect the stronger ion pairing between the magnesium ion and the anion radical moiety in the transition state for the final cyclization step (vide infra).

2.3. Electrolysis of 1c

It had been found in the previously reported work[5] that the introduction of electron donating substituents, such as 4-methoxy, onto the aryl ring of **1a** sharply inhibits cyclobutanation. It is presumed that this is the result, at least in part, of the inability of the distonic anion radical intermediate to cyclize to the product cyclobutane anion radical, which would require the anion radical moiety to



Scheme 3. The electrogenerated base (EGB) catalyzed products (**4** and **5**) obtained in the electrochemical reduction of substrates **1**, in the presence of tetraalkylammonium tetrafluoroborate as the electrolyte.



Scheme 4. Formation of an aldol-type side product (**6**), via reduction of the distonic anion radical to an enolate dianion.

reside in a higher energy SOMO (that of a 4-methoxybenzoyl moiety) than in the case of the unsubstituted substrate. Consequently, the facility of bis(enone) anion radical cyclobutanation of substrates that would provide a lower energy product anion radical SOMO was investigated. Substrate **1c**, which has electron withdrawing 4-chloro substituents on both of its benzoyl groups, was found to undergo smooth anion radical cycloaddition under the tetrabutylammonium tetrafluoroborate electrolyte conditions, affording a 75% yield of total pericyclics, of which 52% was the *trans* cyclobutane. It is of special interest that the chlorine substituent is retained in the product, even though the 4-chlorobenzoyl anion radical moiety was potentially susceptible to chloride ion loss. Presumably, electron transfer from the product anion radical to substrate is sufficiently rapid as to suppress the potential loss of chloride ion.

2.4. Electrolysis of 1d

The introduction of an even more strongly electron withdrawing *meta* chloro substituent into the substrate, in addition to the *para* chloro substituent, as in substrate **1d** would be expected to accelerate the rate of the second cyclization step even further by providing a lower energy SOMO for the product anion radical. However, the considerably increased stabilization of the substrate anion radical, and the expected shift in electron density in the SOMO from the alkene moiety to the now rather strongly electron-deficient aroyl ring could also be expected to have an adverse effect upon the rate of the first cyclization step. In accord with the latter idea, when **1d** is electrolytically reduced in the presence of the tetraethylammonium tetrafluoroborate electrolyte, the yield of pericyclic products falls precipitously to 3%, the main products consisting of a 17% yield of a base-catalyzed cyclization/isomerization product (**5d**) and an uncharacterized polymer (35%). However, in the presence of a mixed lithium perchlorate/magnesium perchlorate electrolyte, the desired pericyclic reactions are observed to occur with moderate efficiency, but the yields of the pericyclic products are lower than in the case of **1c**, and an aldol-type product (**6d**) is also formed. This latter product is considered to result from reduction of the intermediate distonic anion radical to a dianion, which subsequently is protonated and undergoes cyclization (Scheme 4).

2.5. Electrolysis of 1e

The replacement of the phenyl group with a β-naphthyl or 4-biphenylyl group could also provide a more suitable venue for the stabilization of the anion radical of the product than in the case of **1a**, but again the lowering of the SOMO energy and the shifting of the SOMO density toward the aroyl moiety could retard the first cyclization step. The cyclobutanation of substrate **1e** (which has β-naphthyl substituents), using tetrabutylammonium tetrafluoroborate as the electrolyte, was found to proceed, albeit in moderate yield (51%), suggesting that the predominant effect of the increased delocalization provided by the naphthyl group is the lowering of the SOMO energy and the shift in density away from the alkene linkage. However, the retardation of the cyclization is evidently much less than in the case of the dichloro substrate **1d**. As in this latter case, the base-catalyzed cyclization/isomerization product **5e** was also formed (17%; Table 2). It is worth noting that when the reaction is not run to completion (~80% complete), the yield of pericyclic products is relatively unchanged, but the amount of the base catalyzed product is greatly reduced. This may well be indicative of a build up of electrogenerated bases within the solution, accelerating the cyclization to **5** in the latter stages of the reaction. This build up of base could also provide an explanation for the increase in the *trans*/*cis* ratio observed in the more complete reaction (vide infra).

2.6. Electrolysis of 1f

Substrate **1f**, which contains 4-biphenylyl moieties, responds in a manner rather similar to that of **1d**. Limited *trans*-**2f** formation is observed, along with greater formation of the base-catalyzed cyclization/isomerization product **5f** (tetraalkylammonium electrolyte). However the use of $Mg(ClO_4)_2$ afforded a moderate pericyclic yield of 53%. Substrate **1f** has limited solubility in acetonitrile, so that these reductions were carried out in 1:1 THF/acetonitrile solutions.

Table 2. The effect of the extent of reaction upon the yields of anion radical and base-catalyzed products

Substrate[a]	Yield of *trans*-**2**	Yield of *cis*-**2**	Yield of **3**	Total pericyclic yield	Other products	Catalytic factor
1e	29	14	8	51	**5e**; 17%	5.2
1e[b]	17	21	10	48	**5e**; 6%	5.4

[a] The electrolyte was 0.1 M tetrabutylammonium tetrafluoroborate.
[b] Reaction run to 79% completion (based upon recovered **1e**), yields and catalytic factor are corrected for **1e** recovery.

2.7. SOMO requirements for cyclization

2.7.1. Electrolysis of 1g and 1h. In contrast to the aroyl groups considered above, acetyl groups provide a much less extensively delocalized, higher energy SOMO for the product cyclobutane or Diels–Alder anion radical. The potential anion radical pericyclic chemistry of substrate **1h**, which has two acetyl substitutents, was therefore not expected to be as efficient as when aroyl groups are present. In accord with this supposition, no pericyclic products at all could be detected in the electroreduction of this substrate.

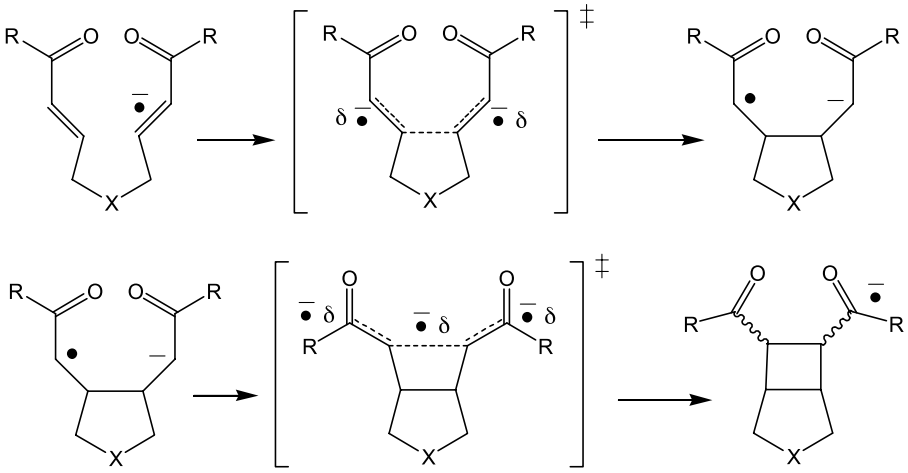
However, since the anion radical of the pericyclic products only requires (and perhaps can only utilize) a single aroyl moiety, it was considered likely that pericyclic chemistry might occur with unsymmetrical substrate **1g**, which has one benzoyl and one acetyl substituent. The previously reported results, using lithium perchlorate as an electrolyte, have already confirmed this conjecture, but further experiments were carried out in the present work in connection with magnesium perchlorate and tetraethylammonium tetrafluoroborate as the electrolytes. The observed yields in both cases are quite modest. However, an additional feature of interest emerges when tetraethylammonium tetrafluoroborate is used as the electrolyte, namely, that both possible *trans*-**2g** isomers are formed, in a 2:1 ratio, with the major cyclobutane having the benzoyl group *syn* to the cyclopentane ring.

2.7.2. Electrolysis of 1i. The reduction of **1i**, which has one benzoyl and one carboethoxy substituent, provides a still further example of the relative inefficiency of pericyclic chemistry when only a single benzoyl group is present. When electrolyzed in the presence of lithium perchlorate, **1i** provides a 32% yield of two isomers of *trans*-**2i**. The major isomer appears, on the basis of NMR comparisons, to be structurally analogous to the major *trans*-**2g** isomer obtained from **1g**. This reduction is unusual in that it is not catalytic. An intriguing possible interpretation of this data is that while benzoyl reduction is occurring readily and reversibly, the initial cyclization step is sharply retarded by the ineffectiveness of the ester function at delocalizing and stabilizing the SOMO in the transition state. This could require cyclization to occur via the rarer reduction of the unsaturated ester function. This higher energy anion radical could then rapidly cyclize to the reactive benzoyl ene function. The key factor here is that catalysis would necessarily involve electron transfer from a product anion radical to a substrate molecule, and this chemical electron transfer undoubtedly is highly selective for formation of the more stable, and apparently unreactive, anion radical corresponding to the benzoyl enone function. Additionally, this chemical electron transfer is likely to be irreversible in nature, halting catalysis. The chemically reduced substrate may prove reactive in non-cyclobutanation mechanisms, which may account for the observed low yield.

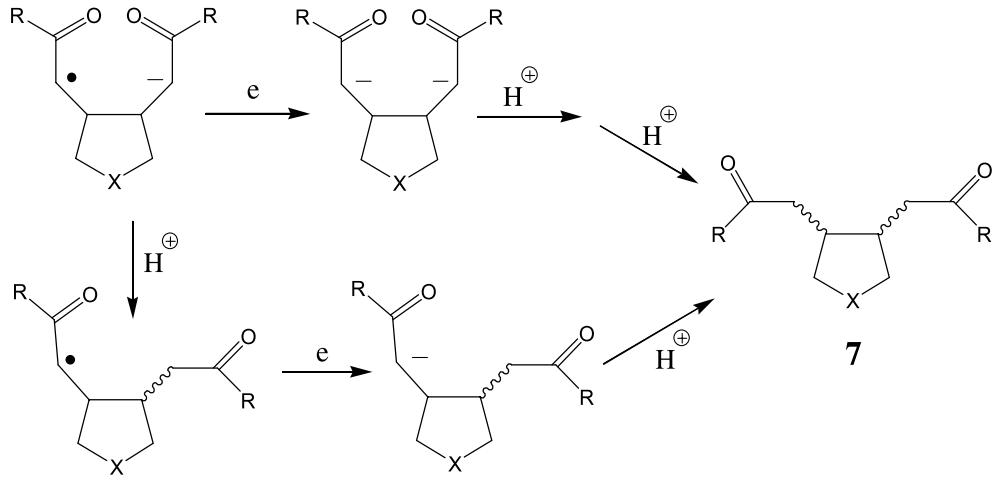
2.7.3. Diminished cyclization rates. Since the desired pericylic reaction products provide the required low energy SOMO associated with an aroyl function (in this case, benzoyl), and the starting substrate provides a readily reducible aroyl enone function, it appears likely that the lower efficiency of the desired pericyclic chemistry in the substrates which contain only a single aroyl function must arise from diminished cyclization rates in either one or both of the cyclization steps. It therefore seems reasonable to propose that, in the transition states for both cyclization steps, the SOMO is at least partially delocalized over both enone moieties, as indicated in Scheme 5. The delocalization is presumably greatest, and the SOMO energy the lowest, when both keto functions are of the aroyl type.

2.8. Evidence for the distonic anion radical intermediate

In most cases the electrolyte systems (lithium/magnesium perchlorate or tetraalkylammonium tetrafluoroborate) lead to the formation of a mixture of the *cis* and *trans* cyclobutane isomers. At the earliest point of the electrochemical reactions at which these products could be detected, the *trans* cyclobutane was always formed in modest excess over the *cis* isomer. As the reaction progressed further toward completion, the *trans*/*cis* ratio progressively increased. The values given in Table 1 correspond to reactions run essentially to completion. This progressive change in the *trans*/*cis* ratio suggested the possibility that a portion of the *cis* isomer was being isomerized to the more stable *trans* isomer in the course of the reaction. Although a base-catalyzed isomerization was



Scheme 5. Proposed delocalization of the SOMO over both carbonyl groups in the transition states for both cyclization steps.



Scheme 6. Mechanism of formation of **7**, via protonation of distonic intermediate.

formally a possibility, it also appeared possible that anion radicals of the *cis*-cyclobutane were being reformed during the reaction and subsequently reverting to the distonic anion radical, which could once again cyclize to give either cyclobutane isomer or the Diels–Alder adduct. A distinction between these two mechanistic possibilities is therefore possible, based upon the predicted formation of small amounts of the Diels–Alder adduct in the latter mechanism. To test this possibility, isomers of **2b** were isolated and used in electrolysis reactions with lithium perchlorate as the electrolyte. A quantity of *cis*-**2b** was reduced in isolation, leading to the formation of *trans*-**2b** (32%), **3b** (7%), an aldol product **6b** (11%), a dihydrocyclopentane product **7b** (20%; see Scheme 6), with a further 18% of unreacted *cis*-**2b**. The attempted reduction of *trans*-**2b**, as expected, failed to lead to any reaction. A degree of reactivity was seen under extreme conditions (very negative potentials, large amounts of charge). Although some *trans*-**2b** was still returned, no other known products were obtained. This clearly indicates that, while the *trans* isomer is stable toward continued reduction at normal potentials, the *cis* isomer readily reverts to the proposed distonic intermediate. This not only allows for the formation of the *trans* and Diels–Alder products, but also of **7b**, which represents protonation after the first cyclization, effectively 'trapping' the distonic anion. In further accord with the postulate of *cis–trans* isomerization via regeneration of the distonic anion radical intermediate is the previously discussed absence of any base-catalyzed products (e.g., **4** and **5**) in any perchlorate reaction system. Since the distonic anion radical intermediate is evidently involved in the reversal of the cycloaddition, an application of the law of microscopic reversibility strongly suggests that the forward reaction also involves the same distonic intermediate.

2.9. Trapping of the distonic anion radical intermediate/inhibition of EGB pathway

It was thought that addition of a slight excess of a weak acid would not only inhibit EGB pathways but would also trap (protonate) the proposed distonic anion radical. Indeed this was realized with a 1.6 M excess of acetic acid placed in the solution from the beginning of electrolysis. The naphthoyl substrate **1e** was chosen as it leads to modest base-catalyzed product formation (17% of **5e**). The expected trapping is clearly the dominant mechanism, represented by both **6e** and **7e** formation (Table 3). The expected reduction in base-catalysis (product **5e**) is also seen, down to just 3%. Also, by limiting the excess of acetic acid, we were still able to obtain small amounts of our primary cyclobutanation product (*trans*-**2e**), although formation of *cis*-**2e** and **3e** were reduced to levels below detection. The proposed mechanism for the formation of **7** is given in Scheme 6.

2.10. Mediated electrolysis

The possibility of developing a mediated electrochemical reduction method was also probed. The strategy adopted was to provide a mediator which is (in the ideal case, selectively) reduced at a less negative potential than the substrate, and which forms a relatively long-lived anion radical capable of mildly endergonic electron transfer to the substrate molecules.[14–16] This strategy should provide for a low substrate anion radical concentration, which could minimize anion radical to anion radical coupling as well as over-reduction of the substrate (dianion formation). Initial attempts utilized **1b** as the substrate and magnesium or lithium perchlorate as the electrolyte. Benzil (diphenyl diketone), dypnone (*E*-3-phenyl-2-butenoylbenzene), and benzophenone were investigated as mediators, but all three

Table 3. Effect of a weak acid in solution during electrolysis of **1e**

Additive	% Yield of *trans*-**2e**	% Yield of *cis*-**2e**	% Yield of **3e**	% Yield of **5e**	% Yield of **6e**	% Yield of **7e**	% Yield of products
None	29	14	8	17	0	0	68
1.6 M excess of acetic acid	6	0	0	3	14	38	61

Table 4. Anion radical versus base-catalyzed reactions in the mediated electrolysis of **1c**

Mediator	% Yield of *trans*-**2c**	% Yield of *cis*-**2c**	% Yield of **3c**	% Yield of **5c**
None	52	11	12	5
Benzophenone	42	11	7	13
Benzil	0	0	0	28[a]

[a] Along with 42% unidentified polymer.

proved to be ineffective. Mediator reduction did occur at less negative potentials (as evidenced by a temporary solution color change) than that of the substrate, but products did not form until the potential was reduced to the usual value for reduction of the substrate.

Further studies were directed toward the use of tetraethylammonium tetrafluoroborate as the electrolyte, this time using **1c** as the substrate. Although these conditions failed to provide an increase in yield of pericyclic products, they did provide important insights into the interplay between anion radical cyclization and electrogenerated base catalysis (Table 4). Benzophenone reduction was found to occur at nearly the same potential as for **1c**, when benzil reduction occurred at a much less negative potential. In the case of benzil, this occurred at a potential that did not lead to substrate reduction, so no pericyclic products were formed. On the other hand, in the absence of a mediator, base-catalyzed products (such as **5c**) were formed in a low yield. When benzophenone was employed as the mediator, both types of products were formed, indicating that both the substrate and mediator are being reduced at the cathode. Apparently, anion radical cyclobutanation occurs only when the substrate is reduced, and reduction of the mediator leads essentially only to the base-catalyzed reaction. These observations indicate that the desired mildly endergonic electron transfer is too slow to compete with the base-catalyzed reactions.

2.11. Efficient base-catalyzed reactions

The observations noted above immediately suggested the possibility of employing an excess of benzil to engender a highly catalytic method for selectively and efficiently forming the base-catalyzed product. This possibility was realized in the case of the electrochemical reduction of **1b** in the presence of a relatively large excess of benzil, which gave only **4b**, in 68% yield. The catalytic factor here was rather modest at 2.8, although low concentrations of starting material and a large excess of benzil made judging the end of the reaction difficult. Comparison of this result with that obtained for **1c** (with benzil) suggests that the use of mediators to engender these base-catalyzed cyclizations may prove problematic, due to competition with polymerization. The efficiency seen with formation of **4b** may be engendered by the greater acidity of the protons (alpha to the bridging oxygen) in **1b**.

3. Conclusions

The present paper reports the development of conditions for carrying out electrochemically initiated, intramolecular anion radical cyclobutanations of bis(enones) and related substrates in high yields and with substantially less than the theoretical consumption of electricity (i.e., electrocatalytically). The solvent/electrolyte combination acetonitrile/tetraalkylammonium tetrafluoroborate is found to be an especially effective one for producing high yields and large catalytic factors. The formation of novel anion radical Diels–Alder adducts in minor amounts is also verified. The scope and limitations of these reactions are rather extensively explored and defined. In particular, the reactions have been found to have an absolute requirement for at least one aroyl ketone moiety and a significant preference for both ketonic moieties to be of the aroyl type. Theoretical rationales for these requirements and preferences are presented. Strongly electron-withdrawing substituents (upon the aroyl moiety) tend to decrease reaction efficiency by diminishing the rate of the first cyclization step, such that a competition between anion radical mediated and electrogenerated base-catalyzed reactions is observed. Evidence for a stepwise (as opposed to concerted) cycloaddition mechanism involving a distonic anion radical intermediate is presented, and the distonic anion intermediate has been trapped.

4. Experimental

4.1. General electrolysis procedure

A typical experiment utilizes 100 mg of a given bis(enone) substrate, which equates to 0.329 mmol for substrate **1a**. The substrate is dissolved in 22 mL of electrolyte solution, giving a typical substrate concentration of 0.0150 M, and added to the working electrode (WE) compartment of the electrolysis cell. The electrolyte solution is 0.100 M (unless stated) in either alkylammonium or perchlorate salt (detailed below) in dry acetonitrile (unless stated). The acetonitrile is distilled fresh for each electrolysis from a reservoir containing phosphorus pentoxide. Electrolyte solution (6 mL) is added to the counter electrode (CE) compartment.

Electrolysis of the substrate was carried out at specific voltages (detailed below) with stirring under positive nitrogen flow at room temperature. The voltage is commonly increased through the course of an electrolysis to help maintain the current (tracked by coulometer). This increase is detailed in the description of each electrolysis. Electrolysis voltages were versus a 'pseudo-standard' silver wire (encased in porous vycor glass) reference electrode (RE).[17] The RE used is seen to have a calibration to SCE of approximately $+0.1$ V, when in 0.1 M Et_4NBF_4 acetonitrile solution. The CE and WE consisted of reticulated vitreous carbon (25 mm$\times$5 mm$\times$5 mm), their corresponding compartments separated by a course frit. The RE was placed within 0.5 cm of the WE. The reaction was stopped when thin-layer chromatography (TLC) indicated that the starting

material had been consumed. The reactant solution (WE compartment only) then underwent an aqueous workup with sequential benzene washings (alkyl ammonium salt) or dichloromethane (perchlorate salt). The organic phase was retained and dried with Na_2SO_4. The benzene/dichloromethane was removed by rotary evaporation, with the crude solution being purified by preparative TLC (1 mm thick, elution with ethyl acetate/petroleum ether mixture, 1:9 ratio, unless stated). Bands were identified, collected by scraping, and extracted with dichloromethane. Filtering removed the silica, with a rotary evaporator again employed to remove the solvent, yielding the desired products.

Notes. In cases when starting material is recovered, the yields of products and the catalytic factors are corrected accordingly. Characterization of products is in most cases completed by comparison to the products obtained from **1b** electrolysis, and to results previously published (as referenced). The products from **1b** are more fully characterized both by 500 MHz NMR ($^1H/^{13}C$) and HRMS. Their ready crystallization also allowed for X-ray structural determination (provided previously[6]). All novel products are also characterized by HRMS or, in two cases, by X-ray crystallography.

4.2. Analysis

Room temperature ^1H NMR spectra were recorded on a Varian Unity+300 as solutions in $CDCl_3$. ^{13}C NMR and COSY spectra were recorded on a Varian Unity Inova 500 spectrometer. Chemical shifts (δ) are relative to tetramethylsilane, and coupling constants (J) are given in Hertz (Hz). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad. X-ray diffraction analyses were conducted using a Nonius Kappa CCD diffractometer. Low-resolution mass spectra (LRMS) were recorded on a Finnigan MAT TSQ-70 mass spectrometer, with high-resolution mass spectra (HRMS) recorded on a VGZAB-2E mass spectrometer.

4.3. Equipment/reagents

A potentiostatic controller, the Electrosynthesis Company (ESC) model 415, was used to control the applied potential. The charge used was tracked by a digital coulometer, ESC model 640. The applied potential was confirmed using a digital multimeter (Wavetek DM7), operating as a potentiometer. The electrode material was Duocel 80 PPI reticulated vitreous carbon. The substrates were kindly produced within the Krische group or by Dr. Jingkui Yang.[5,6] Reagent purity was assayed by NMR/LRMS. Electrolytes were used as purchased, from Alfa Aesar (98% purity).

4.4. Electrolysis of *E,E*-1,7-dibenzoyl-1,6-heptadiene (1a)

Electrolysis of 111 mg (0.0166 M) of **1a** with Bu_4NBF_4 electrolyte, at −2.0 V versus RE (first 3.0 C at −1.5 V). The reaction appeared complete after 7.5 C, or 21.3% (of required charge) had passed through the cell. PTLC purification of the 105 mg of recovered crude yielded *cis*-**2a** (19 mg, 17%), *trans*-**2a** (65 mg, 59%), and **3a** (14 mg, 13%) for a total of 98 mg of pericyclic products (88%). No starting material was recovered, and no other products were identified.

4.4.1. Compound *cis*-2a[5,6]. ^1H NMR (300 MHz, $CDCl_3$): 1.65 (2H, m), 1.84 (2H, m), 2.02 (2H, m), 3.20 (2H, br.s), 3.85 (2H, d, J=4.2 Hz), 7.35 (4H, br.t, J=7.2 Hz,), 7.44 (2H, br.t, J=7.2 Hz), 7.75 (2H, br.d, J=8.1 Hz).

4.4.2. Compound *trans*-2a[5,6]. ^1H NMR (300 MHz, $CDCl_3$): 1.42 (2H, m), 1.52 (1H, m), 1.85 (3H, br.m), 3.06 (1H, q, J=6.9 Hz), 3.24 (1H, m), 4.28 (1H, dd, J=6.6, 7.5 Hz), 4.57 (1H, dd, J=7.8, 10.5 Hz), 7.46 (4H, m), 7.55 (2H, m), 7.95 (2H, br.d, J=6.9 Hz), 8.02 (2H, br.d, J=7.2 Hz).

4.4.3. Compound 3a[5,6]. ^1H NMR (300 MHz, $CDCl_3$): 1.60 (2H, m), 1.84 (2H, m), 2.01 (2H, m), 2.69 (2H, m), 4.89 (1H, d, J=6.6 Hz), 5.59 (1H, d, J=3.0 Hz), 7.26 (3H, m), 7.48 (4H, m), 8.08 (2H, d, J=7.5 Hz).

4.5. Electrolysis of *E,E*-1,7-dibenzoyl-4-oxa-1,6-heptadiene (1b)

Electrolysis of 100 mg (0.0149 M) of **1b** with $Mg(ClO_4)_2$ electrolyte, at increasing voltages versus RE. The first 3.0 C at −2.0 V, then 1.8 C at −3.0 V, followed by 1.3 C at −3.5 V, and 6.0 C at −4.0 V. The reaction appeared complete after 12.1 C, or 38.4% (of the required charge) had passed through the cell. PTLC purification (1:4 ratio of EA/PET) of the 156 mg of recovered crude yielded *cis*-**2b** (26 mg, 39%), *trans*-**2b** (14 mg, 21%), and **3b** (19 mg, 28%), giving a total of 59 mg of pericyclic products (88%). While no other products were identified, 33 mg of starting material was recovered. The above percent of required charge is based upon the 100 mg of starting material being used up; this becomes 54.8% based upon the 67 mg of starting material used up (not recovered).

Electrolysis of 205 mg (0.0305 M) of **1b** with $LiClO_4$ electrolyte, at −1.3 V for 40.0 C (62.7% of required charge). PTLC separation of the 170 mg of crude yielded *cis*-**2b** (41 mg, 20%), *trans*-**2b** (42.2 mg, 21%), **3b** (4 mg, 2%), along with 2.8 mg of unreacted **1b**.

Electrolysis of 105 mg (0.0156 M) of **1b** with Bu_4NBF_4 electrolyte, at −1.6 V for 2.1 C and −2.0 V for 0.9 C. This corresponds to 9.4% of required charge. PTLC separation of the 108 mg of crude yielded *cis*-**2b** (12 mg, 11%), *trans*-**2b** (41 mg, 39%), **3b** (3 mg, 3%), and **4b** (11 mg, 11%).

Electrolysis of 28 mg (0.0042 M) of **1b** with Et_4NBF_4 electrolyte, and 157 mg (0.340 M) of benzil, at −1.4 V for 3.2 C. This corresponds to 36.2% of required charge, or a catalytic factor of 2.76. PTLC separation proved problematic due to the large benzil excess, however a yield of 19.1 mg (68%) of **4b** was obtained by NMR integration of several mixed **4b**/benzil PTLC bands. No other products or unreacted starting material were observed.

Electrolysis of 66 mg (0.0098 M) of *cis*-**2b** with $LiClO_4$ electrolyte, at −2.5 V for 27.5 C, −3.0 V for 4.5 C, and then at −3.5 V for a further 30.0 C. PTLC separation of the crude yielded *trans*-**2b** (17.3 mg, 32%), **3b** (4 mg, 7%), an

aldol product **6b** (5.7 mg, 11%), a dihydro product **7b** (11 mg, 20%), with a further 12 mg (18%) of unreacted *cis*-**2b**.

Electrolysis of 52 mg (0.0077 M) of *trans*-**2b** with $LiClO_4$ electrolyte, at −3.0 V for 11 C, −3.5 V for 130 C, and −4.0 V for 20 C. No product spots were observed until after ~40 C, indicating that no reaction was occurring, hence the continued flow of charge. PTLC of the 68 mg of crude yielded 8 mg of impure *trans*-**2b**, along with 19 mg of unidentified product (single benzoyl moiety). None of the characterized products (such as *cis*-**2b**) were observed.

4.5.1. Compound *cis*-2b.[6] ^{1}H NMR (500 MHz, $CDCl_3$): 3.42 (2H, m), 3.63 (2H, d.m, J=10.2 Hz), 4.14 (4H, m), 7.34 (4H, br.t, J=7.6 Hz), 7.45 (2H, br.t, J=7.3 Hz), 7.72 (4H, br.d, J=8.2 Hz); ^{13}C NMR (500 MHz in $CDCl_3$): 39.72, 47.70, 73.46, 127.81, 128.59, 132.8, 136.05, 198.08; NMR COSY (500 MHz), and X-ray crystallography confirm structure;[6] HRMS (CI+): calcd; 307.133420. Found; 307.132575.

4.5.2. Compound *trans*-2b.[6] ^{1}H NMR (500 MHz, $CDCl_3$): 3.36 (3H, br.m), 3.46 (1H, dd, J=4.6, 9.6 Hz), 3.68 (1H, d, J=9.8 Hz), 4.06 (1H, d, J=9.6 Hz), 4.41 (1H, m), 4.53 (1H, m), 7.45 (4H, m), 7.54 (2H, br.m), 7.90 (2H, m), and 8.01 (2H, m); ^{13}C NMR (500 MHz in $CDCl_3$): 39.71, 40.74, 42.99, 43.01, 69.27, 72.55, 128.29, 128.71, 128.76, 128.91, 133.41, 133.43, 135.27, 135.61, 196.70, 199.70; NMR COSY (500 MHz), and X-ray crystallography confirms the structure;[6] HRMS (CI+): calcd; 307.133420. Found; 307.133048.

4.5.3. Compound 3b.[6] ^{1}H NMR (500 MHz, $CDCl_3$): 2.99 (1H, m), 3.06 (1H, m), 3.58 (1H, m), 3.75 (1H, dd, J=4.4, 9.6 Hz), 4.17 (2H, m), 4.98 (1H, d, J=8.6 Hz), 5.58 (1H, d, J=4.2 Hz), 7.26 (2H, m), 7.48 (5H, m), 7.61 (1H, m), 8.08 (2H, m); ^{13}C NMR (500 MHz in $CDCl_3$): 35.54, 36.94, 70.30, 74.03, 76.30, 98.89, 124.65, 128.24, 128.44, 128.62, 129.51, 133.70, 134.44, 135.41, 151.80, 196.01; NMR COSY (500 MHz) and X-ray crystallography confirms the structure;[6] HRMS (CI+): calcd; 307.133420. Found; 307.132957.

4.5.4. Compound 4b. ^{1}H NMR (300 MHz, $CDCl_3$): 3.08 (1H, m), 3.17 (1H, d, J=5.7 Hz), 3.20 (1H, d, J=7.5 Hz), 3.85 (1H, m), 3.98 (1H, dd, J=3.3, 10.8 Hz), 4.23 (1H, dd, J=2.7, 10.8 Hz), 4.72 (1H, td, J<1.5, 6.0 Hz), 6.52 (1H, dd, J=1.8, 6.0 Hz), 7.48 (4H, br.t, J=7.5 Hz), 7.58 (2H, m), 8.00 (4H, m). X-ray crystallography confirms structure (CCDC 240331).

4.5.5. Compound 6b.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.98 (1H, ddd, J=1.5, 8.1, 12.9 Hz), 2.45 (1H, dd, J=8.1, 12.9 Hz), 3.22 (2H, m), 3.64 (2H, dd, J=6.3, 9.0 Hz), 3.85 (2H, t, J=9.9 Hz), 4.12 (1H, d, J=9.6 Hz), 5.35 (1H, d, J=2.1 Hz), 7.14 (1H, m), 7.24 (2H, m), 7.40 (2H, m), 7.52 (2H, m), 7.59 (1H, m), 7.80 (2H, dd, J=1.5, 8.7 Hz).

4.5.6. Compound *cis*-7b. ^{1}H NMR (300 MHz, $CDCl_3$): 3.04 (4H, br.m), 3.16 (2H, dd, J=3.0, 14.1 Hz), 3.60 (2H, dd, J=4.2, 8.7 Hz), 4.12 (2H, m), 7.47 (4H, br.t, J=7.8 Hz), 7.58 (2H, br.t, J=7.8 Hz), 7.94 (4H, m); HRMS (CI+): calcd; 309.149070. Found; 309.149110.

4.6. Electrolysis of *E*,*E*-1,7-bis(4-chlorobenzoyl)-1,6-heptadiene (1c)

Electrolysis of 99 mg (0.012 M) of **1c** with Bu_4NBF_4 electrolyte, at −1.2 V for 2.1 C, −1.6 V for 2.2 C, and −1.8 V for 0.8 C. The reaction appeared complete after 5.0 C, or 19.5% (of required charge) had passed through the cell. PTLC purification of the 124 mg of recovered crude yielded *cis*-**2c** (11 mg, 11%), *trans*-**2c** (51.5 mg, 52%), and **3c** (11.5 mg, 12%), for a total yield of 74 mg of pericyclic products (75%). No starting material was recovered. However, a further 5 mg (5%) of **5c** was recovered.

Electrolysis of 55 mg (0.0067 M) of **1c** with 32 mg (0.0080 M) of benzophenone and Et_4NBF_4 electrolyte, at −1.8 V for 1.5 C (10.5% of required charge). **1c**/benzophenone=1:1.19. PTLC separation yielded *cis*-**2c** (6 mg, 11%), *trans*-**2c** (23 mg, 42%), and **3c** (4 mg, 7%), for a total yield of 33 mg of pericyclic products (60%). A further 7 mg (13%) of **5c** was recovered.

Electrolysis of 99 mg (0.012 M) of **1c** with 165 mg (0.036 M) of benzil and Et_4NBF_4 electrolyte, at −1.3 V for 2.5 C (9.7% of required charge). **1c**/benzil=1:1.2.96. PTLC separation yielded 28 mg (28%) of **5c** along with 42 mg (42%) of an unidentified polymer.

4.6.1. Compound *cis*-2c.[6] ^{1}H NMR (300 MHz, $CDCl_3$) 1.68 (2H, m), 1.82 (2H, dd, J=9.9, 2.4 Hz), 2.00 (2H, m), 3.16 (2H, m), 3.77 (2H, d, J=3.9 Hz), 7.32 (4H, d, J=8.4 Hz), 7.66 (4H, d, J=9.0 Hz); HRMS (CI+): calcd; 373.076210. Found 373.076164.

4.6.2. Compound *trans*-2c.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.38 (2H, m), 1.58 (1H, m), 1.82 (3H, m), 3.04 (1H, dd, J=6.9, 13.2 Hz), 3.22 (1H, m), 4.20 (1H, dd, J=0.9, 7.5 Hz), 4.49 (1H, dd, J=2.4, 10.2 Hz), 7.44 (4H, dd, J=2.7, 8.4 Hz), 7.88 (2H, br. d, J=8.4 Hz), 7.95 (2H, br.d, J=9.0 Hz):); HRMS (CI+): calcd; 373.076210. Found; 373.075821.

4.6.3. Compound 3c.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.41 (1H, m), 1.59 (2H, m), 1.78 (1H, m), 2.01 (2H, m), 2.68 (2H, m), 4.80 (1H, d, J=6.9 Hz), 5.52 (1H, d, J<1.5 Hz), 7.40 (2H, m), 7.47 (4H, m), 8.01 (2H, d, J=8.4 Hz); HRMS (CI+): calcd; 373.076210. Found; 373.076898.

4.6.4. Compound 5c. ^{1}H NMR (300 MHz, $CDCl_3$): 1.64 (1H, m), 1.72 (3H, m), 2.30 (2H, br.m), 2.79 (1H, dd, J=10.2, 14.7 Hz), 3.34 (1H, dd, J=3.6, 14.7 Hz), 3.43 (1H, br.s), 6.61 (1H, td, J=3.9, 1.2 Hz), 7.43 (3H, m), 7.51 (1H, m), 7.62 (2H, m), 7.99 (2H, m); HRMS (CI+): calcd; 373.076210. Found; 373.076307.

4.7. Electrolysis of *E*,*E*-1,7-bis(3,4-dichlorobenzoyl)-1,6-heptadiene (1d)

Electrolysis of 102 mg (0.0105 M) of **1d** with $LiClO_4$ and $Mg(ClO_4)_2$ electrolyte (both 0.10 M), at −4.0 V (first 1.5 C at −3.0 V). The reaction appeared complete after 17.0 C, or

76.3% (of required charge) had passed through the cell. PTLC purification of the 87 mg of recovered crude yielded *cis*-**2d** (34 mg, 33%), *trans*-**2d** (7 mg, 7%), and **3d** (16 mg, 16%), for a total yield of 57 mg of pericyclic products (56%). A further 6 mg (6%) of a product was isolated and identified as **6d**.

Electrolysis of 100 mg (0.0103 M) of **1d** with Et_4NBF_4 electrolyte, at −3.2 V for 3.0 C (first 0.75 C at −2.5 V, then 0.75 C at −3.0 V). This corresponds to 13.7% of required charge. PTLC purification of the 150 mg of crude yielded 3 mg (3%) of *trans*-**2d**, 17 mg (17%) of **5d**, and 35 mg (35%) of an unidentified polymer.

4.7.1. Compound *cis*-2d.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.74 (2H, m), 1.85 (2H, dd, J=11.7, 3.3 Hz), 2.05 (2H, m), 3.19 (2H, d, J=2.4 Hz), 3.77 (2H, d, J=3.6 Hz), 7.46 (2H, d, J=8.4 Hz), 7.57 (2H, dd, J=8.7, 2.1 Hz), 7.81 (2H, d, J=2.1 Hz); HRMS (CI+): calcd; 440.998266. Found; 440.997859.

4.7.2. Compound *trans*-2d. ^{1}H NMR (300 MHz, $CDCl_3$): 1.38 (2H, m), 1.55 (1H, m), 1.83 (3H, m), 3.04 (1H, m), 3.24 (1H, m), 4.15 (1H, m), 4.47 (1H, dd, J=2.1, 10.2 Hz), 7.55 (1H, d, J=3.3 Hz), 7.57 (1H, d, J=3.0 Hz), 7.76 (1H, br.d), 7.81 (1H, br.d), 8.02 (1H, d, J=2.1 Hz) 8.08 (1H, d, J=1.8 Hz); HRMS (CI+): calcd; 440.998266. Found; 440.997697.

4.7.3. Compound 3d. ^{1}H NMR (300 MHz, $CDCl_3$): 1.60 (2H, m), 1.85 (2H, m), 2.07 (2H, m), 2.83 (2H, m), 5.09 (1H, d, J=6.9 Hz), 5.73 (1H, d, J<3 Hz), 7.39 (2H, m), 7.62 (3H, m), 7.74 (3H, m), 7.95 (4H, m), 8.15 (1H, m), 8.74 (1H, br.s); HRMS (CI+): calcd; 440.998266. Found; 440.997720.

4.7.4. Compound 5d. ^{1}H NMR (300 MHz, $CDCl_3$): 1.73 (4H, m), 2.31 (2H, br.m), 2.84 (1H, dd, J=9.6, 15.0 Hz), 3.66 (1H, dd, J=3.6, 15.0 Hz), 3.40 (1H, br.s), 6.66 (1H, t, J=3.3 Hz), 7.51 (2H, m), 7.56 (1H, d, J=8.4 Hz), 7.74 (1H, d, J=1.8 Hz), 7.90 (1H, dd, J=2.1, 8.4 Hz), 8.12 (1H, d, J=2.1 Hz); HRMS (CI+): calcd; 440.998266. Found; 440.998110.

4.7.5. Compound 6d. ^{1}H NMR (300 MHz, $CDCl_3$): 1.71 (3H, m), 1.98 (1H, m), 2.17 (1H, m), 2.34 (1H, m), 2.96 (3H, m), 3.17 (1H, br.d, J=17.4 Hz), 3.65 (1H, d, J=9.0 Hz), 5.24 (1H, d, J<1.5 Hz), 7.31 (1H, m), 7.54 (2H, m), 7.76 (1H, br.d), 7.81 (1H, d, J=2.1 Hz), 8.00 (1H, m); HRMS (CI+): calcd; 443.013916. Found; 443.012405.

4.8. Electrolysis of *E*,*E*-1,7-di-1-naphthoyl-1,6-heptadiene (1e)

Electrolysis of 97 mg (0.0109 M) of **1e** with Bu_4NBF_4 electrolyte, at −1.8 V (first 3.0 C at −1.5 V). The reaction appeared complete after 4.5 C, or 19.4% (of required charge) had passed through the cell. PTLC purification of the 123 mg of recovered crude yielded *cis*-**2e** (14 mg, 14%), *trans*-**2e** (28 mg, 29%), and **3e** (8 mg, 8%), for a total yield of 50 mg of pericyclic products (51%). No starting material was recovered. A further 16 mg (17%) of **5e** was recovered.

Electrolysis of 104 mg (0.0117 M) of **1e**, with Et_4NBF_4 electrolyte and 25 mg of acetic acid, giving a 1.6:1 excess of acetic acid. Initially at −2.5 V for 15.0 C and then at −3.0 V for 32.0 C. PTLC purification of the crude yielded *trans*-**2e** (6.0 mg, 6%), **5e** (2.8 mg, 3%), **6e** (14.1 mg, 14%), and **7e** (39.2 mg, 35%).

Electrolysis of 98 mg (0.0110 M) of **1e** with Bu_4NBF_4 electrolyte, at −1.5 V. The reaction was stopped after 3.4 C, or 14.5% (of required charge, corrected to 18.4%) had passed through the cell. PTLC purification of the 122 mg of recovered crude yielded *cis*-**2e** (16.6 mg, 21%), *trans*-**2e** (13 mg, 17%), and **3e** (8 mg, 10%), for a total yield of 37.6 mg of pericyclic products (48%). 20.4 mg (21%) of starting material was recovered, along with 5 mg (6%) of **5e**. Reaction is 79% complete based upon recovered **1e**.

4.8.1. Compound *cis*-2e.[6] ^{1}H NMR (300 MHz, $CDCl_3$) 1.74 (2H, m), 1.93 (2H, dd, J=14.1, 5.4 Hz), 2.15 (2H, m), 3.29 (2H, d, J=2.4 Hz), 4.08 (2H, d, J=4.2 Hz), 7.45 (4H, m), 7.74 (4H, m); 7.81 (4H, m), 8.22 (2H, s); HRMS (CI+): calcd; 405.185455. Found 405.185760.

4.8.2. Compound *trans*-2e.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (1H, m), 1.62 (1H, m), 1.85 (2H, m), 1.99 (2H, m), 3.16 (1H, m), 3.35 (1H, m), 4.50 (1H, m), 4.79 (1H, dd, J=2.4, 10.2 Hz), 7.58 (4H, m), 7.89 (4H, m), 8.03 (4H, br.m), 8.48 (1H, br.s), 8.60 (1H, br.s); HRMS (CI+): calcd; 405.185455. Found; 405.186095.

4.8.3. Compound 3e.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.60 (2H, m), 1.85 (2H, m), 2.07 (2H, m), 2.83 (2H, m), 5.09 (1H, d, J=6.9 Hz), 5.73 (1H, d, J<3 Hz), 7.39 (2H, m), 7.62 (3H, m), 7.74 (3H, m), 7.95 (4H, m), 8.15 (1H, m), 8.74 (1H, br.s); HRMS (CI+): calcd; 405.185455. Found; 405.186005.

4.8.4. Compound 5e.[11] ^{1}H NMR (300 MHz, $CDCl_3$): 1.71 (1H, m), 1.87 (3H, m), 2.35 (2H, br.m), 3.00 (1H, dd, J=11.4, 15.6 Hz), 3.66 (1H, dd, J=3.6, 15.6 Hz), 3.77 (1H, br.s), 6.75 (1H, br.t), 7.60 (4H, m), 7.92 (5H, m), 7.99 (1H, m), 8.05 (1H, m), 8.14 (1H, m), 8.22 (1H, s), 8.71 (1H, s).

4.8.5. Compound 6e.[6] ^{1}H NMR (300 MHz, $CDCl_3$). Partial only: 1.60 (m), 1.91 (m), 3.20 (2H, m), 5.74 (1H, d, J=1.8 Hz), 7.41 (2H, m), 7.59 (6H, br.m), 7.76 (2H, m), 7.87 (2H, m), 8.00 (2H, m).

4.8.6. Compound *trans*-7e. ^{1}H NMR (300 MHz, $CDCl_3$): 1.35 (1H, m), 1.67 (2H, m), 1.88 (1H, m), 2.04 (2H, m), 2.31 (1H, m), 2.78 (1H, m), 2.95 (1H, dd, J=8.1, 15.6 Hz), 3.10 (1H, dd, J=8.1, 16.2 Hz), 3.27 (1H, dd, J=5.7, 15.3 Hz), 3.38 (1H, dd, J=4.8, 16.2 Hz), 7.56 (4H, m), 7.88 (4H, m), 7.95 (2H, br.d, J=7.8 Hz), 8.02 (2H, m), 8.47 (2H, br.d, J=6.0 Hz); HRMS (CI+): calcd; 407.201105. Found; 407.202010.

4.9. Electrolysis of *E*,*E*-1,7-bis(4-phenylbenzoyl)-1,6-heptadiene (1f)

Electrolysis of 76 mg (0.0076 M) of **1f** with Bu_4NBF_4 electrolyte (in a 1:1 THF/acetonitrile solution), at −3.5 V (first 1.8 C at −2.5 V, then 1.1 C at −3.0 V). The reaction

appeared complete after 11.7 C, or 69.6% (of required charge) had passed through the cell. PTLC purification of the 107 mg of recovered crude yielded *trans*-**2f** (9 mg, 12%). Also recovered was 13 mg (17%) of **5f**.

Electrolysis of 55 mg (0.0055 M) of **1f** with $Mg(ClO_4)_2$ (0.1 M in 1:1 THF/acetonitrile) at −2.0 V for 5.0 C (corrected for recovered **1f** to 53.7% of required charge), PTLC purification of the 61 mg of crude yielded *cis*-**2f** (9 mg, 21%), *trans*-**2f** (3.1 mg, 7%), and **3f** (11 mg, 25%), for a total yield of 23.1 mg of pericyclic products (53%). 11 mg of unreacted **1f** was recovered, allowing the corrected yields given above. Two additional products were isolated; 5.8 mg (13%) of **6f**; and 3.2 mg (7%) of **7f**.

4.9.1. Compound *cis*-2f.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.84 (4H, m), 2.06 (2H, m), 3.27 (2H, m), 3.92 (2H, m), 7.37 (6H, m), 7.55 (8H, m), 7.84 (4H, d, J=8.7 Hz).

4.9.2. Compound *trans*-2f. ^{1}H NMR (300 MHz, $CDCl_3$): 1.47 (2H, m), 1.66 (2H, m), 1.91 (2H, m), 3.13 (1H, m), 3.30 (1H, m), 4.33 (1H, m), 4.61 (1H, m), 7.45 (6H, m), 7.65 (2H, m), 7.70 (2H, d, J=8.4 Hz), 8.04 (2H, d, J=9.0 Hz), 8.11 (2H, d, J=8.7 Hz); HRMS (CI+): calcd; 457.216755. Found; 457.215380.

4.9.3. Compound 3f. ^{1}H NMR (300 MHz, $CDCl_3$): 1.56 (3H, m), 1.78 (1H, m), 2.05 (2H, m), 2.75 (2H, m), 4.93 (1H, m), 5.61 (1H, m), 7.40–7.72 (12H, m), 8.19 (2H, m): calcd; 457.216755. Found; 457.218026.

4.9.4. Compound 5f. ^{1}H NMR (300 MHz, $CDCl_3$): 1.67 (1H, m), 1.78 (3H, m), 2.31 (2H, br.m), 2.85 (1H, dd, J=10.5, 14.7 Hz), 3.47 (1H, dd, J=6.6, 13.8 Hz), 3.54 (1H, br.s), 6.70 (1H, m), 7.43 (6H, m), 7.66 (6H, m), 7.79 (2H, d, J=8.4 Hz), 8.03 (2H, d, J=8.7 Hz), 8.16 (2H, d, J=8.7 Hz); HRMS (CI+): calcd; 457.216755. Found; 457.216312.

4.9.5. Compound 6f.[6] ^{1}H NMR (300 MHz, $CDCl_3$). Partial only: 3.94 (1H, d, J=8.7 Hz), 5.63 (1H, d, $J\sim$1.5 Hz).

4.9.6. Compound *cis*-7f. ^{1}H NMR (300 MHz, $CDCl_3$): 1.34 (2H, m), 1.67 (2H, m), 2.02 (2H, m), 2.24 (2H, m), 2.98 (2H, dd, J=7.2, 17.4 Hz), 3.26 (2H, dd, J=4.5, 16.2 Hz), 7.44 (6H, m), 7.65 (8H, m), 8.03 (4H, d, J=8.7 Hz); HRMS (CI+): calcd; 459.232406. Found; 459.231734.

4.10. Electrolysis of *E*,*E*-1-acetyl-7-benzoyl-1,6-heptadiene (1g)

Electrolysis of 98 mg (0.018 M) of **1g** with $Mg(ClO_4)_2$ electrolyte, at −4.5 V for 150 C (initial 4.0 C at −4.0 V, last 16 C at −5.0 V), corresponding to 459% of required charge. PTLC separation yielded *cis*-**2g** (7 mg, 9%), and **7g** (14 mg, 17%), along with 11 mg (13%) of an unidentified product, tentatively described as an isomer of **7g** (LRMS (CI+): 245, 227). 16 mg of unreacted **1g** was also recovered.

Electrolysis of 73 mg (0.014 M) of **1g** with Et_4NBF_4 electrolyte, at −2.0 V for 16.0 C (initial 2.2 C at −1.6 V), corresponding to 55.0% of required charge. PTLC separation yielded two isomers of *trans*-**2g**, 9 mg (12%) of the isomer where the benzoyl group is *syn* to the cyclopentane ring, and 5 mg (7%) with an *anti* benzoyl group.

4.10.1. Compound *cis*-2g.[6] ^{1}H NMR (300 MHz, $CDCl_3$): 1.59 (2H, m), 1.68 (4H, br.m), 2.03 (3H, s), 3.00 (2H, m), 3.11 (1H, m), 3.79 (1H, dd, J=4.5, 9.9 Hz), 7.45 (2H, br.t, J=7.2 Hz), 7.52 (1H, br.t, J=7.2 Hz), 7.83 (2H, br.d, J=8.1 Hz); HRMS (CI+): calcd; 243.138505. Found; 243.138743.

4.10.2. Compound *trans*-2g (benzoyl group *syn* to the cyclopentane ring). ^{1}H NMR (300 MHz, $CDCl_3$): 1.36 (2H, m), 1.74 (4H, m), 2.13 (3H, s), 2.93 (1H, m), 3.13 (1H, m), 3.49 (1H, t, J=8.1 Hz), 4.32 (1H, dd, J=2.1, 10.5 Hz), 7.47 (2H, br.t, J=7.2 Hz), 7.57 (1H, br.t, J=6.9 Hz), 7.93 (1H, br.d, J=7.2 Hz). X-ray crystallography confirms structure (CCDC240332).

4.10.3. Compound *trans*-2g.[6] **(benzoyl group *anti* to the cyclopentane ring)** ^{1}H NMR (300 MHz, $CDCl_3$): 1.58 (2H, m), 1.80 (4H, m), 2.11 (3H, s), 2.94 (1H, m), 3.07 (1H, m), 3.38 (1H, m), 3.86 (1H, dd, J=2.4, 10.5 Hz), 3.99 (1H, t, J=6.3 Hz), 7.45 (2H, br.t, J=7.2 Hz), 7.55 (1H, br.t, J=7.2 Hz), 7.95 (1H, br.d, J=7.2 Hz).

4.10.4. Compound 7g. ^{1}H NMR (300 MHz, $CDCl_3$). 1.23 (2H, m), 1.61 (2H, m), 1.98 (4H, br.m), 2.13 (3H, s), 2.40 (1H, dd, J=7.8, 16.8 Hz), 2.67 (1H, dd, J=4.2, 16.8 Hz), 2.91 (1H, dd, J=7.8, 16.5 Hz), 3.14 (1H, dd, J=4.2, 16.8 Hz), 7.46 (2H, br.t, J=7.5 Hz), 7.56 (1H, br.t, J=7.2 Hz), 7.95 (1H, br.d, J=7.2 Hz); HRMS (CI+): calcd; 245.154155. Found; 245.154390.

4.11. Electrolysis of *E*,*E*-1,7-diacetyl-1,6-heptadiene (1h)

Electrolysis of 97 mg (0.025 M) of **1h** with Et_4NBF_4 electrolyte, at −2.5 V for 10.0 C (initial 4.0 C at −2.0 V). ^{1}H NMR (300 MHz, $CDCl_3$) of the 121 mg of recovered crude showed only starting material present (plus electrolyte).

4.12. Electrolysis of *E*,*E*-7-ethoxy-1-benzoyl-1,6-heptadiene (1i)

Electrolysis of 117 mg (0.020 M) of **1i** with $LiClO_4$ electrolyte (0.3 M), at −2.0 V for 10.0 C, −2.2 V for 20.0 C, and −3.0 V for 10.0 C (136% of required charge). PTLC separation yielded 23 mg (28%) of one isomer of *trans*-**2i**. Thought to be the same isomer as the major isomer seen in the **1g** electrolysis (based upon NMR comparison). A further 3 mg (4%) of the alternate *trans*-**2i** isomer was also obtained. 34 mg of starting material **1i** was recovered.

Electrolysis of 136 mg (0.023 M) of **1i** with Et_4NBF_4 electrolyte, at −2.0 V for 10.5 C. Yielding only unidentified polymers

4.12.1. Compound *trans*-2i (benzoyl group *syn* to the cyclopentane ring). ^{1}H NMR (300 MHz, $CDCl_3$): 0.98 (3H, t, J=7.2 Hz), 1.63 (2H, m), 1.72 (2H, m), 1.91 (2H, m), 3.04 (2H, m), 3.22 (1H, m), 3.69 (1H, dd, J=5.1, 9.9 Hz), 3.87

(2H, q, $J=7.2$ Hz), 7.43 (2H, br.t, $J=8.1$ Hz), 7.53 (1H, br.t, $J=6.9$ Hz), 7.84 (1H, br.d, $J=7.2$ Hz). HRMS (CI+): calcd; 273.149070. Found; 273.148638.

4.12.2. Compound *trans*-2i (benzoyl group *anti* to the cyclopentane ring). ^{1}H NMR (300 MHz, $CDCl_3$): 0.98 (3H, t, $J=7.2$ Hz), 1.69 (4H, m), 2.01 (2H, m), 2.99 (1H, m), 3.21 (1H, m), 3.38 (1H, m), 4.14 (2H, q, $J=7.2$ Hz), 4.34 (1H, dd, $J=2.7$, 10.5 Hz), 7.47 (2H, br.t, $J=6.3$ Hz), 7.56 (1H, br.t, $J=6.9$ Hz), 7.93 (1H, br.d, $J=6.6$ Hz). HRMS (CI+): calcd; 273.149070. Found; 273.148198.

4.13. Electrolysis of *E,E*-1,7-dicarbethoxy-1,6-heptadiene (1j)

Electrolysis of 112 mg (0.021 M) of **1j** with Et_4NBF_4 electrolyte, at −2.5 V for 10.0 C, corresponding to 22.2% of required charge. PTLC purification of the 112 mg of recovered crude yielded 47 mg (42%) of **5j**. No starting material was recovered.

Electrolysis of 96 mg (0.018 M) of **1j** with $LiClO_4$ electrolyte, at −3.5 V for 4.5 C, −3.5 V for 7.9 C, and −4.0 V for 55 C. ^{1}H NMR (300 MHz, $CDCl_3$) of the recovered crude showed only starting material present.

4.13.1. Compound 5j. ^{1}H NMR (500 MHz, $CDCl_3$): 1.26 (3H, t, $J=7.5$ Hz), 1.29 (3H, t, $J=7.0$ Hz), 1.64 (4H, m), 2.18 (2H, br.m), 2.27 (1H, dd, $J=10.5$, 15.0 Hz), 2.64 (1H, dd, $J=3.5$, 15.0 Hz), 3.09 (1H, br.s), 4.16 (4H, m), 7.03 (1H, t, $J=4.0$ Hz). ^{13}C NMR (500 MHz in $CDCl_3$): 14.21 (2C), 17.11, 25.77, 26.52, 29.92, 38.40, 60.20, 60.26, 132.79, 140.99, 166.86, 172.53; NMR COSY (500 MHz) (consistent with structure). HRMS (CI+): calcd; 241.143984. Found; 241.142945.

4.14. X-ray data

Crystallographic data (excluding structure factors) for **4b** and the primary *trans*-**2g** isomer, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 240331 and CCDC 240332, respectively. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/data_request/cif or 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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Nitroalkylation and nitroalkenylation reactions of γ-lactone enolates. A facile ring switch from polysubstituted γ-lactones to polysubstituted γ-lactams

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Abstract—Michael addition of lithium enolates of γ-butyrolactone **1** and α-methyl-γ-butyrolactone **1′** to (*E*)-1-nitropropene **2**, (*E*)-β-nitrostyrene **3** and (*E*)-2-nitro-1-phenylpropene **4** is described. Reactions of the lithium enolate of **1′** with **2** and **4** occurred with high diasteroselectivity (80 and 92% d.e., respectively). Reactions of the zinc enolate of **1′** with two β-nitroenamines and two methylthio-substituted 1-amino-2-nitro-1,3-dienes were also examined. Catalytic reduction of the nitroalkylated and nitroalkenylated products allowed the achievement of functionalized γ-lactams and/or cyclic hydroxamic acids.

1. Introduction

Polyfunctionalized γ-lactones are frequently encountered in the literature,[1] owing to the fact that many natural products, in particular those belonging to the sesquiterpene series,[2] contain the γ-lactone ring in their structure. Many examples of α-functionalization and α,α-difunctionalization of γ-lactone rings are present in the literature[3] and among them a new class of anticonvulsant drugs can be mentioned.[4] α-Nitroalkenylation reactions were extensively studied,[5] with the aim of preparing compounds possessing quaternary stereocentres,[6] whereas no examples of nitroalkylation reactions of γ-lactones can be found. On the contrary, Enders and co-workers[7] obtained excellent results in the diastereo- and enantio-selective Michael additions of enolates of γ-lactams to aliphatic and aromatic nitroolefins. Seebach and coworkers[8] investigated the nitroalkylation reactions of lithium enolates of other five-membered ring heterocycles, such as chiral non-racemic 2-*t*-butyl-1,3-dioxolan-4-ones, 2-*t*-butylimidazolidin-4-ones and 2-*t*-butyloxazolidin-5-ones, to verify the 1,3 asymmetric induction on the reaction products. In all cases examined the diastereoselectivity was high, depending however on whether the position α to the carbonyl group was substituted or not.

In this paper we describe the nitroalkylation reactions of the lithium enolates of γ-butyrolactone **1** and α-methyl-γ-butyrolactone **1′** with a few conjugated nitroolefins, such as (*E*)-1-nitropropene **2**, (*E*)-β-nitrostyrene **3** and (*E*)-2-nitro-1-phenylpropene **4**. Nitroalkenylation reactions have also been carried out, by reacting the zinc enolate of compound **1′** with the β-nitroenamines **5**[9] and **6**[10] as well as with the nitrodienes **7**,[11,12] and **7′**[12] (Fig. 1).

2. Results and discussion

2.1. Nitroalkylation reactions

The butanolides **1** and **1′** were enolized with lithium diisopropylamide in THF at −78 °C to the corresponding lithium enolates **8** and **8′**, which reacted with the nitroolefins **2**, **3**, and **4**, to provide the corresponding nitronate salts **9**–**14** (Scheme 1).

No attempt to isolate the lithium nitronate intermediates **9**–**14** was undertaken. Treatment of the crude reaction mixtures with a weak acid afforded the corresponding nitroalkylated lactones **15**–**20**. The nitroalkylated lactones **15**, **16**, **17** and **18**, for which R^2=H, were mixtures of *syn*/

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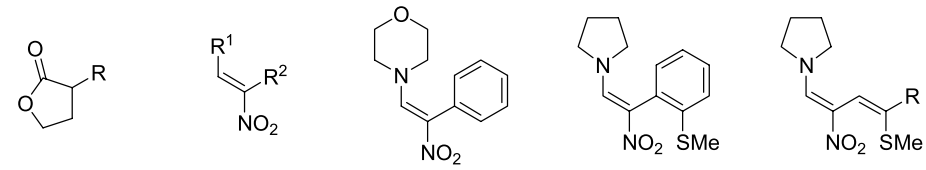


Figure 1.

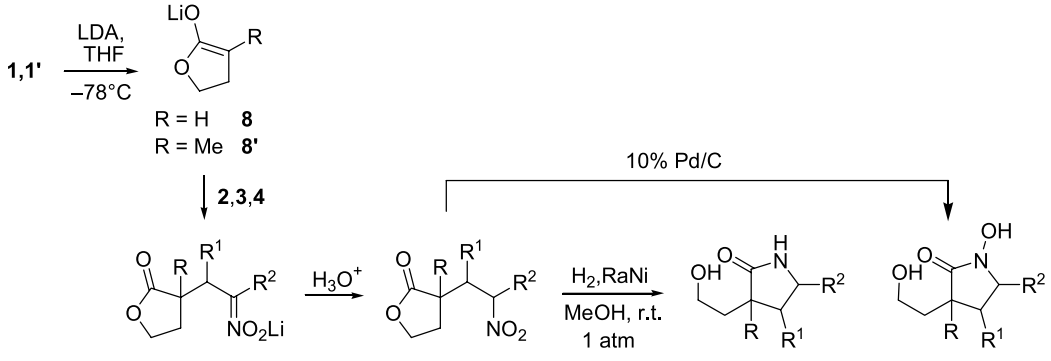
anti diastereomers, **a** and **b** respectively, owing to the presence of two adjacent chiral centres, while **19** was a mixture of four diastereomers and **20** was a mixture of three diastereomers out of the four possible ones. In order to evaluate the diastereoselectivity of the reaction, the *syn* and *anti* descriptors were also used for **19** and **20**, to indicate the relative configurations of the two stereocentres of the newly formed C–C bond.

Since for the nitroalkylated γ-lactones **15**–**20** the *syn*/*anti* stereochemical assignments were not straightforward, a stereochemical correlation was desirable: therefore, such lactones were converted into the corresponding *trans* and *cis* lactam derivatives **21**–**26** to take advantage of the more rigid polysubstituted lactams to determine the configurations of the stereocentres. On the other hand, γ-lactams themselves are attractive targets because they possess a variety of biological activities[13] and have been used to produce γ-aminobutyric acid (GABA) analogues by hydrolysis.[14] Thus, reduction of the nitro group of compounds **15**–**20** with hydrogen on Raney Ni and subsequent cyclization[15] of the corresponding aminoalkyl lactone intermediates, which were not isolated, afforded the corresponding lactam derivatives **21**–**26** (Scheme 1). In this manner, the stereochemical assignments were made on the lactam derivatives **21**–**26** either by a comparison of their ^{13}C NMR spectra or by means of NOE measurements. When this latter method was unsatisfactory, the nitroalkylated γ-lactones **15**–**19** were transformed into the corresponding cyclic hydroxamic acids **27**–**31**,[16] using 10% Pd/C as the catalyst. The latter compounds proved better substrates for NOE measurements, which supported the stereochemical assignments previously made on the lactam derivatives. All resonances of each compound were identified by means of 2D correlated experiments.

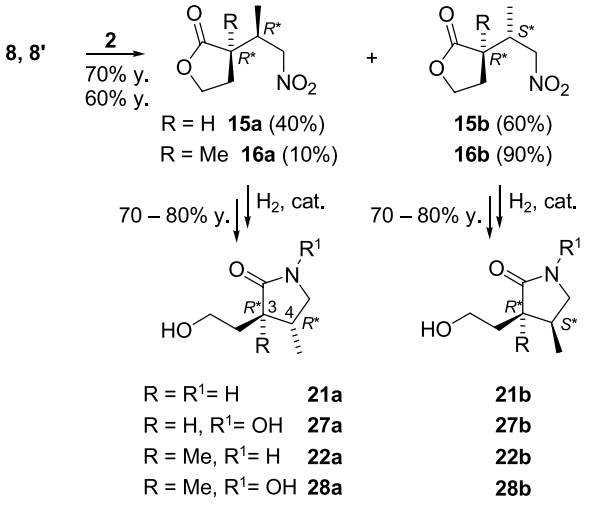
2.2. Reactions of enolates 8 and 8′ with (*E*)-1-nitropropene 2

The reaction of lithium enolate **8** with (*E*)-1-nitropropene **2** led, after acidification with aqueous satd. NH_4Cl, to the formation of two diastereomeric (nitroalkyl)lactones **15a** and **15b** in 2:3 ratio, which were separated by flash chromatography (Scheme 2). They were assigned the *syn* and *anti* configuration, respectively, after transformation into the corresponding lactams **21a** and **21b** whose geometries were demonstrated to be *trans* and *cis*, respectively. In fact the ^{13}C NMR spectrum of **21b** showed an upfield shift for the methyl group with respect to the same resonance in **21a**, thus demonstrating its *cis* relationship with the hydroxyethyl chain (Table 1). The same *trans*/*cis* assignment was made for the corresponding cyclic hydroxamic acids **27a** and **27b** that were obtained in admixture with the corresponding lactams **21a** and **21b** when the reduction was performed using Pd on carbon as the catalyst.

Similarly, the reaction between the enolate **8′** and **2** afforded the corresponding nitroalkylated products **16a** and **16b** in



Scheme 1.



Scheme 2.

1:9 ratio, as determined by HRGC analysis of the crude reaction mixture. However, since in this case the two diastereomers were not separable by flash chromatography, the subsequent reductions of the nitro group were performed on the mixture. When Raney Ni was used as the catalyst, a 1:9 mixture of the corresponding lactams **22a** and **22b** was isolated. They were assigned the (3*R**,4*R**) and (3*R**,4*S**) configurations, respectively, by comparison of their ^{13}C NMR spectra (Table 1): an upfield shift was always observed for those carbon atoms which suffered from steric effects.[17] Thus, the methyl group at C-3 resonated at 15.1 ppm in **22a** and at 20.5 ppm in **22b**, as a consequence of a less constrained situation in the latter diastereomer.

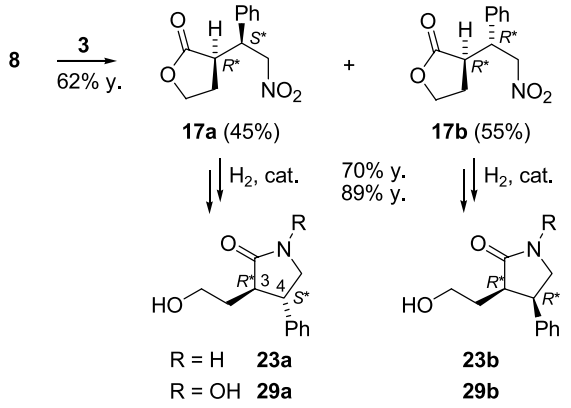
When the reduction of **16a**,**b** was performed using Pd on carbon, two cyclic hydroxamic acids, namely **28a** and **28b**, were obtained in 1:9 ratio (Scheme 2). The relevant configurations were assigned on the basis of NOE measurements performed on the major product **28b**, which was separated in pure form by fractional crystallization. Irradiation of its methyl singlet at 1.18 ppm enhanced the signal of H-4 (5%), while irradiation of the α-methylene hydrogens of the hydroxyethyl chain at 1.74 and 1.50 ppm produced enhancement of the methyl doublet at 1.04 ppm (2%). The NOE enhancement values were low, however this assignment was supported by a comparison of the ^{13}C NMR spectra of the two isomers, whose significant digits are reported in Table 1. Again an upfield shift was observed for those carbon atoms which suffered from steric effects. Thus the methyl group at C-3 is shifted to higher field in **28a**, being *cis* to the methyl group at C-4. The same trend was observed for the α-methylene hydrogens of the hydroxyethyl chain in **28b**. As a consequence, the configuration of the chiral centres in compounds **22a** and **28a** is (3*R**,4*R** or like[18]) and that of **22b** and **28b** is (3*R**,4*S** or unlike[18]). The same configurations can be assigned to the corresponding parent lactones **16a** and **16b**, whose relative configurations are therefore *syn* and *anti* respectively.

2.3. Reactions of enolates 8 and 8′ with (*E*)-β-nitrostyrene 3

The reactions between the nitroalkene **3** and the enolates **8**

Table 1. Selected ^{13}C NMR absorption values (ppm) for the γ-lactams **21–24** and the corresponding cyclic hydroxamic acid derivatives **27–30**

	γ-Lactams						Cyclic hydroxamic acids						
Entry	Me at C-3	Me at C-4	CH_2CH_2OH	C-3	C-4	C-5	Entry	Me at C-3	Me at C-4	CH_2CH_2OH	C-3	C-4	C-5
21a	—	17.3	32.4	49.7	37.1	48.7	**27a**	—	17.6	33.0	47.8	31.5	55.2
21b	—	14.6	28.5	45.5	33.5	48.6	**27b**	—	14.9	28.8	43.4	28.4	55.5
22a	15.1	11.4	38.2	45.9	39.7	47.0	**28a**	16.0	11.5	38.5	44.7	33.8	53.6
22b	20.5	12.6	34.0	44.6	42.0	46.6	**28b**	21.3	12.0	35.0	43.6	37.3	53.6
23a	—	—	32.4	49.0	48.4	48.9	**29a**	—	—	34.1	46.4	43.5	56.3
23b	—	—	29.9	45.3	44.3	48.0	**29b**			30.5	42.6	40.0	55.8
24a	17.4	—	38.5	47.5	51.3	44.5	**30a**	19.5	—	40.1	47.1	45.0	52.5
24b	21.4		35.7	46.5	53.6	44.4	**30b**	23.3		37.0	46.5	45.0	52.4



Scheme 3.

and **8′** were poorly diastereoselective, as the former reaction afforded a ca. 1:1 mixture of diastereomers **17a** and **17b** (Scheme 3), and the latter reaction gave a ca. 2:1 mixture of **18a** and **18b** (Scheme 4). In both cases the diastereomers could not be completely separated: anyway, for an easier stereochemical assignment, different mixtures of **17a**,**b** or **18a**,**b**, enriched in either diastereomer, were converted into the corresponding lactams (**23a**,**b** or **24a**,**b**) or cyclic hydroxamic acids (**29a**,**b** or **30a**,**b**).

The *trans* and *cis* stereochemical assignments for the γ-lactams **23a** and **23b** and for the cyclic hydroxamic acids **29a** and **29b** were based on ^{13}C NMR spectra (Table 1). The carbon resonances for the *cis* diastereomers **23b** and **29b** were shifted upfield with respect to those for the *trans* diastereomers **23a** and **29a**. Furthermore, NOE measurements carried out on **29a** and **29b** confirmed the previous assignments. Irradiation of the H-3 signal at 2.71 ppm in **29a** produced enhancement (4%) of the *ortho* hydrogens of the phenyl ring, while irradiation of the H-3 signal at 2.95 ppm in **29b** enhanced the H-4 signal at 3.64 ppm (5%). Therefore, since the configuration of **23a** and **29a** is ($3R^*$,$4S^*$) and that of **23b** and **29b** is ($3R^*$,$4R^*$), the relative configurations of lactones **17a** and **17b**, from which they are derived, are *syn* and *anti*, respectively.

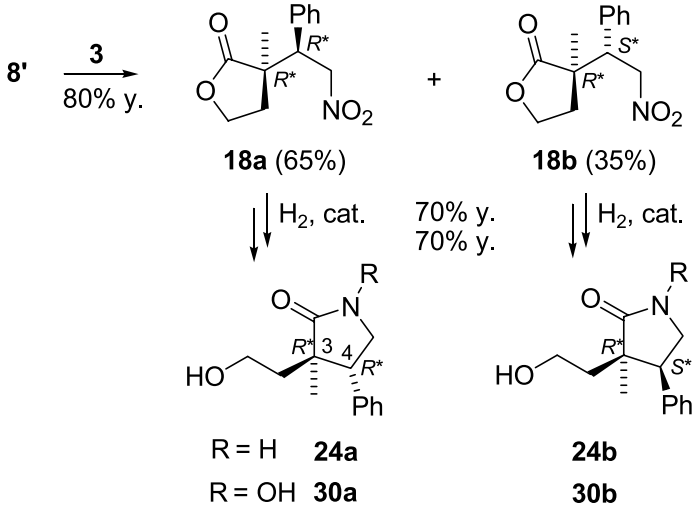
In a similar manner, the NOE experiments performed on the diastereomeric cyclic hydroxamic acids **30a** and **30b**, allowed the correct *syn* and *anti* attributions to the parent lactones **18a** and **18b** to be made. Thus, the configuration of the cyclic hydroxamic acid **30a**, derived from **18a**, was proved to be ($3R^*$,$4R^*$) and that of **30b**, derived from **18b**, was ($3R^*$,$4S^*$). In fact, upon irradiation of the methyl group at 1.30 ppm in **30b**, the H-4 signal was enhanced (10%). On the other hand, irradiation of the H-4 signal at 3.63 ppm in **30a** caused enhancement of the α-methylene protons of the chain (5%), while irradiation of the methyl group at 0.74 ppm enhanced the aromatic *o*-hydrogens (6%). All these assignments were also supported by a comparison of the ^{13}C NMR spectra of each pair of diastereomers, as shown in Table 1.

It should be noted that in spite of the fact that the geometries of the products are the same as those observed for the products of the reaction between **8** or **8′** with 1-nitropropene, the descriptors are different, owing to a different priority of the groups.

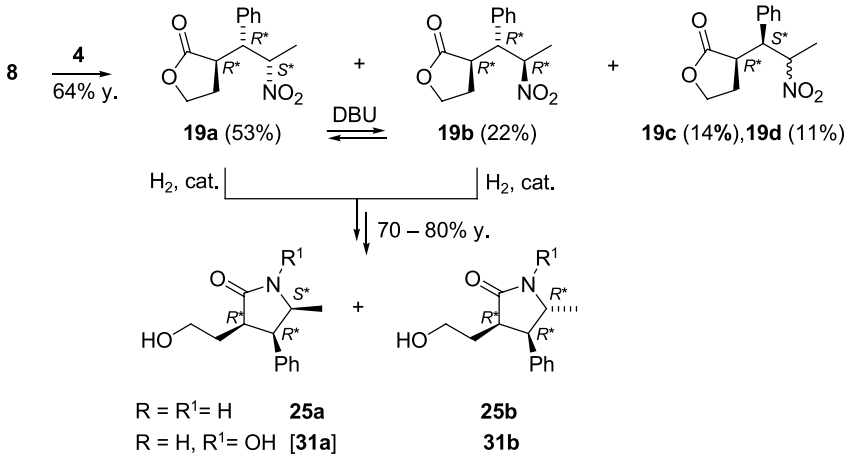
2.4. Reactions of enolates 8 and 8′ with (*E*)-2-nitro-1-phenylpropene 4

In the reaction between the enolate **8** and (*E*)-2-nitro-1-phenylpropene **4** four diastereomers, namely **19a**, **19b**, **19c**, and **19d** were formed, in 53:22:14:11 relative ratio (Scheme 5), as determined by HRGC analysis of the crude reaction mixture. Their separation on chromatographic column allowed the isolation of all stereoisomers as pure compounds with the exception of **19c** which was isolated in admixture with **19a**. Treatment under basic conditions (DBU in chloroform) of the pure diastereomer **19a** afforded a 1:1 mixture of **19a** and **19b**, thus demonstrating that they differed in the configuration of the nitromethine carbon atom. The same was proved for compounds **19c** and **19d**.

As above, the stereochemical assignments for **19a** and **19b** were made on the corresponding lactam **25a** and on the cyclic hydroxamic acid **31b**, respectively. Reduction of **19a** with hydrogen on Raney Ni afforded lactam **25a** as a single



Scheme 4.



Scheme 5.

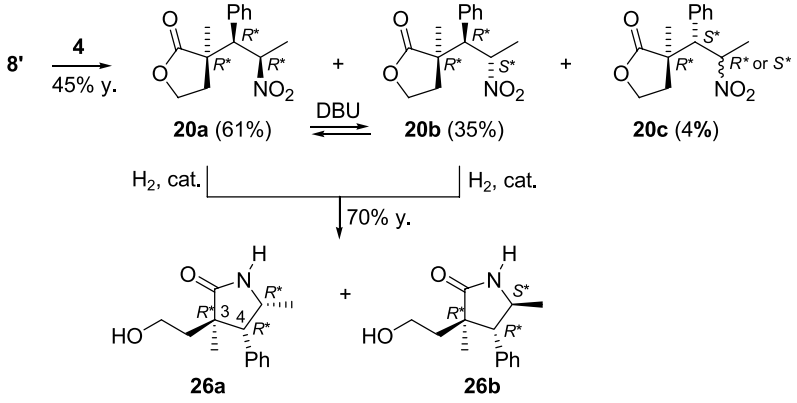
diastereomer, while reduction of **19b** using 10% Pd/C as the catalyst afforded a mixture of lactam **25b** and cyclic hydroxamic acid **31b** in the 1:3 ratio. The stereochemistry of **25a** was established by means of NOE measurements. In fact, irradiation of the H-4 signal enhanced the signals of H-3 (4%) and H-5 (5%). Compound **31b** was less soluble than the corresponding lactam **25b** in ethyl acetate and therefore it could be separated from the mixture in pure state. The NOE experiment carried out on **31b** revealed that the hydroxyalkyl chain was *cis* to the phenyl group which in turn was *trans* to the methyl group. In fact, irradiation of the methyl group enhanced the signal of H-4 (6%) as well as that of H-3 (3%), while irradiation of H-4 enhanced the signals of H-3 (8%) and that of the methyl group (6%). Its configuration was therefore (3*R**,4*R**,5*R**) and, accordingly, the relative configuration of **19b** was assigned as *anti*, *anti*. Since the stereochemical relationship between **19a** and **19b** was known from the previous equilibration reaction, the configuration of **19a** must be *anti*, *syn*.

The reaction between the enolate **8′** and the nitroolefin **4** was somewhat more complicated by the fact that acidification of the nitronate salt intermediate **14** (Scheme 1) required strictly controlled conditions and the use of a weak acid (see Section 4) in order to obtain the nitroalkylated lactones **20**. When glacial acetic acid in THF was used, a 61:35:4 mixture of **20a**, **20b** and **20c** was obtained (Scheme 6), which were isolated by flash chromatography. Equilibration of **20a**, carried out under basic conditions with DBU at room temperature, partially converted it into **20b**, thus demonstrating that **20a** and **20b** differed in the configuration of the nitromethine carbon atom.

Reduction of a 1:1 mixture of lactones **20a** and **20b** using Raney Ni as catalyst furnished a 1:1 mixture of lactams **26a** and **26b**. The stereochemistry of lactam **26a** was assigned by means of NOE measurements: irradiation of the α-methylene hydrogens of the hydroxyethyl chain at 1.90 ppm produced enhancement of the signal of H-4 (5%) as well as that of H-5 (8%) indicating that the hydroxyalkyl chain was *trans* to the phenyl group, which in turn was *cis* to the methyl group at C-5. Its configuration was therefore (3*R**,4*R**,5*R**) and that of **26b** was (3*R**,4*R**,5*S**). Accordingly, the relative configuration of **20a** was assigned as *syn*, *syn* and that of **20b** as *syn*, *anti*, both deriving from the same type of attack of the enolate onto the nitroolefin. The diastereoselective excess of the reaction, with reference to the *syn* configuration around the newly formed C–C bond, was 92%.

2.5. Products of the Nef reaction

The nitronate salt intermediates **13** (R=H) and **14** (R=Me) (Scheme 1) were treated with 3 N HCl,[19] with the aim of obtaining the corresponding Nef products.[20] Thus, a 75:25 diastereomeric mixture of **13** furnished **32a** (isolated in19%



Scheme 6.

yield) and **32b** in a ca. 3:2 ratio, in admixture with the oxime **34** (isolated in 15% yield), the latter most likely resulting from the autoxidation–reduction of the not detected nitronic acid intermediate **36**.[21] Acidic equilibration of the 3:2 mixture of **32a** and **32b** changed its composition to 3:1. The thermodynamically more stable **32a** was tentatively assigned the (3*R**,1′*R**) configuration, by a comparison of the values of the ^{3}J coupling constants between H-3 and the benzylic proton in the two isomers: 7.7 and 5.1 Hz for **32a** and **32b**, respectively.[22] In the ^{13}C NMR spectra, the only significant difference between the two diastereomers was the resonance value of C-3, 42.8 ppm for **32b** and 41.3 ppm for **32a**, suggesting a slightly more crowded situation for the latter compound.

From the nitronic salt intermediates **14** (96:4 diastereomeric ratio) a single Nef product **33** (isolated in 17% yield) and a single oxime **35** (isolated in 10% yield) were obtained by the same acid treatment as above.

Remarkably, when acidification of the crude reaction mixture was performed with a saturated solution of ammonium chloride, followed by separation of the organic phase, the subsequent treatment of the mother liquors with 3 N HCl afforded the nitronic acid **37** (isolated in 10% yield). This latter compound was separated as a white solid, stable at −20 °C. It must be underlined that reduction of the nitronic acid **37** with Raney Ni afforded the same lactams **26a** and **26b**, in the ratio of 7:3, as previously obtained from **20a** and **20b**, thus demonstrating their stereochemistry. The relative configuration reported in Figure 2 for the products of the Nef reaction are correlated with the diastereomeric values of the nitronate lithium salt formation.

2.6. Mechanism of the nitroalkylation reactions

The results relating to the geometry of the products are summarized in Table 2 (the *syn* and *anti* descriptors are also used for **19** and **20**, to indicate the relative configurations of the two stereocentres of the newly formed C–C bond). The diastereoselectivity observed is generally low except for compounds **16**, for which the *anti* diastereomer largely prevailed, and for compound **20**, for which the *syn* diastereomer was formed almost exclusively.

Table 2. Diastereomeric ratios and yields for the nitroalkylated lactones **15–20**

Entry	Product	*syn*/*anti*	Yield (%)
1	**15**	40/60	70
2	**16**	10/90	60
3	**17**	45/55	62
4	**18**	65/35	80
5	**19**	25/75	64
6	**20**	96/4	45

Formation of the *syn* and *anti* diastereomers would involve a different topological approach of the donor and acceptor.[23] Thus the *Re**,*Re** (like) approach of the enolate to the nitroolefin would lead to the *syn* products, while the *Re**,*Si** (unlike) one would give the *anti* products. It appears that the unlike approach was slightly preferred over the like one when the lactone enolate was unsubstituted (R = H) (entries 1, 3, 5). When R was methyl (entries 2, 4, 6) the reactions showed the opposite diastereoselection, with the exception of the reaction of 1-nitropropene. The following simplified model transition states A and B (Fig. 3), in which the pyramidalization of the reacting carbon atoms is ignored as are the role of the solvent and the state of aggregation of the lithium enolates,[24] would account for the different selectivity observed. When R and R^2 are hydrogens no remarkable differences in the transition states exist, and the resulting products *syn* and *anti* **15** and *syn* and *anti* **17** are formed in almost equal amount. Substitution of a hydrogen for a methyl group (R^2 = Me) slightly disfavours the like approach of the reactants and in fact compound *anti*-**19** was formed with 50% d.e. When the lactone bears a methyl group at the α-position, the steric situation seems to be dominated by the presence of the phenyl group (R^1 = Ph), which disfavours the unlike approach and consequently favours the formation of the *syn* products (30% d.e. for **18** and 92% d.e. for **20**).

The prevalent formation of compound **16** in *anti* configuration from 1-nitropropene is not in accordance with the results found for the Michael addition of cyclohexanone lithium enolate to the same nitroolefin[25] which always afforded the *syn*-product under several reaction conditions. Probably this is due to the fact that in our case the presence of the heterocyclic oxygen atom allows the unlike or *endo* orientation of the nitroolefin.

2.7. Nitroolefination and nitrodienylation reactions

The reactivity of lithium enolates of γ- and δ-lactones bearing no substituent at α-position with a few β-nitroenamines has already been reported[26] to lead to the corresponding Nef products[20] and not to the desired nitroolefinated lactones. On the contrary, when the lactone bears a substituent at the α-position, nitroolefination of the lithium enolate by β-nitroenamines proceeds diastereo- and enantio-selectively, as proved by Severin and coworkers.[5a,27] An exchange of the counter ion from lithium to zinc had the

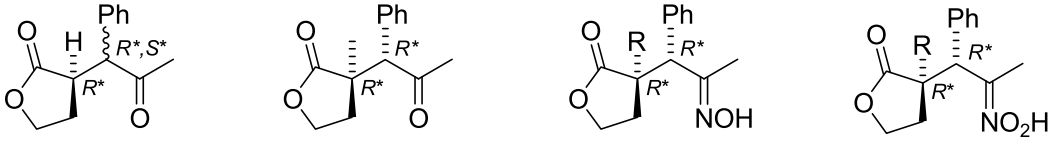


Figure 2.

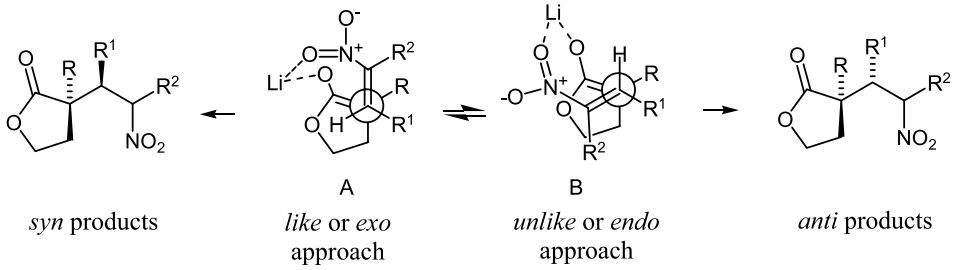


Figure 3.

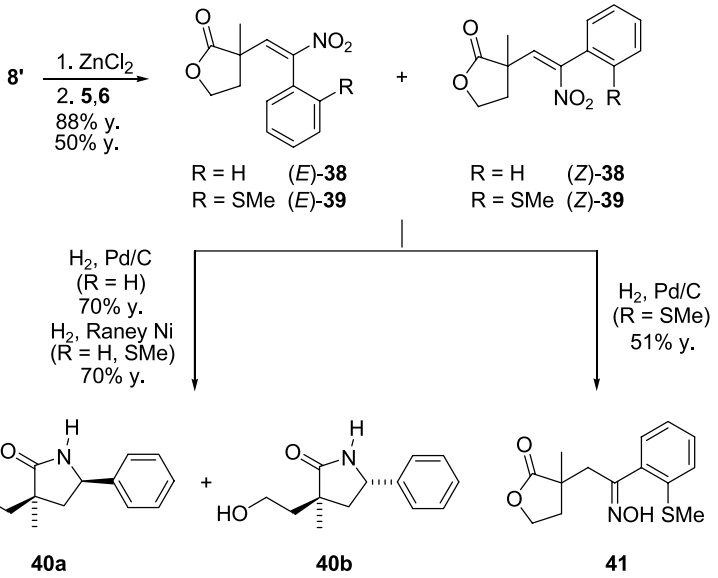
effect of increasing the reactivity and the enantioselectivity of the reactions when a chiral non-racemic β-nitroenamine derived from (*S*)-prolinol was used.[28] In particular, when the zinc enolate[29] of lactone **1′** reacted with (*E*)-1-(1-morpholinyl)-2-nitroethene and (*E*)-1-(1-morpholinyl)-2-nitropropene[5c] the corresponding addition–elimination products in (*E*) configuration were obtained.

Herein an analogous reaction has been carried out on the lithium enolate **8′** with the nitroenamines (*E*)-1-(1-morpholinyl)-2-nitro-2-phenylethene **5** and (*E*)-1-(1-pyrrolidinyl)-2-nitro-2-[2-(methylthio)phenyl]ethene **6** (Scheme 7). The corresponding products, **38** and **39**, were obtained as 85:15 and 65:35 *E*/*Z* mixtures, respectively, as determined by ^{1}H NMR analysis of the crude reaction mixtures. In fact, when the vinyl proton was *cis* to the nitro group, it resonated at lower field (7.75 ppm for **38** and 7.81 ppm for **39**) than in the case it was *trans* to it (6.43 ppm for **38** and 7.73 ppm for **39**).[12,30]

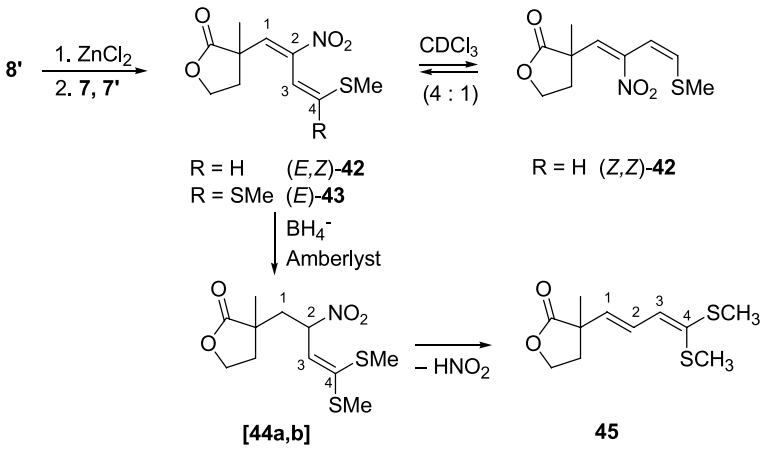
The *E*/*Z* mixtures **38** and **39** were reduced under different conditions. When Pd on carbon was used as the catalyst, lactones **38** afforded a 4:1 mixture of *cis* and *trans* diastereomers of lactam derivatives **40a** and **40b**. Differently from the cases previously reported for the nitroalkylated γ-lactones, no traces of the corresponding cyclic hydroxamic acid derivatives were detected. The geometry of the lactams **40a** and **40b** was established by NOE measurements. Irradiation of the methyl group signal at 1.33 ppm in **40a** caused enhancement of the H-5 signal at 4.75 ppm (6%). On the contrary, under the same conditions, the nitroalkenylated lactones **39** furnished the corresponding oxime **41**. Using Raney Ni as the catalyst, both mixtures **38** and **39** afforded the same diastereomeric mixture of lactams **40a** and **40b**, as a result of the concomitant hydrogenolysis of the methylthio group in **39**. Reduction with sodium borohydride was not satisfactory, even using the reagent supported on Amberlyst® A 26, which is known to reduce regioselectively the carbon–carbon double bond of the nitrovinyl moiety to the corresponding nitroalkane.[31]

The same conditions as above were used for the nitroalkenylation reaction of the enolate **8′** with the dienes **7** and **7′** to afford the corresponding addition–elimination products **42** and **43**, isolated from the respective reaction mixtures in 52 and 70% yield, the former as the (*E*,*Z*) diastereomer, the latter as the (*E*) isomer (Scheme 8).

Interestingly, in deuteriated chloroform, compound **42** slowly equilibrated into a 4:1 mixture of (*E*,*Z*) and (*Z*,*Z*)-diastereomers. This equilibration did not occur in the parent nitrodienamine **7′**. In the major isomer the H-1 vinyl proton resonated at 7.24 ppm, while in the minor isomer it absorbed at 6.29 ppm, values which are consistent with the *cis* and *trans* relationship of the same proton with the nitro group. DIFNOE measurements supported the *Z* geometry for the



Scheme 7.



Scheme 8.

C(3)–C(4) double bond, as it was originally in the reagent. On the contrary, an analogous equilibration between the (*E*) and (*Z*) forms was not observed for compound **43**, under the same conditions.

Reductions with hydrogen and metal, as a catalyst, were unsatisfactory as furnished complex mixtures of products not identified as yet. Treatment of compound **43** with polymer-supported borohydride resulted in the reduction of the sole C(1)–C(2) double bond,[31] affording a 3:2 **44a**,**b** diastereomeric mixture which was assigned the structure indicated in Scheme 8. These compounds however were not stable in $CDCl_3$ solution and were converted into the fully conjugated system **45** in (*E*) configuration. In this manner a conjugated ketene *S*,*S*-acetal was obtained whose reactivity as a precursor of an acyl anion[32] will be further investigated.

3. Conclusions

Differently from the cases of lithium enolates and enamines from cycloalkanones, for which the Michael addition of nitroolefins proceeded with high diastereoselectivity,[24,33] in general the lactone lithium enolates **1** and **1′** showed low to moderate diastereoselectivity, with the exception of the case in which both reactants were substituted by bulky groups. The stereochemical assignments were made either on the lactam derivatives or on the cyclic hydroxamic acids formed by reduction of the nitro group under different reaction conditions. The reduction with Raney Ni however needed milder conditions than those reported in the literature for other heterocyclic nitroalkylated compounds.[8b,15]

The nitroolefination reaction proceeded smoothly and quantitatively on the zinc enolates of **1′** and afforded new α,β-unsaturated nitroderivatives in *E* and *Z* configurations, the percentage of the latter increasing with the size of the substituent on the carbon bearing the nitro group.

4. Experimental

4.1. General

IR spectra were recorded on a Thermo Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 spectrometer (400 MHz for proton, 100.5 MHz for carbon) and on a Jeol EX-270 (270 MHz for proton, 67.9 MHz for carbon), using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Coupling constants are given in Hz. Mass spectra were recorded on a VG 7070 (70 eV) spectrometer and on an ion trap instrument Finnigan GCQ (70 eV). GLC analyses were run on a Carlo Erba GC 8000 instrument, the capillary columns being OV 1701 (25 m×0.32 mm) (carrier gas He, 40 KPa, split 1:50). TLC's were performed on Polygram® Sil G/UV_{254} silica gel pre-coated plastic sheets (eluant: light petroleum–ethyl acetate). CHN analyses were run on a Carlo Erba 1106 Elemental Analyser. Flash chromatography was run on silica gel 230–400 mesh ASTM (Kieselgel 60, Merck). Light petroleum refers to the fraction with bp 40–70 °C and ether to diethyl ether. γ-Butyrolactone **1**, α-methyl-γ-butyrolactone **1′** and (*E*)-2-nitrostyrene **3** were purchased from Aldrich. (*E*)-1-Nitropropene **2**,[34] (*E*)-2-nitro-1-phenylpropene **4**,[35] (*E*)-1-(2-methylthiophenyl)-1-nitro-2-pyrrolidinoethene **6**,[10] (1*E*,3*Z*)-4-methylthio-2-nitro-1-pyrrolidino-1,3-butadiene **7**[11] and 4,4-bis(methylthio)-2-nitro-1-pyrrolidino-1,3-butadiene **7′**[12] were prepared according to the literature.

4.1.1. (*E*)-2-Morpholinyl-1-nitro-1-phenylethene 5.[9] The synthesis was accomplished in accordance with a literature procedure,[36] using phenylnitromethane[37] as the nitroaliphatic component. Thus phenylnitromethane (0.09 mol, 12.3 ml), triethyl orthoformate (0.1 mol, 17 ml), morpholine (0.09 mol, 7.8 ml) and *p*-toluenesulfonic acid (0.09 g, 0.5 mmol) were heated under reflux for 1 h. Then the solvent was evaporated, the residue diluted with dichloromethane and purified through an alumina column (30× 2.5 cm) using dichloromethane as eluting agent. Although the crude reaction mixture contained both diastereomers, the nitroenamine **5** was isolated as pure *E*-isomer and crystallized from ethanol. 21% Yield, mp 150–152 °C, [lit.[9] for a 1:1 mixture of *E*- and Z-isomers, mp 125 °C]; IR (cm^{-1}, nujol): 3056 (=CH), 1626, 1592, 1573, 785, 772, 725, 696 (Ph), 1488, 1377 (NO_2); ^{1}H NMR (δ, ppm): 8.41 (1H, s, H–C=C), 7.42 (3H, m, Ph), 7.26 (2H, m, Ph) 3.59 (4H, s, CH_2–O), 3.14 (4H, s, CH_2–N).

4.2. General procedure for the Michael addition of nitroalkenes to lactone enolates

To a solution of lithium diisopropylamide (3.5 mmol, 2.3 ml of a 1.5 M solution in THF) in THF (16 ml), a solution of the γ-lactone (2.9 mmol) in 2.5 ml of THF was slowly added, at −78 °C. The mixture was stirred at −78 °C for 1 h and the appropriate nitroalkene (3.5 mmol) dissolved in 2.5 ml of THF was added dropwise. The mixture was stirred at −78 °C for 2 h, the temperature was allowed to raise to −40 °C and the reaction mixture was kept at this temperature for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was analysed by HRGC and purified by flash chromatography (light petroleum/ethyl acetate).

4.2.1. Reaction of the lactone 1 with (*E*)-1-nitropropene 2. *syn*- and *anti*-4,5-Dihydro-3-(1-methyl-2-nitroethyl)-2(3*H*)-furanone 15a and 15b. The isomers **15a** and **15b** (70% yield) were only partially separable by column chromatography, yellow oil, IR (cm^{-1}, neat): 1760 (OC=O), 1550, 1380 (NO_2); MS (*m*/*z*): 126 (7), 86 (56), 83 (10), 82 (16), 81 (10), 69 (14), 68 (16), 67 (34), 55 (100). Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.4; H, 6.20; N, 7.89.

Compound **15a**. ^{1}H NMR (δ, ppm): 4.73 (1H, dd, J_1= 6.6 Hz, J_2=12.8 Hz, $CHNO_2$), 4.48 (1H, dd, J_1=7.1 Hz, J_2=12.8 Hz, $CHNO_2$), 4.39 (1H, dt, J_1=2.4 Hz, J_2=J_3= 9.0 Hz, H-5), 4.24 (1H, dt, J_1=6.9 Hz, J_2=J_3=9.0 Hz, H-5), 2.74 (2H, m, H-3 and C*H*CH_3), 2.42 (1H, m, H-4), 2.14 (1H, m, H-4), 1.15 (3H, d, *J*=6.6 Hz, CH_3); ^{13}C NMR (δ, ppm): 176.7 (s), 78.5 (t, CH_2NO_2), 66.5 (t, C-5), 41.2 (d, C-3), 32.4 (d, *C*HCH_3), 26.2 (t, C-4), 13.3 (q, CH_3).

Compound **15b**. ^{1}H NMR (δ, ppm): 4.71 (1H, dd, J_1= 6.2 Hz, J_2=12.4 Hz, $CHNO_2$), 4.51 (1H, dd, J_1=7.1 Hz, J_2=12.4 Hz, $CHNO_2$), 4.38 (1H, dt, J_1=1.8 Hz, J_2=J_3= 9.0 Hz, H-5), 4.21 (1H, dt, J_1=6.7 Hz, J_2=J_3=9.0 Hz, H-5), 2.79 (1H, sept, *J*=6.9 Hz, C*H*CH_3), 2.69 (1H, ddd, J_1=11.3 Hz, J_2=8.4 Hz, J_3=6.9 Hz, H-3), 2.36 (1H, m, H-4), 2.10 (1H, m, H-4), 1.08 (3H, d, *J*=6.9 Hz, CH_3); ^{13}C NMR (δ, ppm): 177.1 (s), 78.9 (t, CH_2NO_2), 66.3 (t, C-5), 41.2 (d, C-3), 32.5 (d, *C*HCH_3), 25.3 (t, C-4), 14.5 (q, CH_3).

4.2.2. Reaction of the lactone 1′ with (*E*)-1-nitropropene 2. *syn*- and *anti*-4,5-Dihydro-3-methyl-3-(1-methyl-2-nitroethyl)-2(3*H*)-furanone 16a and 16b. The isomers **16a** and **16b** (60% yield) were obtained as a 1:9 inseparable mixture, yellow oil, IR (cm^{-1}, neat): 1764 (OC=O), 1550, 1380 (NO_2); MS (*m*/*z*): 140 (3), 100 (35), 97 (8), 96 (18), 83 (10), 82 (16), 81 (34), 71 (10), 69 (29), 67 (24), 57 (20), 55 (100). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.4; H, 6.92; N, 7.19.

For clarity sake the NMR values are given separately for each isomer.

Compound **16a**. ^{1}H NMR (δ, ppm): 4.93 (1H, dd, J_1= 4.0 Hz, J_2=12.4 Hz, $CHNO_2$), 4.19 (1H, dd, J_1=9.9 Hz, J_2=12.4 Hz, $CHNO_2$), 1.22 (3H, s, CH_3), 1.05 (3H, d, *J*= 7.0 Hz, CH_3); ^{13}C NMR (δ, ppm): 180.0 (s), 77.6 (t, CH_2NO_2), 64.8 (t, C-5), 44.5 (s, C-3), 36.9 (d, *C*HCH_3), 32.8 (t, C-4), 18.7 (q, CH_3 at C-3), 13.5 (q, CH_3 of the chain).

Compound **16b**. ^{1}H NMR (δ, ppm): 4.53 (1H, dd, J_1= 4.0 Hz, J_2=12.1 Hz, $CHNO_2$), 4.33 (1H, dd, J_1=10.4 Hz, J_2=12.1 Hz, $CHNO_2$), 4.26 (2H, m, 2H-5), 2.63 (1H, m, C*H*CH_3), 2.22 (1H, dt, J_1=13.2 Hz, J_2=J_3=8.8 Hz, H-4), 1.98 (1H, ddd, J_1=4.0 Hz, J_2=7.3 Hz, J_3=13.2 Hz, H-4), 1.31 (3H, s, CH_3), 1.10 (3H, d, *J*=7.0 Hz, CH_3); ^{13}C NMR (δ, ppm): 179.5 (s), 78.2 (t, CH_2NO_2), 65.0 (t, C-5), 44.6 (s, C-3), 37.6 (d, *C*HCH_3), 32.5 (t, C-4), 21.5 (q, CH_3 at C-3), 13.1 (q, CH_3 of the chain).

4.2.3. Reaction of lactone 1 with (*E*)-2-nitrostyrene 3. *syn* and *anti*-4,5-Dihydro-3-(2-nitro-1-phenylethyl)-2(3*H*)-furanone 17a and 17b. The isomers **17a** and **17b** (62% yield) were obtained as a 45:55 inseparable mixture, white solid, mp 65–69 °C, IR (cm^{-1}, nujol): 1762 (OC=O), 1603 (Ph), 1552, 1378 (NO_2); ^{13}C NMR (δ, ppm): 176.9 (s), 176.8 (s), 136.7 (s), 135.4 (s), 129.2 (d), 129.1 (d), 128.5 (d), 128.4 (d), 128.3 (d), 127.7 (d), and for **17a**: 77.7 (t, CH_2NO_2), 66.3 (t, C-5), 44.3 (d, CHPh), 41.3 (d, C-3), 27.6 (t, C-4), and for **17b**: 76.6 (t, CH_2NO_2), 66.7 (t, C-5), 43.8 (d, CHPh), 41.7 (d, C-3), 26.1 (t, C-4). MS (*m*/*z*): 235 ($M^{+\cdot}$, 2), 217 (8), 189 (21), 188 (66), 160 (23), 145 (51), 143 (22), 131 (18), 130 (100), 128 (19), 118 (34), 116 (34), 106 (26), 105 (90), 103 (33), 91 (85), 86 (13), 78 (18), 77 (30). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.3; H, 5.50; N, 6.04.

For clarity sake the NMR values are given separately for each isomer.

Compound **17a**. ^{1}H NMR (δ, ppm): 7.30 (5H, m, Ph), 5.44 (1H, dd, J_1=5.5 Hz, J_2=13.2 Hz, $CHNO_2$), 4.80 (1H, dd, J_1=9.9 Hz, J_2=13.2 Hz, $CHNO_2$), 4.25 (1H, dt, J_1= 2.8 Hz, J_2=J_3=8.8 Hz, H-5), 4.12 (1H, m, H-5), 3.80 (1H, m, CHPh), 2.92 (1H, q, *J*=9.8 Hz, H-3), 1.98 (2H, m, 2H-4); ^{1}H NMR (δ, ppm, $CDCl_3$ + drops of C_6D_6): 7.20 (5H, m, Ph), 5.33 (1H, dd, J_1=5.3 Hz, J_2=12.9 Hz, $CHNO_2$), 4.67 (1H, dd, J_1=9.9 Hz, J_2=12.9 Hz, $CHNO_2$), 4.06 (1H, dt, J_1=2.5 Hz, J_2=J_3=8.8 Hz, H-5), 3.93 (1H, m, H-5), 3.63 (1H, m, CHPh), 2.69 (1H, dt, J_1=8.8 Hz, J_2=J_3=10.2 Hz, H-3), 1.84 (1H, m, H-4), 1.71 (1H, m, H-4).

Compound **17b**. ^{1}H NMR (δ, ppm): 7.30 (5H, m, Ph), 5.20 (1H, dd, J_1=7.3 Hz, J_2=13.5 Hz, $CHNO_2$), 5.05 (1H, dd, J_1=8.4 Hz, J_2=13.5 Hz, $CHNO_2$), 4.12 (1H, m, H-5), 3.80 (2H, m, CHPh, H-5), 3.06 (1H, dt, J_1=4.6 Hz, J_2=J_3= 9.4 Hz, H-3), 2.38 (1H, m, H-4), 1.98 (1H, m, H-4); ^{1}H NMR (δ, ppm, $CDCl_3$ + drops of C_6D_6): 7.20 (5H, m, Ph), 5.07 (1H, dd, J_1=6.9 Hz, J_2=13.4 Hz, $CHNO_2$), 4.93 (1H, dd, J_1=8.0 Hz, J_2=13.4 Hz, $CHNO_2$), 3.93 (1H, m, H-5), 3.71 (1H, dt, J_1=4.5 Hz, J_2=J_3=8.0 Hz, CHPh), 3.63 (1H, m, H-5), 2.85 (1H, dt, J_1=4.5 Hz, J_2=J_3=9.3 Hz, H-3), 2.10 (1H, m, H-4), 1.84 (1H, m, H-4).

4.2.4. Reaction of lactone 1′ with (*E*)-2-nitrostyrene 3. *syn*- and *anti*-4,5-Dihydro-3-methyl-3-(2-nitro-1-phenylethyl)-2(3*H*)-furanone 18a and 18b. The isomers **18a** and

18b (80% yield), obtained in the ratio of 65:35 were not separable by flash chromatography, white solid, mp 99–101 °C; IR (cm^{-1}, nujol): 1756 (OC═O), 1602 (Ph), 1548, 1339 (NO_2); MS (*m/z*): 250 (MH^+, 1), 204 (4), 203 (13), 143 (16), 129 (13),128 (10), 116 (14), 114 (13), 106 (26), 105 (100), 104 (18), 101 (85), 100 (10), 98 (10), 92 (40), 85 (15), 83 (11), 78 (13), 77 (26), 71 (23), 69 (20), 57 (40), 56 (12), 55 (34). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.5; H, 6.17; N, 5.81.

For clarity sake the NMR values are given separately for each isomer.

Compound **18a**. ^{1}H NMR (δ, ppm): 7.28 (5H, m, Ph), 5.28 (1H, dd, J_1=4.0 Hz, J_2=13.4 Hz, $CHNO_2$), 4.93 (1H, dd, J_1=11.5 Hz, J_2=13.4 Hz, $CHNO_2$), 4.17 (1H, m, H-5), 4.08 (1H, m, H-5), 3.82 (1H, dd, J_1=4.0 Hz, J_2=11.5 Hz, CHPh), 2.28 (1H, m, H-4), 1.72 (1H, ddd, J_1=5.5 Hz, J_2=7.3 Hz, J_3=13.2 Hz, H-4), 1.29 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 179.8 (s), 135.0 (s), 128.8 (d), 128.5 (d), 128.3 (d), 75.2 (t, CH_2–NO_2), 64.8 (t, C-5), 47.3 (d, CHPh), 44.6 (s, C-3), 34.0 (t, C-4), 19.6 (q, CH_3).

Compound **18b**. ^{1}H NMR (δ, ppm): 7.28 (5H, m, Ph), 5.09 (1H, dd, J_1=11.2 Hz, J_2=13.2 Hz, $CHNO_2$), 4.89 (1H, dd, J_1=4.2 Hz, J_2=13.2 Hz, $CHNO_2$), 4.08 (1H, m, H-5), 3.70 (1H, dd, J_1=4.2 Hz, J_2=11.2 Hz, CHPh), 3.59 (1H, dt, J_1=J_2=9.0 Hz, J_3=4.8 Hz, H-5), 2.28 (1H, m, H-4), 1.98 (1H, ddd, J_1=4.8 Hz, J_2=8.1 Hz, J_3=12.8 Hz, H-4), 1.36 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 179.9 (s), 135.8 (s) 129.0 (d), 128.4 (d), 128.3 (d), 76.5 (t, CH_2–NO_2), 65.5 (t, C-5), 50.2 (d, CHPh), 45.5 (s, C-3), 33.3 (t, C-4), 23.4 (q, CH_3).

4.2.5. Reaction of the lactone 1 with (*E*)-2-nitro-1-phenylpropene 4. 4,5-Dihydro-3-(2-nitro-1-phenylpropyl)-2(3*H*)-furanone 19a,b,c,d. Four isomers **19a**, **19b**, **19c** and **19d** in 53:22:14:11 ratio were identified in the ^{1}H NMR spectrum of the crude reaction mixture. They were separated by flash chromatography.

Compound **19a**. 30% Yield, white solid, mp 125–126 °C, from ether; IR (cm^{-1}, nujol): 1756, (OC═O), 1546, 1377 (NO_2); ^{1}H NMR (δ, ppm): 7.28 (5H, m, Ph), 5.72 (1H, dq, J_1=11.0 Hz, J_2=J_3=J_4=6.6 Hz, $CHNO_2$), 4.09 (1H, q, J=8.2 Hz, H-5), 3.64 (1H, dt, J_1=4.8 Hz, J_2=J_3=8.2 Hz, H-5), 3.45 (1H, dd, J_1=4.8 Hz, J_2=11.0 Hz, CHPh), 3.12 (1H, dt, J_1=4.8 Hz, J_2=J_3=8.2 Hz, H-3), 2.38 (1H, m, H-4), 1.92 (1H, dq, J_1=13.0 Hz, J_2=J_3=J_4=8.2 Hz, H-4), 1.82 (3H, d, J=6.6 Hz, CH_3), ^{13}C NMR (δ, ppm): 177.0 (s), 135.6 (s), 128.9 (d), 128.5 (d), 128.4 (d), 85.4 (d, $CHNO_2$), 66.8 (t, C-5), 50.0 (d, CHPh), 39.9 (d, C-3), 26.1 (t, C-4), 18.6 (q, CH_3); MS (*m/z*): 250 (MH^+, 4), 203 (26), 202 (31), 144 (25), 143 (63), 142 (38), 131 (29), 129 (21), 118 (100), 116 (27), 106 (19), 103 (31), 102 (29), 91 (57), 79 (13), 77 (19). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.5; H, 5.87; N, 5.28.

Compound **19b**. 17% Yield; white solid, mp 95–97 °C, IR (cm^{-1}, nujol): 1762, (OC═O), 1600 (Ph), 1550, 1388 (NO_2); ^{1}H NMR (δ, ppm): 7.36 (3H, m, Ph), 7.26 (2H, m, Ph), 5.89 (1H, dq, J_1=11.1 Hz, J_2=J_3=J_4=6.7 Hz, $CHNO_2$), 4.06 (1H, q, J=8.5 Hz, H-5), 3.70 (1H, dt, J_1=4.3 Hz, J_2=J_3=8.5 Hz, H-5), 3.44 (1H, dd, J_1=4.2 Hz, J_2=11.1 Hz, CHPh), 2.88 (1H, dt, J_1=4.2 Hz, J_2=J_3=8.5 Hz, H-3), 2.46 (1H, m, H-4), 1.91 (1H, dq, J_1=12.8 Hz, J_2=J_3=J_4=8.5 Hz, H-4), 1.33 (3H, d, J=6.7 Hz, CH_3); ^{13}C NMR (δ, ppm): 176.8 (s), 135.0 (s), 129.4 (d), 129.3 (d), 128.6 (d), 83.5 (d, $CHNO_2$), 66.6 (t, C-5), 50.6 (d, CHPh), 40.5 (d, C-3), 26.5 (t, H-4), 19.5 (q, CH_3); MS (*m/z*): 249 ($M^{+\cdot}$, 3), 203 (26), 202 (36), 143 (14), 131 (37), 129 (27), 118 (38), 117 (100), 115 (29), 105 (15), 91 (67), 84 (13), 77 (14). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.9; H, 6.23; N, 5.33.

Compound **19c** (in admixture with **19a**). ^{1}H NMR (δ, ppm): 7.21 (5H, m, Ph), 5.68 (1H, dq, J_1=5.5 Hz, J_2=J_3=J_4=6.6 Hz, $CHNO_2$), 4.13 (2H, m, 2H-5), 3.40 (2H, m, CHPh and H-3), 2.12 (1H, m, H-4), 1.85 (1H, m, H-4), 1.54 (3H, d, J=6.6 Hz, CH_3); ^{13}C NMR (δ, ppm): 177.5 (s), 134.6 (s), 128.7 (d), 128.6 (d), 128.2 (d), 82.5 (d, $CHNO_2$), 66.2 (t, C-5), 50.1 (d, CHPh), 39.7 (d, C-3), 27.2 (t, H-4), 17.5 (q, CH_3).

Compound **19d**. Oil, 6% yield; IR (cm^{-1}, neat): 1766, 1712 (OC═O), 1602 (Ph), 1550, 1390 (NO_2); ^{1}H NMR (δ, ppm): 7.34 (3H, m, Ph), 7.16 (2H, m, Ph), 5.31 (1H, dq, J_1=9.1 Hz, J_2=J_3=J_4=6.6 Hz, $CHNO_2$), 4.13 (2H, m, 2H-5), 3.87 (1H, dd, J_1=6.2 Hz, J_2=9.1 Hz, CHPh), 2.84 (1H, dt, J_1=6.2 Hz, J_2=J_3=9.6 Hz, H-3), 2.34 (1H, m, H-4), 2.09 (1H, m, H-4), 1.45 (3H, d, J=6.6 Hz, CH_3); MS,(*m/z*): 203 (15), 202 (34), 176 (19), 148 (28), 143 (15), 131 (46), 130 (47), 129 (36), 118 (35), 117 (100), 116 (20), 115 (42), 105 (18), 104 (14), 103 (10), 91 (95), 77 (22).

4.2.6. Reaction of the lactone 1′ with (*E*)-2-nitro-1-phenylpropene 4. 4,5-Dihydro-3-methyl-3-(2-nitro-1-phenylpropyl)-2(3*H*)-furanone 20a,b,c. The isomers **20a**, **20b** and **20c** (61%, 35% and 4% relative ratio) were obtained acidifying the reaction mixture with 0.43 ml (7 mmol) of glacial acetic acid in 1.5 ml of THF, at −78 °C. The temperature was allowed to raise to −40 °C and, after 15 min, 25 ml of water was added. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the crude reaction mixture was purified by flash chromatography (light petroleum/ethyl acetate) to give the mixture of lactones **20a**,**b**,**c** (45% yield) which could not be separated. White solid, mp 89–92 °C, IR (cm^{-1}, nujol): 1755 (OC═O), 1602 (Ph), 1545, 1334 (NO_2); MS (*m/z*): 263 ($M^{+\cdot}$, 0.8), 221 (10), 206 (44), 145 (14), 131 (18), 129 (13), 119 (100), 118 (39), 116 (21), 106 (42), 102 (13), 101 (75), 99 (10), 91 (48), 77 (20), 69 (14), 57 (36), 56 (16), 55 (43). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.0; H, 6.74; N, 5.31.

For clarity sake the NMR values are given separately for each isomer.

Compound **20a**. ^{1}H NMR (δ, ppm): 7.31 (3H, m, Ph), 7.23 (2H, m, Ph), 5.31 (1H, quintet, J_1=6.6 Hz, $CHNO_2$), 4.18 (1H, dt, J_1=8.0 Hz, J_2=9.2 Hz, H-5), 4.02 (1H, ddd, J_1=4.8 Hz, J_2=8.0 Hz, J_3=9.2 Hz, H-5), 3.44 (1H, d, J=6.6 Hz, CHPh), 2.44 (1H, dt, J_1=8.0 Hz, J_2=13.2 Hz, H-4), 2.08 (1H, ddd, J_1=4.8 Hz, J_2=8.0 Hz, J_3=13.2 Hz, H-4), 1.59 (3H, d, J=6.6 Hz, CH_3), 1.50 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 180.2 (s), 135.6 (s), 130.0 (d), 128.7 (d),

128.1 (d), 83.2 (d, $CHNO_2$), 64.8 (t, C-5), 54.3 (d, CHPh), 45.7 (s, C-3), 33.3 (t, C-4), 22.2 (q, CH_3), 19.9 (q, CH_3).

Compound **20b**. ^{1}H NMR (δ, ppm): 7.33 (5H, m, Ph), 5.22 (1H, dq, $J_1=9.5$ Hz, $J_2=J_3=6.6$ Hz, $CHNO_2$), 4.18 (1H, m, H-5), 4.10 (1H, ddd, $J_1=4.8$ Hz, $J_2=8.4$ Hz, $J_3=9.5$ Hz, H-5), 3.62 (1H, d, $J=9.5$ Hz, CHPh), 2.47 (1H, m, H-4), 2.05 (1H, m, H-4), 1.34 (3H, d, $J=6.6$ Hz, CH_3), 1.26 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 179.4 (s), 135.3 (s), 129.8 (d), 128.6 (d), 128.2 (d), 83.6 (d, $CHNO_2$), 65.1 (t, H-5), 53.4 (d, CHPh), 45.7 (s, C-3), 33.4 (t, H-4), 22.2 (q, CH_3), 19.9 (q, CH_3).

Compound **20c**. Only a few signals were identified: ^{1}H NMR (δ, ppm): 5.45 (1H, dq, $J_1=6.6$ Hz, $J_2=9.5$ Hz, $CHNO_2$), 3.89 (1H, dt, $J_1=3.9$ Hz, $J_2=9.2$ Hz, H-5), 3.61 (1H, d, $J=9.5$ Hz, CHPh), 2.63 (1H, m, H-4), 1.93 (1H, m, H-4), 1.29 (3H, d, $J=6.6$ Hz, CH_3); ^{13}C NMR (δ, ppm): 129.1 (d), 82.5 (d, $CHNO_2$), 65.7 (t, C-5), 54.8 (d, CHPh), 32.6 (s).

4.3. Acidification of the lithium nitronates 13 and 14 with 3 N HCl

The crude reaction mixture containing the lithium nitronate was acidified with 20 ml of 3 N HCl, the mixture was stirred overnight and extracted three times with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography (light petroleum/ethyl acetate). In the case of nitronate **13**, from the complex mixture containing the Nef products **32a** and **32b** in 3:2 ratio and the oxime **34**, only **32a** and **34** could be isolated as pure compounds, by flash chromatography. In the case of nitronate **14** the Nef product **33** and the oxime **35** could be isolated by flash chromatography (see text).

4.3.1. 4,5-Dihydro-3-(2-oxo-1-phenylpropyl)-2(3*H*)-furanone 32a. 19% Yield, white solid, mp 87–88 °C from ether; IR (cm^{-1}, nujol): 1753 (OC=O), 1714 (C=O); ^{1}H NMR (δ, ppm): 7.33 (3H, m, Ph), 7.21 (2H, m, Ph), 4.15 (2H, m, 2H-5), 4.08 (1H, d, $J=7.7$ Hz, CHPh), 3.56 (1H, ddd, $J_1=7.7$ Hz, $J_2=8.7$ Hz, $J_3=12.1$ Hz, H-3), 2.20 (3H, s, CH_3), 2.12 (1H, m, H-4), 1.82 (1H, m, H-4); ^{13}C NMR (δ, ppm): 206.1 (s, C=O), 177.9 (s, COO), 134.7 (s), 129.0 (d), 128.8 (d), 128.0 (d), 66.9 (t, C-5), 58.3 (d, CHPh), 41.3 (d, C-3), 29.4 (q, CH_3), 26.4 (t, C-4); MS (*m*/*z*): 218 ($M^{+\cdot}$, 1), 176 (53), 149 (76), 148 (32), 132 (47), 131 (100), 118 (18), 117 (19), 116 (28), 105 (31), 92 (74), 77 (18). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.3; H, 6.39.

4.3.2. 4,5-Dihydro-3-(2-oxo-1-phenylpropyl)-2(3*H*)-furanone 32b. The lactone **19d** was submitted to the Nef reaction conditions according to the literature,[19] furnishing a 3:1 mixture of **32a** and **32b**.

Compound **32b**. ^{1}H NMR (δ, ppm): 7.36 (5H, m, Ph), 4.48 (1H, dt, $J_1=2.3$ Hz, $J_2=J_3=9.0$ Hz, H-5), 4.28 (1H, d, $J=5.1$ Hz, CHPh), 4.16 (1H, m, H-5), 2.89 (1H, ddd, $J_1=5.1$ Hz, $J_2=9.5$ Hz, $J_3=11.0$ Hz, H-3), 2.56 (1H, quintet, $J=10.4$ Hz, H-4), 2.21 (1H, m, H-4), 2.08 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 206.3 (s, C=O), 177.8 (s, COO), 136.3 (s), 129.3 (d), 128.7 (d), 127.9 (d), 66.6 (t, C-5), 58.2 (d, CHPh), 42.8 (d, C-3), 29.1 (q, CH_3), 25.1 (t, C-4).

4.3.3. 4,5-Dihydro-3-methyl-3-(2-oxo-1-phenylpropyl)-2(3*H*)-furanone 33. 17% Yield; white solid, mp 67–70 °C; IR (cm^{-1}, nujol): 1772 (OC=O), 1701(C=O), 1580 (Ph); ^{1}H NMR (δ, ppm): 7.33 (3H, m, Ph), 7.28 (2H, m, Ph), 4.27 (1H, s, CHPh), 4.06 (1H, q, $J_1=8.6$ Hz, H-5), 3.58 (1H, dt, $J_1=5.1$ Hz, $J_2=8.6$ Hz, H-5), 2.63 (1H, m, H-4), 2.23 (1H, m, H-4), 2.12 (3H, s, CH_3–CO), 1.38 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 205.6 (s, C=O), 180.6 (s, COO), 133.4 (s), 130.0 (d), 128.9 (d), 128.2 (d), 65.6 (t, C-5), 62.7 (d, CHPh), 46.1 (s, C-3), 31.1 (q, CH_3–CO), 30.9 (t, C-4), 23.3 (q, CH_3); MS (*m*/*z*): [232 ($M^{+\cdot}$) at 20 eV], 190 (25), 175 (15), 162 (21), 144 (44), 129 (25), 117 (22), 115 (20), 106 (52), 105 (65), 91 (100), 77 (41), 65 (10), 57 (10). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.5; H, 6.80.

4.3.4. 4,5-Dihydro-3-(2-hydroxyimino-1-phenylpropyl)-2(3*H*)-furanone 34. 15% Yield; white solid, mp 127–129 °C from light petroleum/ether; IR (cm^{-1}, nujol): 3329 (OH), 1730 (OC=O), 1655 (C=N), 1600 (Ph); ^{1}H NMR (δ, ppm): 8.00 (1H, bs, OH), 7.27 (5H, m, Ph), 4.40 (1H, dt, $J_1=3.0$ Hz, $J_2=J_3=8.8$ Hz, H-5), 4.16 (1H, q, $J=8.8$ Hz, H-5), 4.10 (1H, d, $J=5.9$ Hz, CHPh), 2.99 (1H, dt, $J_1=5.9$ Hz, $J_2=J_3=8.8$ Hz, H-3), 2.66 (1H, dq, $J_1=12.0$ Hz, $J_2=J_3=J_4=8.8$ Hz, H-4), 1.99 (1H, m, H-4), 1.75 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 178.3 (s, COO), 155.8 (s, C=N), 138.5 (s), 128.8 (d), 128.4 (d), 127.4 (d), 66.7 (t, C-5), 50.4 (d, CHPh), 43.2 (d, C-3), 24.7 (t, C-4), 13.8 (q, CH_3); MS (*m*/*z*): 233 ($M^{+\cdot}$, 15), 216 (79), 185 (20), 175 (22), 174 (40), 173 (32), 172 (18), 170 (26), 157 (26), 156 (17), 149 (41), 148 (49), 147 (20), 132 (32), 130 (49), 128 (22), 121 (26), 118 (30), 116 (65), 92 (100), 89 (29), 81 (39),77 (65). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.2; H, 6.58; N, 6.02.

4.3.5. 4,5-Dihydro-3-methyl-3-(2-hydroxyimino-1-phenylpropyl)-2(3*H*)-furanone 35. 10% Yield, white solid, mp 117–119 °C. IR (cm^{-1}, nujol): 3271 (OH), 1758 (C=O), 1670 (C=N); ^{1}H NMR (δ, ppm): 7.80 (1H, bs, OH), 7.30 (5H, m, Ph), 4.03 (1H, dt, $J_1=7.3$ Hz, $J_2=8.8$ Hz, H-5), 3.89 (1H, s, CHPh), 3.56 (1H, dt, $J_1=5.1$ Hz, $J_2=8.8$ Hz, H-5), 2.65 (1H, ddd, $J_1=7.3$ Hz, $J_2=8.8$ Hz, $J_3=13.6$ Hz, H-4), 2.17 (1H, m, H-4), 1.79 (3H, s, CH_3C=N–OH), 1.45 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 181.4 (s, COO), 156.6 (s, C=N), 136.1 (s), 130.1 (d), 128.5 (d), 127.8 (d), 65.4 (t, C-5), 56.5 (d, CHPh), 46.7 (s, C-3), 31.7 (t, C-4), 24.5 (q, CH_3), 15.5 (q, CH_3); MS (*m*/*z*): 247 ($M^{+\cdot}$,16), 202 (10), 186 (18), 149 (43), 148 (100), 131 (25), 130 (42), 129 (26), 117 (19), 116 (15), 115 (33), 106 (25), 105 (17), 100 (13), 95 (17), 91 (42), 77 (25), 69 (10), 55(13). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.9; H, 7.00; N, 5.56.

4.3.6. 1-(Tetrahydro-3-methyl-2-oxofuryl)-1-phenylpropan-2-ylideneazinic acid 37. The reaction between the lithium enolate of **1′** and (*E*)-2-nitro-1-phenylpropene **4**, carried out in accordance with the general procedure, was quenched by addition of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 three times in order to separate the nitroalkylated lactones. From

the mother liquors, acidified to pH 2 with 3 N HCl, the nitronic acid **37** precipitated as a white solid which was washed with ether. 10% Yield, mp 100–102 °C; IR (cm^{-1}, nujol): 2668 (OH); 1754 (COO), 1658 (C=N); ^1H NMR (DMSO-d_6, δ, ppm) 7.20 (5H, m, Ph), 4.70 (1H, s, CHPh), 4.18 (1H, q, $J=8.4$ Hz, H-5), 3.93 (1H, dt, $J_1=2.7$ Hz, $J_2=J_3=8.4$ Hz, H-5), 2.43 (1H, m, H-4), 2.12 (1H, m, H-4), 2.03 (3H, s, CH_3), 1.23 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6, δ, ppm): 180.9 (s), 137.9 (s), 129.3 (d), 129.0 (d), 127.7 (d), 121.2 (s), 65.4 (t), 50.8 (d), 46.4 (t), 31.2 (s), 23.0 (q), 16.6 (q); MS (*m/z*): 262 ($M-H^{\neg+}$, 0.3), 247 (0.4), 216 (1.3), 190 (30), 175 (18), 162 (13), 145 (27), 144 (58), 130 (35), 118 (27), 116 (28), 106 (44), 100 (10), 99 (5), 92 (100), 77 (47), 55 (7), 51 (17). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.7; H, 6.71; N, 5.26.

4.4. General procedure for the reduction with Raney Ni

The nitro compound (0.85 mmol) was dissolved in 1:1 EtOH/ethyl acetate (20 ml) and one teaspoon of Raney Ni (Aldrich) was added. The apparatus was evacuated and flushed with H_2. The mixture was stirred at room temperature under H_2 atmosphere for 16 h, then filtered on Celite and the solvent was evaporated.

4.4.1. (3*R,4*R**)- and (3*R**,4*S**)-3-(2-Hydroxyethyl)-4-methyl-2-pyrrolidinone 21a and 21b.** Reduction of the nitroalkylated lactone **15a** gave the *trans* isomer **21a**: 80% yield, white solid, mp 78–80 °C, IR (cm^{-1}, nujol): 3165 (OH and NH), 1672 (NHC=O); ^1H NMR (δ, ppm): 7.03 (1H, bs, NH), 4.9 (1H, bs, OH), 3.84 (1H, m, CHOH), 3.72 (1H, m, CHOH), 3.49 (1H, t, $J=9.0$ Hz, H-5), 2.99 (1H, t, $J=9.0$ Hz, H-5), 2.18 (1H, m), 2.09 (1H, m), 1.78 (2H, m, CH_2CH_2OH), 1.15 (3H, d, $J=6.9$ Hz, CH_3); ^{13}C NMR (δ, ppm): 181.6 (s), 62.2 (t, CH_2OH), 49.7 (d, C-3), 48.7 (t, C-5), 37.1 (d, C-4), 32.4 (t, CH_2CH_2OH), 17.3 (q, CH_3); MS (*m/z*): 144 (MH^+, 41), 126 (6), 113 (9), 112 (10), 99 (22), 98 (33), 96 (17), 85 (18), 84 (100), 67 (9). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.5; H, 8.90; N, 9.59.

Reduction of nitroalkylated lactone **15b** gave the *cis* isomer **21b**: 80% yield, white solid, mp 62–65 °C, IR (cm^{-1}, nujol): 3165 (OH and NH), 1672 (NHC=O); ^1H NMR (δ, ppm): 6.77 (1H, bs, NH), 4.4 (1H, bs, OH), 3.82 (1H, m, CHOH), 3.70 (1H, m, CHOH), 3.48 (1H, dd, $J_1=6.0$ Hz, $J_2=9.5$ Hz, H-5), 2.94 (1H, bd, $J=9.5$ Hz, H-5), 2.50 (2H, m, H-3 and H-4), 1.70 (2H, m, CH_2CH_2OH), 0.97 (3H, d, $J=6.9$ Hz, CH_3); ^{13}C NMR (δ, ppm): 180.3 (s), 62.2 (t, CH_2OH), 48.6 (t, C-5), 45.5 (d, C-3), 33.5 (d, C-4), 28.5 (t, CH_2CH_2OH), 14.6 (q, CH_3); MS (*m/z*): 144 (MH^+, 49), 126 (14), 112 (22), 99 (27), 98 (69), 96 (23), 85 (23), 84 (100), 67 (22). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58. 5; H, 9.00; N, 9.58.

4.4.2. (3*R,4*R**)- and (3*R**,4*S**)-3-(2-Hydroxyethyl)-3,4-dimethyl-2-pyrrolidinone 22a and 22b.** The two isomers were obtained as a 1:9 inseparable mixture, 80% yield, white solid, mp 88 °C (from light petroleum/ethyl acetate); IR (cm^{-1}, nujol): 3330 (OH and NH), 1680 (NHC=O); MS (*m/z*): 158 ($M+H^{\neg+}$, 13), 113 (40), 112 (54), 98 (100), 84 (17), 67 (11), 55 (22). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.3; H, 9.41; N, 9.14.

For clarity sake the NMR values of the two isomers are given separately.

Compound **22a** in admixture with **22b**. ^1H NMR (δ, ppm) (only few signals were identified): 6.97 (1H, bs, NH), 2.25 (1H, m, H-4), 1.70 (1H, ddd, $J_1=5.8$ Hz, $J_2=10.2$ Hz, $J_3=15.7$ Hz, C*H*CH_2OH), 1.42 (1H, m, C*H*CH_2OH), 0.94 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 184.5 (s), 58.7 (t, CH_2OH), 47.0 (t, C-5), 45.9 (s, C-3), 39.7 (d, C-4), 38.2 (t, *C*H_2CH_2OH), 15.1 (q, CH_3 at C-3), 11.4 (q, CH_3 at C-4).

Compound **22b**. ^1H NMR (δ, ppm). 6.92 (1H, bs, NH), 3.82 (1H, m, C*H*OH), 3.79 (1H, bs, OH), 3.63 (1H, m, C*H*OH), 3.35 (1H, dd, $J_1=8.2$ Hz, $J_2=9.0$ Hz, H-5), 2.92 (1H, dd, $J_1=8.2$ Hz, $J_2=9.7$ Hz, H-5), 2.13 (1H, m, H-4), 1.73 (1H, ddd, $J_1=5.3$ Hz, $J_2=9.0$ Hz, $J_3=14.1$ Hz, C*H*CH_2OH), 1.35 (1H, dt, $J_1=4.7$ Hz, $J_2=14.1$ Hz, C*H*CH_2OH), 1.13 (3H, s, CH_3), 0.96 (3H, d, $J=7.3$ Hz, CH_3); ^{13}C NMR (δ, ppm): 184.0 (s), 58.9 (t, CH_2OH), 46.6 (t, C-5), 44.6 (s, C-3), 42.0 (d, C-4), 34.0 (t, *C*H_2CH_2OH), 20.5 (q, CH_3 at C-3), 12.6 (q, CH_3 at C-4).

4.4.3. (3*R,4*S**)- and (3*R**,4*R**)-3-(2-Hydroxyethyl)-4-phenyl-2-pyrrolidinone 23a and 23b.** Treatment of the crude reaction mixture with light petroleum/ethyl acetate gave a 3:2 mixture of **23a** and **23b** as a white solid (70% yield), mp 90–93 °C, IR (cm^{-1}, nujol): 3366, 3262 (OH and NH), 1693 (NHC=O), 1638 (Ph); MS (*m/z*): 206 (MH^+, 16), 160 (100), 159 (90), 147 (13), 118 (13), 117 (43), 115 (33), 104 (16), 91 (13), 84 (14), 78 (11). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.0; H, 7.11; N, 6.64.

For clarity sake the NMR values of the isomeric mixture are given separately for each isomer.

Compound **23a**. ^1H NMR (δ, ppm): 7.64 (1H, bs, NH), 7.28 (5H, m, Ph), 4.5 (1H, bs, OH), 3.74–3.50 (3H, m, CH_2OH, H-5), 3.41 (1H, t, $J=9.5$ Hz, H-5), 3.27 (1H, q, $J=9.5$ Hz, H-4), 2.70 (1H, dt, $J_1=J_2=9.5$ Hz, $J_3=4.0$ Hz, H-3), 1.85 (1H, m, C*H*CH_2OH), 1.74 (1H, m, C*H*CH_2OH); ^{13}C NMR (δ, ppm): 180.4 (s), 140.0 (s), 129.0 (2d), 128.7 (2d), 127.6 (d), 61.6 (t, CH_2OH), 49.0 (d, C-3), 48.9 (t, C-5), 48.4 (d, C-4), 32.4 (t, *C*H_2CH_2OH).

Compound **23b**. ^1H NMR (δ, ppm): 7.67 (1H, bs, NH), 7.28 (5H, m, Ph), 4.5 (1H, bs, OH), 3.79 (1H, dd, $J_1=7.1$ Hz, $J_2=9.7$ Hz, H-5), 3.74–3.50 (4H, m, CH_2OH, H-5, H-4), 2.92 (1H, dt, $J_1=J_2=8.7$ Hz, $J_3=5.0$ Hz, H-3), 1.48 (1H, m, C*H*CH_2OH), 1.30 (1H, m, C*H*CH_2OH); ^{13}C NMR (δ, ppm): 181.2 (s), 140.4 (s), 127.8 (2d), 127.5 (2d), 127.3 (d), 61.4 (t, CH_2OH), 48.0 (t, C-5), 45.3 (d, C-3), 44. 3 (d, C-4), 29.9 (t, *C*H_2CH_2OH).

4.4.4. (3*R,4*R**)- and (3*R**,4*S**)-3-(2-Hydroxyethyl)-3-methyl-4-phenyl-2-pyrrolidinone 24a and 24b.** The 65:35 crude mixture of **24a** and **24b** (70% overall yield), obtained from the reduction, was purified by flash chromatography. The two isomeric lactams could be separated only partially. Semisolid material, IR (cm^{-1}, neat): 3260 (OH and NH), 1685 (NHC=O); MS (*m/z*): 220 (MH^+, 20), 204 (27), 175 (100), 174 (69), 160 (68), 158 (28), 131 (14), 129 (18), 128 (15), 117 (11), 115 (19), 104 (21), 98 (54), 91 (16), 78 (11).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.0; H, 7.88; N, 6.25.

Compound **24a**. ^{1}H NMR (δ, ppm). 7.33 (3H, m, *m*-, *p*-ArH), 7.23 (2H, m, *o*-ArH), 6.31 (1H, bs, NH), 4.53 (1H, dd, $J_1=8.4$ Hz, $J_2=2.6$ Hz, OH), 3.85–3.60 (4H, m, CH_2OH, 2H-5), 3.48 (1H, dd, $J_1=10.1$ Hz, $J_2=7.8$ Hz, H-4), 1.90 (1H, m, CHCH$_2$OH), 1.72 (1H, m, CHCH$_2$OH), 0.93 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.4 (s), 136.4 (s), 129.1 (2d), 128.5 (2d), 127.7 (d), 58.6 (t, CH_2OH), 51.3 (d, C-4), 47.5 (s, C-3), 44.5 (t, C-5), 38.5 (t, *C*H$_2$CH$_2$OH), 17.4 (q, CH_3).

Compound **24b**. ^{1}H NMR (δ, ppm). 7.33 (3H, m, *m*-, *p*-ArH), 7.21 (2H, m, *o*-ArH), 6.34 (1H, bs, NH), 3.85–3.60 (4H, m, CH_2OH, H-5, H-4), 3.62 (1H, dd, $J_1=2.1$ Hz, $J_2=$ 10.1 Hz, OH), 3.36 (1H, t, $J=7.7$ Hz, H-5), 1.66 (1H, m, CHCH$_2$OH), 1.37 (3H, s, CH_3), 0.98 (1H, m, CHCH$_2$OH); ^{13}C NMR (δ, ppm): 183.6 (s), 137.8 (s), 128.7 (2d), 128.4 (2d), 127.6 (d), 58.7 (t, CH_2OH), 53.6 (d, C-4), 46.5 (s, C-3), 44.4 (t, C-5), 35.7 (t, *C*H$_2$CH$_2$OH), 21.4 (q, CH_3).

4.4.5. (3*R,4*R**,5*S**)-3-(2-Hydroxyethyl)-5-methyl-4-phenyl-2-pyrrolidinone 25a.** The crude reaction mixture obtained from the reduction of **19a** was treated with light petroleum/ethyl acetate to afford **25a** (70% yield) as a white solid, mp 123–125 °C; IR (cm^{-1}, nujol): 3260 (OH and NH), 1690 (NHC=O), 1600 (Ph); ^{1}H NMR (CD_3OD, δ, ppm): 7.27 (3H, m, *m*-, *p*-ArH), 7.12 (2H, bd, *o*-ArH), 4.09 (1H, dq, $J_1=6.6$ Hz, $J_2=5.8$ Hz, H-5), 3.54 (1H, dd, $J_1=$ 7.7 Hz, $J_2=5.8$ Hz, H-4), 3.45 (2H, m, CH_2OH), 3.03 (1H, ddd, $J_1=8.9$ Hz, $J_2=7.7$ Hz, $J_3=5.8$ Hz, H-3), 1.86 (1H, m, CHCH$_2$OH), 1.30 (1H, m, CHCH$_2$OH), 0.83 (3H, d, $J=$ 6.6 Hz, CH_3); ^{13}C NMR (δ, ppm): 183.7 (s), 139.3 (s), 132.5 (2d), 131.3 (2d), 130.4 (d), 65.1 (t, CH_2OH), 56.0 (d), 54.2 (d), 51.2 (d, C-3), 32.4 (t, *C*H$_2$CH$_2$OH), 19.5 (q, CH_3); MS (*m*/*z*): 220 (MH$^+$, 14), 175 (100), 174 (19), 131 (15), 118 (27), 117 (65), 115 (33), 91 (10). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 69.9; H, 7.41; N, 6.14.

4.4.6. (3*R,4*R**,5*R**)- and (3*R**,4*R**,5*S**)-3,5-Dimethyl-3-(2-hydroxyethyl)-4-phenyl-2-pyrrolidinone 26a and 26b.** A 1:1 mixture of nitroalkylated lactones **20a** and **20b** was reduced under the above mentioned conditions to give a 1:1 mixture of the corresponding lactams **26a** and **26b** (70% overall yield). The same compounds were obtained from the reduction with Raney Ni of the nitronic acid **37**, although in a 7:3 molar ratio. The two isomers could not be separated. White solid, mp 94–100 °C, IR (cm^{-1}, $CHCl_3$): 3336 (OH and NH), 1680 (NHC=O), 1602 (Ph); MS (*m*/*z*): 234 (MH$^+$, 14), 218 (49), 203 (16), 190 (27), 189 (100), 188 (82), 174 (62), 162 (28), 161 (14), 160 (15), 132 (28), 131 (87), 129 (42), 128 (20), 118 (28), 117 (55), 116 (22), 115 (37), 112 (35), 91 (46). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.9; H, 8.11; N, 5.89.

For clarity sake the NMR values of the isomeric mixture are given separately for each isomer.

Compound **26a**. ^{1}H NMR (CD_3OD, δ, ppm). 7.25 (3H, m, *m*-, *p*-ArH), 7.12 (2H, bd, *o*-ArH), 4.25 (1H, dq, $J_1=6.2$ Hz, $J_2=6.9$ Hz, H-5), 3.8–3.6 (2H, m, CH_2OH), 3.38 (1H, d, $J_1=6.2$ Hz, H-4), 1.90 (2H, m, CH_2CH$_2$OH), 0.91 (3H, d, $J=6.9$ Hz, CH_3), 0.81 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.0 (s), 136.9 (s), 130.1 (2d), 128.1 (2d), 127.7 (d), 59.2 (t, CH_2OH), 57.4 (d, C-4), 50.6 (d, C-5), 47.7 (s, C-3), 40.5 (t, *C*H$_2$CH$_2$OH), 18.7 (q, CH_3 at C-3), 17.1 (q, CH_3 at C-5).

Compound **26b**. ^{1}H NMR (CD_3OD, δ, ppm). 7.25 (3H, m, *m*-, *p*-ArH), 7.12 (2H, bd, *o*-ArH), 4.12 (1H, dq, $J_1=6.2$ Hz, $J_2=9.9$ Hz, H-5), 3.8–3.6 (2H, m, CH_2OH), 3.07 (1H, d, $J_1=9.9$ Hz, H-4), 1.70 (2H, m, CH_2CH$_2$OH), 1.15 (3H, d, $J=6.2$ Hz, CH_3), 0.85 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 181.9 (s), 134.8 (s), 129.4 (2d), 128.5 (2d), 127.9 (d), 60.7 (d, C-4), 58.3 (t, CH_2OH), 51.7 (d, C-5), 48.8 (s, C-3), 38.4 (t, *C*H$_2$CH$_2$OH), 19.7 (q, CH_3 at C-3), 19.6 (q, CH_3 at C-5).

4.5. Reduction of the nitro group with 10% Pd on carbon

The appropriate nitroalkylated γ-lactone (0.8 mmol) was dissolved in 6 ml of MeOH and 10% Pd on activated carbon (54 mg) was added. The mixture was stirred at room temperature under H_2 for 4 h. The mixture was filtered on Celite and the solvent was evaporated.

4.5.1. (3*R,4*R**)- and (3*R**,4*S**)-1-Hydroxy-3-(2-hydroxyethyl)-4-methyl-2-pyrrolidinone 27a and 27b.** The two isomers were obtained in admixture with the corresponding lactams **21a** and **21b** from the corresponding parent lactones **15a** and **15b**. For clarity sake the NMR values of the isomeric mixture are given separately for each isomer.

Compound **27a**. ^{1}H NMR (δ, ppm): 9.0 (1H, vbs, OH), 4.6 (1H, bs, OH), 3.75 (2H, m, CH_2OH), 3.72 (1H, m, H-5), 3.22 (1H, bd, $J=9.1$ Hz, H-5), 2.14 (2H, m, H-3 and H-4), 1.80 (2H, m, CH_2CH$_2$OH), 1.14 (3H, d, $J=6.2$ Hz, CH_3); ^{13}C NMR (δ, ppm): 172.4 (s), 61.5 (t, CH_2OH), 55.2 (t, C-5), 47.8 (d, C-3), 33.0 (t, *C*H$_2$CH$_2$OH), 31.5 (d, C-4), 17.6 (q, CH_3).

Compound **27b**. ^{1}H NMR (δ, ppm): 9.0 (1H, vbs, OH), 4.6 (1H, bs, OH), 3.75 (2H, m, CH_2OH), 3.73 (1H, m, H-5), 3.21 (1H, dd, $J_1=9.5$ Hz, $J_2=11.0$ Hz, H-5), 2.66 (1H, m, H-3), 2.52 (1H, m, H-4), 1.70 (2H, m, CH_2CH$_2$OH), 1.04 (3H, d, $J=7.0$ Hz, CH_3); ^{13}C NMR (δ, ppm): 172.0 (s), 61.5 (t, CH_2OH), 55.5 (t, C-5), 43.4 (d, C-3), 28.8 (t, *C*H$_2$CH$_2$OH), 28.4 (d, C-4), 14.9 (q, CH_3).

4.5.2. (3*R,4*R**) and (3*R**,4*S**)-1-Hydroxy-3-(2-hydroxyethyl)-3,4-dimethyl-2-pyrrolidinone 28a and 28b.** The two isomers were obtained from the corresponding nitroalkylated lactones **16a** and **16b**.The crude reaction mixture was purified by flash chromatography (eluant: ethyl acetate, 70% yield) and the isomer **28b** crystallized on standing at room temperature.

Compound **28a** (in admixture with **28b**). Oil, only a few signals were identified; ^{1}H NMR (δ, ppm): 3.36 (1H, m), 2.95 (1H, m), 2.23 (1H, m, H-4), 0.94 (3H, s, CH_3), 0.92 (3H, d, $J=7.3$ Hz, CH_3); ^{13}C NMR (δ, ppm): 58.5 (t, CH_2OH), 53.6 (t, C-5), 44.7 (s, C-3), 38.5 (t, *C*H$_2$CH$_2$OH), 33.8 (d, C-4), 16.0 (q, CH_3 at C-3), 11.5 (q, CH_3 at C-4).

Compound **28b**. White solid, mp 90–92 °C, IR (cm^{-1}, neat): 3350 (OH), 1680 (NC=O); ^{1}H NMR (δ, ppm): 10.0 (1H,

vbs, NOH), 5.00 (1H, vbs, OH), 3.82 (1H, m, C*H*OH), 3.66 (2H, m, H-5 and CHOH), 3.29 (1H, t, $J=9.0$ Hz, H-5), 2.18 (1H, sextet, $J=7.3$ Hz, H-4), 1.74 (1H, m, C*H*CH_2OH), 1.50 (1H, dt, $J_1=J_2=5.1$ Hz, $J_3=13.9$ Hz, C*H*CH_2OH), 1.18 (3H, s, CH_3), 1.04 (3H, d, $J=7.3$ Hz, CH_3); ^{13}C NMR (δ, ppm): 174.0 (s), 58.3 (t, CH_2OH), 53.6 (t, C-5), 43.6 (s, C-3), 37.3 (d, C-4), 35.0 (t, *C*H_2CH_2OH), 21.3 (q, CH_3 at C-3), 12.0 (q, CH_3 at C-4). MS (*m*/*z*): 156 ($M-OH^{\neg+}$, 12), 129 (18), 128 (34), 127 (11), 114 (100), 113 (33), 100 (14), 99 (68), 83 (21), 82 (39), 81 (13), 70 (22), 69 (66), 67 (65), 55 (80). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.4; H, 8.29; N, 7.89.

4.5.3. (3*R,4*S**)- and (3*R**,4*R**)-1-Hydroxy-3-(2-hydroxyethyl)-4-phenyl-2-pyrrolidinone 29a and 29b.** Treatment of the crude reaction mixture, obtained by reduction of **17a** and **17b**, with ethyl acetate led to the crystallization of the isomer **29a** (6% yield). The isomer **29b** was recovered in 1:1 admixture with **29a** (89% yield).

Compound **29a**. White solid, mp 171–173 °C; IR (cm^{-1}, nujol): 3210 (OH), 1685 (NC=O); ^{1}H NMR (CD_3OD, δ, ppm): 7.35 (5H, m, Ph), 3.85 (1H, t, $J=8.6$ Hz, H-5), 3.66–3.48 (3H, m, CH_2OH and H-5), 3.25 (1H, q, $J=8.5$ Hz, H-4), 2.71 (1H, m, H-3), 1.94 (1H, sextet, $J=6.9$ Hz, C*H*CH_2OH), 1.73 (1H, sextet, $J=6.9$ Hz, C*H*CH_2OH); ^{13}C NMR (CD_3OD, δ, ppm): 173.3 (s), 141.2 (s), 129.9 (d), 128.6 (d), 128.4 (d), 60.6 (t, CH_2OH), 56.3 (t, C-5), 46.4 (d, C-3), 43.5 (d, C-4), 34.1 (t, *C*H_2CH_2OH); MS (*m*/*z*): 175 (19), 174 (13), 161 (93), 160 (43), 148 (16), 131 (25), 130 (16), 129 (16), 128 (11), 118 (26), 117 (100), 116 (33), 115 (48), 104 (67), 91 (48), 84 (30), 78 (17), 77 (25). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.4; H, 6.71; N, 6.16.

Compound **29b**. ^{1}H NMR (CD_3OD, δ, ppm): 7.35 (5H, m, Ph), 3.99 (1H, t, $J=8.2$ Hz, H-5), 3.64 (2H, m, H-5 and H-4), 3.47 (2H, m, C*H*$_2$OH), 2.95 (1H, q, $J=7.7$ Hz, H-3), 1.59 (1H, sextet, $J=7.2$ Hz, C*H*CH_2OH), 1.25 (1H, m, C*H*CH_2OH); ^{13}C NMR (CD_3OD, δ, ppm): 172.9 (s), 141.6 (s), 129.6 (d), 128.2 (d), 128.1 (d), 60.6 (t, CH_2OH), 55.8 (t, C-5), 42.6 (d, C-3), 40.0 (d, C-4), 30.5 (t, *C*H_2CH_2OH).

4.5.4. (3*R,4*R**)- and (3*R**,4*S**)-1-Hydroxy-3-(2-hydroxyethyl)-3-methyl-4-phenyl-2-pyrrolidinone 30a and 30b.** Treatment of the crude reaction mixture, obtained by reduction of **18a** and **18b**, with ethyl acetate led to the crystallization of the isomer **30a**, while **30b** was obtained by flash chromatography of the mother liquors (eluant: ethyl acetate).

Compound **30a**. 57% Yield, white solid, mp 175–178 °C; IR (cm^{-1}, nujol): 3200 (OH), 1681 (NC=O); ^{1}H NMR (CD_3OD, δ, ppm): 7.31 (5H, m, Ph), 3.90 (1H, dd, $J_1=8.4$ Hz, $J_2=9.1$ Hz, H-5), 3.80 (1H, dd, $J_1=7.8$ Hz, $J_2=9.0$ Hz, H-5), 3.77–3.66 (2H, m, CH_2OH) 3.63 (1H, t, $J=8.1$ Hz, H-4), 1.80 (2H, m, C*H*$_2CH_2$OH), 0.74 (3H, s, CH_3); ^{13}C NMR (CD_3OD, δ, ppm): 175.3 (s), 138.7 (s), 129.9 (d), 129.5 (d), 128.4 (d), 59.3 (t, CH_2OH), 52.5 (t, C-5), 47.1 (s, C-3), 45.0 (d, C-4), 40.1 (t, *C*H_2CH_2OH), 19.5 (q, CH_3); MS (*m*/*z*): 218 ($M-OH^{\neg+}$, 1), 190 (18), 189 (18), 175 (100), 174 (37), 160 (23), 131 (43), 129 (23), 117 (28), 116 (19), 115 (27), 104 (77), 98 (57), 91 (62), 78 (15), 77 (18). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.5; H, 7.31; N, 5.81.

Compound **30b**. 12% Yield; oil, IR (cm^{-1}, film): 3200 (OH), 1681 (NC=O); ^{1}H NMR (CD_3OD, δ, ppm): 7.31 (5H, m, Ph), 3.92 (1H, dd, $J_1=7.9$ Hz, $J_2=9.3$ Hz, H-5), 3.81 (1H, dd, $J_1=7.7$ Hz, $J_2=9.2$ Hz, H-5), 3.55 (1H, m, C*H*OH), 3.35 (2H, m, C*H*OH and H-4), 1.57 (1H, ddd, $J_1=6.4$ Hz, $J_2=9.5$ Hz, $J_3=13.9$ Hz, C*H*CH_2OH), 1.30 (3H, s, CH_3), 1.15 (1H, ddd, $J_1=5.2$ Hz, $J_2=9.4$ Hz, $J_3=14.1$ Hz, C*H*CH_2OH); ^{13}C NMR (CD_3OD, δ, ppm): 175.2 (s), 138.7 (s), 129.7 (d), 129.5 (d), 128.6 (d), 58.9 (t, CH_2OH), 52.4 (t, C-5), 46.5 (s, C-3), 45.0 (d, C-4), 37.0 (t, *C*H_2CH_2OH), 23.3 (q, CH_3).

4.5.5. (3*R,4*R**,5*R**)-1-Hydroxy-3-(2-hydroxyethyl)-5-methyl-4-phenyl-2-pyrrolidinone 31b.** Reduction of **19b** afforded a 1:3 mixture of the lactam **25b** and the cyclic hydroxamic acid **31b** (80% yield), from which **31b** was isolated by treatment with ethyl acetate.

Compound **25b** not separated: ^{1}H NMR ($CDCl_3+CD_3OD$, δ, ppm) (only a few signals were identified): 3.96 (1H, bq, $J=5.7$ Hz, H-5), 3.25 (1H, dd, $J_1=4.6$ Hz, $J_2=8.6$ Hz, H-4), 1.29 (3H, d, $J=6.2$ Hz, CH_3); ^{13}C NMR ($CDCl_3+CD_3OD$, δ, ppm): 180.1 (s), 138.8 (s), 128.6 (2d), 127.9 (2d), 127.1 (d), 61.0 (t, CH_2OH), 54.8 (d, C-5), 52.1 (d, C-4), 44.2 (d, C-3), 29.6 (t, *C*H_2CH_2OH), 20.6 (q, CH_3).

Compound **31b**. White solid, mp 158 °C, 18% yield, IR (cm^{-1}, nujol): 3220 (OH), 1676 (NC=O); ^{1}H NMR ($CDCl_3+CD_3OD$, δ, ppm): 7.24 (3H, m, Ph), 7.14 (2H, m, Ph), 3.94 (1H, dq, $J_1=4.4$ Hz, $J_2=J_3=J_4=6.2$ Hz, H-5), 3.45 (2H, m, C*H*$_2$OH,), 3.20 (1H, dd, $J_1=4.4$ Hz, $J_2=8.8$ Hz, H-4), 2.91 (1H, dt, $J_1=8.8$ Hz, $J_2=J_3=6.2$ Hz, H-3), 1.47 (1H, m, C*H*CH_2OH), 1.33 (3H, d, $J=6.2$ Hz, CH_3), 1.24 (1H, m, C*H*CH_2OH); ^{13}C NMR ($CDCl_3+CD_3OD$, δ, ppm): 171.3 (s), 138.3 (s), 128.7 (2d), 128.0 (2d), 127.3 (d), 60.8 (d, C-5), 60.7 (t, CH_2OH), 47.6 (d, C-4), 41.7 (d, C-3), 30.0 (t, *C*H_2CH_2OH), 17.1 (q, CH_3); MS (*m*/*z*): 217 ($M-H_2O^{\neg+\cdot}$, 1), 216 (1), 176 (28), 175 (32), 148 (13), 133 (11), 132 (25), 131 (13), 119 (51), 118 (100), 117 (29), 116 (38), 92 (35), 77 (14); MS (*m*/*z*, 20 eV): 236 (MH^+, 2), 235 ($M^{+\cdot}$, 2). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.5; H, 7.27; N, 5.90.

4.6. Reactions of α-methyl-γ-butyrolactone 1′ with (*E*)-2-morpholinyl-1-nitro-1-phenylethene (5), (*E*)-1-(2-methylthiophenyl)-2-pyrrolidinyl-1-nitroethene (6), (*Z*,*E*)-1-methylthio-4-pyrrolidinyl-2-nitrobutadiene (7) and (*E*)-1,1-dimethylthio-4-pyrrolidinyl-2-nitrobutadiene (7′). General procedure for the Michael addition of nitroenamines to α-methyl-γ-butyrolactone zinc enolate 8′

To a solution of lithium diisopropylamide (1.5 M solution in THF) (2 mmol, 1.3 ml for the reaction with **5**, **7** and **7′**; 3.5 mmol, 2.3 ml for the reaction with **6**) in THF (1.3 ml), a solution of the lactone **1′** (0.162 g, 1.62 mmol) in 1.3 ml of THF was slowly added, at −78 °C. The mixture was stirred for 1 h at −78 °C. A solution of 1M $ZnCl_2$ (1.62 ml) was then added and the temperature was raised to −40 °C. After 1 h at this temperature, the solution was transferred to the

appropriate aminonitroalkene (0.81 mmol) dissolved in 5.2 ml of THF at −78 °C. The mixture was stirred at −78 °C for 2 h, the temperature was allowed to raise and the solution was kept overnight at room temperature. The reaction mixture was then quenched with 2 N HCl and extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography (light petroleum/ethyl acetate 3:2).

4.6.1. (*E*)- and (*Z*)-4,5-Dihydro-3-methyl-3-(2-nitro-2-phenylethenyl)-2(3*H*)-furanone 38. The crude reaction mixture (88% yield), whose composition was 85:15 in favour of the (*E*)-isomer, was treated with ether and ethanol at 0 °C. The major isomer (*E*)-**38** was isolated as pure compound (30% yield), mp 90–92 °C; IR (cm^{-1}, nujol): 1778 (COO), 1672 (C=C), 1528 (NO_2). ^1H NMR (δ, ppm): 7.75 (1H, s, HC=C), 7.50 (3H, m, Ar–H), 7.32 (2H, m, Ar–H), 4.13 (2H, m, 2H-5), 2.10 (1H, dt, $J_1=9.3$ Hz, $J_2=13.2$ Hz, H-4), 1.60 (1H, ddd, $J_1=2.9$ Hz, $J_2=6.2$ Hz, $J_3=13.2$ Hz, H-4), 1.41 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 177.8 (s, COO), 152.2 (s, C=CNO_2), 137.6 (d, CH=CNO_2), 130.7 (2d, *o*-Ar–H), 130.4 (2d, *m*-Ar–H), 129.1 (s), 128.6 (d, *p*-Ar–H), 65.1 (t, C-5), 43.2 (s, C-3), 34.6 (t, C-4), 23.5 (q, CH_3). MS (*m*/*z*): 247 ($M^{+\cdot}$, 0.01), 201 (72), 174 (15), 173 (100), 171 (14), 170 (13), 156 (13), 155 (10), 145 (23), 143 (20), 142 (43), 141 (38), 130 (12), 129 (65), 128 (67), 127 (25), 117 (17), 115 (49), 105 (58), 104 (18), 103 (52), 102 (31), 99 (10), 91 (40), 84 (32), 77 (73), 76 (28), 75 (15), 69 (17), 65 (10), 63 (17), 56 (11), 55 (29), 51 (66), 53 (13). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.0; H, 5.19; N, 5.90.

The compound (*Z*)-**38** was not isolated as pure isomer.

^1H NMR (δ, ppm): 7.43 (5H, m, Ar–H), 6.43 (1H, s, HC=C), 4.44 (1H, dt, $J_1=1.5$ Hz, $J_2=J_3=9.2$ Hz, H-5), 4.32 (1H, ddd, $J_1=6.3$ Hz, $J_2=9.2$ Hz, $J_3=10.7$ Hz, H-5), 2.51 (1H, ddd, $J_1=9.2$ Hz, $J_2=10.7$ Hz, $J_3=12.8$ Hz, H-4), 2.35 (1H, ddd, $J_1=1.5$ Hz, $J_2=6.3$ Hz, $J_3=12.8$ Hz, H-4), 1.58 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 178.2 (s), 152.2 (s), 137.6 (d), 128.8 (d), 128.5 (d), 128.2 (d), 65.3 (t, C-5), 43.8 (s, C-3), 32.9 (t, C-4), 22.7 (q, CH_3); the singlet relative to C-1 of the phenyl ring was hidden under other signals.

4.6.2. (*E*)- and (*Z*)-4,5-Dihydro-3-methyl-3-[2-(2-methylthiophenyl)-2-nitroethenyl]-2(3*H*)-furanone 39. The crude reaction mixture, whose composition was 67:33 in favour of the (*E*)-isomer, was purified on flash chromatography, 50% yield, yellow oil, IR (cm^{-1}, neat): 1775 (COO), 1520, (C=C–NO_2); ^1H NMR (δ, ppm): 7.81 (0.67H, s, C=CH), 7.73 (0.33H, s, C=CH), 7.47 (1H, m, Ar–H), 7.31 (1H, bd, $J=7.7$ Hz, Ar–H), 7.23 (2H, m, Ar–H), 4.23 (0.67H, dt, $J_1=9.0$ Hz, $J_2=2.6$ Hz, H-5), 4.09 (1.33H, m, H-5), 2.45 (3H, s, SCH_3), 2.26 (0.33H, dt, $J_1=8.9$ Hz, $J_2=13.1$ Hz, H-4), 2.16 (0.67H, dt, $J_1=9.1$ Hz, $J_2=12.8$ Hz, H-4), 1.78 (0.33H, ddd, $J_1=3.7$ Hz, $J_2=6.6$ Hz, $J_3=13.1$ Hz, H-4), 1.48 (0.67H, ddd, $J_1=2.4$ Hz, $J_2=6.6$ Hz, $J_3=12.8$ Hz, H-4), 1.43 (0.90H, s, CH_3), 1.38 (2.1H, s, CH_3); ^{13}C NMR (δ, ppm): (*E*)-**39**: 177.7 (s), 150.8 (s), 140.6 (s), 139.0 (d), 131.6 (d), 131.3 (d), 128.5 (s), 126.0 (d), 125.0 (d), 65.4 (t), 43.6 (s), 33.3 (t), 23.3 (q), 15.7 (q); (*Z*)-**39**: 178.0 (s), 150.2 (s), 140.1 (s), 139.2 (d), 132.2 (d), 131.3 (d), 127.9 (s), 126.1 (d), 125.0 (d), 65.4 (t), 43.3 (s), 34.6 (t), 22.9 (q), 15.8 (q); MS (*m*/*z*): 293 ($M^{+\cdot}$, 28), 248 (12), 247 (49), 220 (16), 219 (100), 201 (12), 194 (36), 191 (12), 189 (17), 186 (14), 174 (15), 173 (36), 161 (14), 151 (41), 149 (25), 148 (13), 147 (28), 129 (14), 128 (12), 115 (18), 83 (11). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77; S, 10.93. Found: C, 56.4; H, 5.19; N, 4.60.

4.6.3. *cis*- and *trans*-3-(2-Hydroxyethyl)-3-methyl-5-phenyl-2-pyrrolidinone 40a and 40b. The nitroalkenylated lactones **38** and **39** were reduced using Pd on carbon and Raney Nickel as a catalyst as reported in the general procedure.

A 2:3 mixture of lactams **40a** and **40b** were obtained in 70% yield. The two isomers were only partially separable by flash chromatography; yellow oil, IR (cm^{-1}, $CHCl_3$): 3420, 3153 (NH and OH), 1685 (NHC=O); MS (*m*/*z*): 220 (MH^+, 33), 219 ($M^{+\cdot}$, 38), 202 (10), 191 (65), 190 (46), 175 (100), 174 (69), 173 (35), 172 (29), 160 (40), 158 (40), 147 (18), 146 (49), 145 (17), 144 (13), 143 (14), 132 (13), 131 (41), 130 (26), 129 (34), 128 (32), 120 (11), 117 (12), 115 (23), 106 (16), 104 (21), 91 (26), 84 (11), 77 (14). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.5; H, 7.65; N, 6.30.

For sake of clarity the NMR values of the isomeric mixture are given separately for each isomer.

Compound **40a**. ^1H NMR (δ, ppm): 7.33 (5H, m, Ph), 6.23 (1H, bs, NH), 4.75 (1H, t, $J=6.6$ Hz, H-5), 4.09 (1H, bd, $J=6.2$ Hz, OH), 3.92 (1H, m, C*H*OH), 3.70 (1H, m, C*H*OH), 2.30 (1H, dd, $J_1=6.6$ Hz, $J_2=12.6$ Hz, H-4), 1.90 (2H, m, C*H*CH_2OH and H-4), 1.71 (1H, m, C*H*CH_2OH), 1.33 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.3 (s), 141.6 (s), 129.0 (2d), 128.0 (d), 125.7 (2d), 58.7 (t, CH_2OH), 55.8 (d, C-5), 46.6 (t, C-4), 44. 6 (s, C-3), 40.3 (t, *C*H_2CH_2OH), 21.8 (q).

Compound **40b**. ^1H NMR (δ, ppm): 7.38 (2H, m, Ph), 7.31 (3H, m, Ph), 5.94 (1H, bs, NH), 4.77 (1H, t, $J=7.3$ Hz, H-5), 3.94 (1H, m, C*H*OH), 3.75 (1H, m, C*H*OH), 2.97 (1H, bd, OH), 2.55 (1H, dd, $J_1=7.3$ Hz, $J_2=13.0$ Hz, H-4), 2.02 (1H, m, C*H*CH_2OH), 1.90 (1H, dd, $J_1=7.3$ Hz, $J_2=13.0$ Hz, H-4), 1.71 (1H, m, C*H*CH_2OH), 1.28 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 183.3 (s), 142.2 (s), 129.1 (2d), 128.1 (d), 125.8 (2d), 59.4 (t, CH_2OH), 55.0 (d, C-5), 46.8 (t, C-4), 43. 3 (s, C-3), 40.6 (t, *C*H_2CH_2OH), 23.5 (q).

4.6.4. 4,5-Dihydro-3-(2-(hydroxyimino)-2-(2-methylthiophenyl))ethyl-3-methyl-2(3*H*)-furanone 41. 51% Yield, yellow oil, IR (cm^{-1}) 3350 (OH), 1766 (COO), 1625 (C=N), 1587, 1560 (Ph), ^1H NMR (δ, ppm): 8.8 (1H, vbs, OH), 7.27 (4H, m, Ph), 4.25 (2H, m, 2H-5), 3.21 (2H, AB system, $J=13.2$ Hz, CH_2 of the chain), 2.44 (3H, s, SCH_3), 2.30 (1H, dt, $J_1=J_2=7.6$ Hz, $J_3=12.9$ Hz, H-4), 1.90 (1H, ddd, $J_1=5.1$ Hz, $J_2=7.3$ Hz, $J_3=12.9$ Hz, H-4), 1.17 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 181.0 (s), 156.7 (s), 137.7 (s), 135.7 (s), 129.4 (d), 129.1 (d), 126.6 (d), 124.9 (d), 65.3 (t, C-5), 42.4 (s, C-3), 34.6 (t), 34.3 (t), 22.9 (q, CH_3), 16.5 (q, CH_3); MS (*m*/*z*): 264 ($M-CH_3^{\cdot+}$, 100), 262 (76), 247 (50), 232 (42), 229 (16), 203 (13), 188 (10), 164 (17), 152 (14).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 60.3; H, 6.25; N, 4.96.

4.6.5. (*E*,*Z*)- and (*Z*,*Z*)-4,5-Dihydro-3-methyl-3-(4-methylthio-2-nitrobutadienyl)-2(3*H*)-furanone 42. The product (*E*,*Z*)-**42** was purified on column chromatography (52% yield). Oil, IR (cm^{-1}, $CHCl_3$): 1775 (COO), 1525 (C═C–NO_2); ^1H NMR (δ, ppm): 7.32 (1H, d, $J=1.5$ Hz, H-1 of the chain), 6.64 (1H, d, $J=10.2$ Hz, H-3 of the chain), 6.04 (1H, dd, $J_1=10.2$ Hz, $J_2=1.5$ Hz, H-4 of the chain), 4.32 (2H, m, 2H-5), 2.55 (1H, dt, $J_1=8.5$ Hz, $J_2=13.1$ Hz, H-4), 2.32 (1H, m, H-4), 2.36 (3H, s, SCH_3), 1.52 (3H, s, CH_3); ^{13}C NMR (δ, ppm): (*E*,*Z*)-**42**: 177.7 (s), 148.5 (s), 141.3 (d), 141.2 (d), 113.1 (d), 65.4 (t, C-5), 43.4 (s, C-3), 33.3 (t, C-4), 23.3 (q, SCH_3), 15.7 (q, CH_3); Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found: C, 48.8; H, 5.49; N, 5.64. On standing in $CDCl_3$, the (*E*,*Z*)-isomer converted into its (*Z*,*Z*) isomer for an amount of 20%.

Compound (*Z*,*Z*)-**42**. ^1H NMR (δ, ppm) (a few signals were hidden under those of the (*E*)-isomer): 6.54 (1H, d, $J=$ 11.0 Hz, H-3 of the chain), 6.29 (1H, s, H-1 of the chain), 6.09 (1H, d, $J=11.0$ Hz, H-4 of the chain), 4.44 (1H, dt, $J_1=1.5$ Hz, $J_2=9.2$ Hz, H-5), 2.41 (3H, s, SCH_3), 1.57 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 180.6 (s), 147.5 (s), 137.9 (d), 132.6 (d), 115.2 (d), 65.4 (t, C-5), 43.6 (s, C-3), 34.3 (t, C-4), 23.9 (q, SCH_3), 18.9 (q, CH_3).

4.6.6. (*E*)-4,5-Dihydro-3-methyl-3-(4,4-dimethylthio-2-nitro)butadienyl-2(3*H*)-furanone 43. The product (70% yield) was purified by flash chromatography (eluant: light petroleum:ethyl acetate, gradient), mp 82–84 °C; IR (cm^{-1}, film): 1770 (COO), 1666 (C═C), 1528, 1368 (NO_2); ^1H NMR (δ, ppm): 7.24 (1H, d, $J=1.8$ Hz, H-1 of the chain), 5.96 (1H, d, $J=1.8$ Hz, H-3 of the chain), 4.32 (2H, dd, $J_1=$ 6.0 Hz, $J_2=7.7$ Hz, 2H-5), 2.48 (1H, dt, $J_1=7.7$ Hz, $J_2=$ 12.8 Hz, H-4), 2.45 (3H, s, SCH_3), 2.35 (3H, s, SCH_3), 2.30 (1H, dt, $J_1=6.0$ Hz, $J_2=12.8$ Hz, H-4), 1.51 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 177.7 (s), 149.8 (s), 147.9 (s), 137.0 (d, C-1 of the chain), 111.0 (d, C-3 of the chain), 65.3 (t, C-5), 43.2 (s, C-3), 35.9 (t, C-4), 22.6 (q, CH_3), 16.4 (q, SCH_3), 16.2 (q, SCH_3); MS (*m*/*z*): 289 ($M^{+\cdot}$, 3), 243 (100), 215 (48), 195 (11), 167 (22), 139 (11), 91 (11). Anal. Calcd for $C_{11}H_{15}NO_4S_2$: C, 45.66; H, 5.22; N, 4.84; S, 22.16. Found: C, 46.5; H, 5.35; N, 4.76.

4.6.7. 4,5-Dihydro-3-methyl-3-[(4,4-dimethylthio-2-nitro)but-3-enyl]-2(3*H*)-furanone 44a,b. To a solution of the nitrodiene **43** (0.04 g, 0.14 mmol) in MeOH (7 ml), 0.105 g of supported borohydride (2 mmol/g of Amberlyst A26, Aldrich product) was added under stirring and the reaction was monitored by TLC. After 15 min, the polymer was filtered off and washed with MeOH, the filtrated was evaporated and purified by flash chromatography. Compounds **44a** and **44b** (60 and 40%, respectively) were not separable by flash chromatography. For sake of clarity the NMR values of the isomeric mixture are given separately for each isomer.

Compound **44a**. ^1H NMR (δ, ppm): 5.52 (1H, d, $J=8.8$ Hz, H–C═C), 4.50 (1H, dt, $J_1=J_2=8.8$ Hz, $J_3=4.8$ Hz, CH–NO_2), 4.26 (2H, m, 2H-5), 2.44 (1H, m), 2.35 (3H, s, SCH_3), 2.31 (3H, s, SCH_3), 2.03 (2H, m), 1.70 (1H, m), 1.29 (3H, s, CH_3).

Compound **44b**. ^1H NMR (δ, ppm): 5.57 (1H, d, $J=8.4$, H–C═C), 4.58 (1H, ddd, $J_1=3.0$, $J_2=8.4$, $J_3=10.6$, CH–NO_2), 4.26 (2H, m, 2H-5), 2.44 (1H, m), 2.35 (3H, s, SCH_3), 2.30 (3H, s, SCH_3), 2.03 (2H, m), 1.70 (1H, m), 1.30 (3H, s, CH_3).

4.6.8. (*E*)-4,5-Dihydro-3-methyl-3-(4,4-dimethylthio)butadienyl-2(3*H*)-furanone 45. On standing in $CDCl_3$, **44a** and **44b** convert into the diene system **45**. Oil. IR (cm^{-1}, $CHCl_3$): 1770 (COO), 1605, 1558 (C═C); ^1H NMR (δ, ppm): 6.78 (1H, dd, $J_1=15.7$ Hz, $J_2=10.2$ Hz, H-2 of the chain), 6.32 (1H, d, $J=10.2$ Hz, H-3 of the chain), 5.77 (1H, d, $J=15.7$ Hz, H-1 of the chain), 4.29 (2H, m, 2H-5), 2.40 (1H, m, H-4), 2.33 (3H, s, SCH_3), 2.32 (3H, s, SCH_3), 2.17 (1H, m, H-4), 1.40 (3H, s, CH_3); ^{13}C NMR (δ, ppm): 168.0 (s), 133.6 (s), 133.2 (d), 129.4 (d), 126.9 (d), 65.2 (t), 45.3 (s), 35.8 (t), 23.3 (q), 17.4 (q,), 16.7 (q); MS (*m*/*z*): 245 (MH^+, 19), 244 ($M^{+\cdot}$, 21), 231 (19), 230 (24), 229 (100), 213 (13), 212 (15), 201 (36), 185 (12), 183 (43), 155 (10), 138 (10), 137 (13), 123 (10), 91 (19), 77 (12). Anal. Calcd for $C_{11}H_{16}O_2S_2$: C, 54.06; H, 6.60; S, 26.24. Found: C, 55.0; H, 6.67.

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Kinetic versus thermodynamic access to imidazoisoindolones, benzimidazoisoindolones, and [1,4]diazepinoisoindolones: intramolecular nitrogen and π-aromatic trapping of *N*-acyliminium cation

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Abstract—Efficient assembly of substituted imidazo[2,1-*a*]isoindolones **I** is reported from suitable α,β-diamine **IV** (or corresponding β-nitroamine) and phthalic anhydride (**1**) in a three- or four-step sequence in good yields. The key step of this methodology is based on an intramolecular α-aza-amidoalkylation of the *N*-acyliminium species. Furthermore, when R_2 is an aromatic moiety a competing α-amidoalkylation took place and imidazo[2,1-*a*]isoindolones (or benzimidazo[2,1-*a*]isoindolones) **I** and/or isoindolo[1,4]benzodiazepines **III** were obtained under kinetic or thermodynamic control. The chemoselectivity of these transformations is also discussed.

1. Introduction

The importance of the imidazo[2,1-*a*]isoindolone skeleton is well recognized due to its significance as a subunit of a wide panel of synthetic pharmaceutical compounds. Some of these structures are patented and have been reported to possess a wide variety of biological activities as: psychostimulant, analgesic, anti-inflammatory, antifungal, antipyretic and hypertensive,[1] blood pressure lowering, spasmolytic, anti-tussive and tranquilizer properties,[2] and use in the treatment of rheumatism.[3] Furthermore, they are useful intermediates in organic synthetic chemistry, especially in the elaboration of imidazo[2,1-*a*]isoindolol-based anorectics,[1,4a,b] central nervous system (CNS) stimulants[1,4c,d] and antidepressants,[5] respectively. Finally, this class of compounds has also demonstrated to be highly effective plant growth regulating agents[6] with effects on the plant budding process.[7] More recently related benzimidazo[2,1-*a*]isoindolones have been reported and their biological activities evaluation show Batracylin comparable anti-tumor activities[8] as well as their ability to induce unscheduled DNA synthesis in rat hepatocytes.[9]

The traditional synthesis of imidazo[2,1-*a*]isoindolones involves the reaction between a 1,2-diamine and an aromatic or non aromatic keto acid, or equivalent, under azeotropic removal of water with[10] or without[11] a catalytic amount of acid (i.e., *p*-toluenesulfonic acid). More recent methods include a reaction of a 1,2-diamine with phthalic anhydride (or dicarboxylic acid equivalent) followed by thermal cyclodehydration,[9,12] a palladium catalyzed reaction via carbonylative cyclization between an α,β-diamine and 2-bromobenzaldehyde under controlled carbon monoxide pressure,[13] an iminocyclization of *N*-azidoalkyl(or aryl) phthalimides[14a] or the *N*-(*O*-aminoaryl)phthalimides[14b] via intramolecular Aza–Wittig reaction, and finally a cationic cyclization involving *N*-acyliminium species.[15,16]

2. Results and discussion

In our laboratory we are interested in the development of synthetic methodologies towards original aza-heterocyclic systems containing imidazole, benzimidazole and benzodiazepine moieties with promising pharmaceutical activities. In association with our recent reports dealing with

Keywords: Isoindole; Imidazole; Benzimidazole; [1,4]Diazepine; *N*-Acyliminium ion; α-Aza-amidoalkylation; Kinetic versus thermodynamic control.
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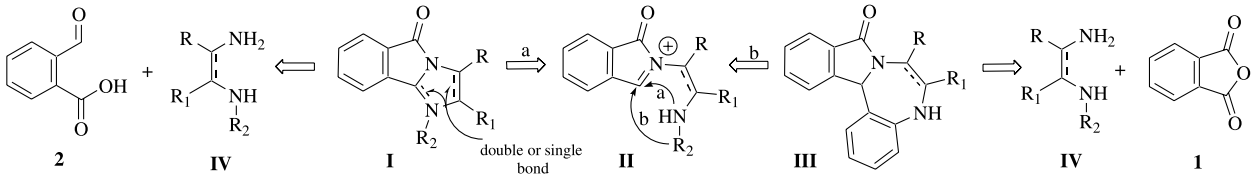


Scheme 1. Retrosynthetic scheme leading to imidazo(or benzimidazo)[2,1-*a*]isoindolones **I** and related isoindolo[1,4]benzodiazepines **III**.

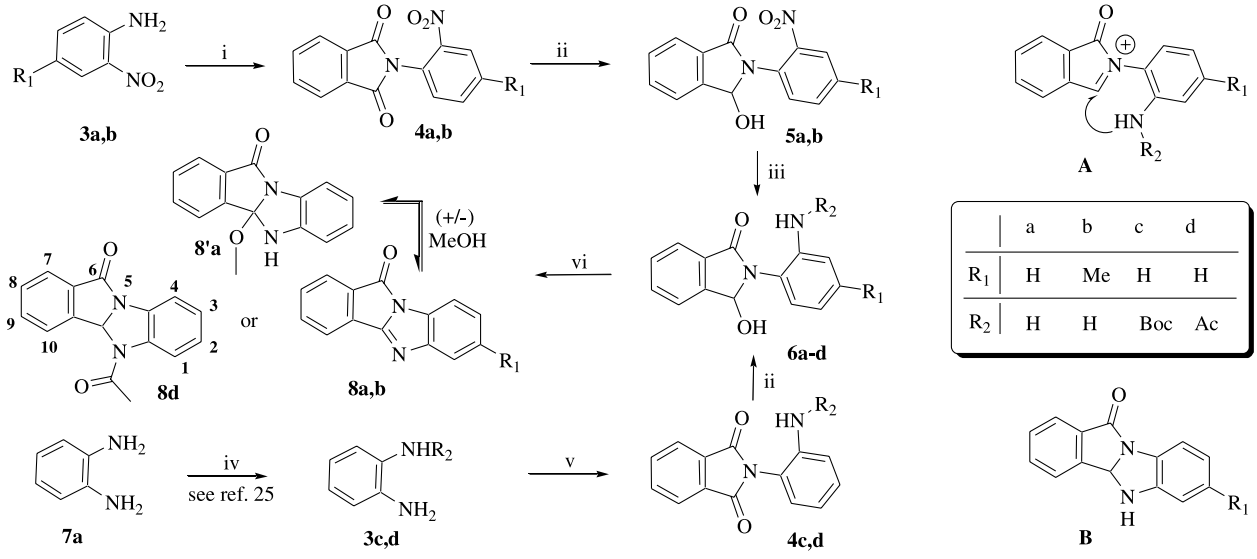
intramolecular α-thio-amidoalkylation[17] and α-oxo-amidoalkylation,[18] we reasoned that a suitably substituted *N*-acyliminium precursor of type **II** (Scheme 1) could allow a facile approach to the tricyclic derivative (**I**) or tetracyclic (**I** and **III**) cores of the title targets. The cationic cyclization using a nitrogen atom as an internal nucleophile has been mentioned first during the synthesis of 9*a*-phenyl-5,6,6*a*,11-tetrahydroisoindolo[2,1*a*]quinazoline-5,11-dione without isolation of the opened amide-hydroxylactam intermediate.[16a] Some 10 years later it was used by Speckamp et al.[16b] in the total synthesis of (±)-physostigmine ((±)-eserine), the principal alkaloid of Calabar bean. The essence of the few reports of this process concern its use in chiral version to access imidazo[2,1-*a*]isoindole-2,5-diones,[15] imidazoisoquinolinones,[16c] functionalized peptidomimetics,[16d] and azabicyclo[4.4.0]alkane amino acids.[19] To the best of our knowledge utilization of the present application in an intramolecular *N*-acyliminium mediated cyclization reaction, as depicted in Scheme 1, to form a central five- or seven-membered ring as a cyclic *N*,*N*-acetal or [1,4]diazepine structure, represents a novel illustration of this chemistry. In the intermediate **II**, cyclisation to the *N*-acyliminium cation may indeed be originated from intramolecular attack of either the nitrogen nucleophile or from the π-aromatic system, in case the latter is sufficiently activated.

As a starting point of our study, the α-hydroxylactam derivative **5a**, as *N*-acyliminium precursor, constituted a valuable target molecule. We expected to obtain it in a two-step sequence from phthalic anhydride (**1**) and *o*-nitro-aniline (**3a**) by thermal amino-anhydride condensation in refluxing acetic acid for 24 h,[20] followed by selective sodium borohydride reduction of one of the carbonyl functions of the imide function under mild conditions (Scheme 2). In the case of borohydride reduction of **4a**, the process led to a mixture of compounds containing none of the desired amino-alcohol product **5a**. Instead, the isoindolobenzimidazole **8a** was identified as a minor product (13%), while the major compound proved to be 10*b*-methoxyisoindolobenzimidazole **8′a** (39% yield) which resulted from the methanol

Table 1. Yields of the intermediates **4a–c**, **5a–c**, **6a–c** and the cyclized isoindolo[2,1-*a*]benzimidazole **8a**,**b**,**d** and **8′a** produced via Scheme 1

Products **4**	Yield (%)	Products **5**	Yield (%)	Products **6**	Yield (%)	Products **8**	Yield (%)[a]
4a	89	**5a**	—[b]	**6a**	—[b]	**8a**	45–61 (82)[c]
4b	91	**5b**	65	**6b**	—[b]	**8b**	63 (54)[a]
4c	91	**5c**	—	**6c**	85	**8′a**	39
4d	91	**5d**	—	**6d**	89	**8d**	91

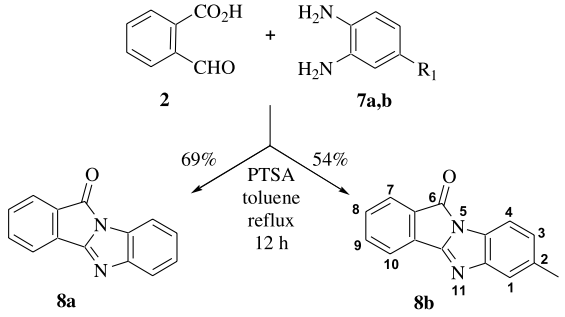
[a] After recrystallization or chromatographic purification.
[b] Product not isolated.
[c] Isolated yields after reaction of diamines **7a**,**b** and 2-formylbenzoic acid (**2**).



Scheme 2. Reagents and conditions: (i) Phthalic anhydride (**1**), AcOH, reflux, 24 h; (ii) 1.5–3 equiv of $NaBH_4$, MeOH, −5 to 0 °C, 45 min to 1 h; (iii) Fe, 50% aq. AcOH, 60 °C, 4 h or H_2/Pd-C, AcOH–H_2O (v/v), 50 psi, 6 h; (iv) see Ref. 25a for product **3c** and Ref. 25b for product **3d**; (v) **1**, toluene, reflux, NEt_3, Dean–Stark, 12 h; (vi) (a) acid hydrolysis during the work-up of the reduction of **5a**,**b** with 10% HCl or 6 M H_2SO_4; (b) For **6c**,**d**: TFA, CH_2Cl_2, rt, 4 h.

addition onto the imine function of **8a** under the protic acid activation conditions used during the reduction. Furthermore, in the presence of 2 equiv of additional nickel (II) chloride hexahydrate, the borohydride reduction reaction showed the same profile with however product **8a** obtained in larger quantity. Interestingly, treatment of **4a** with conjointly iron powder as a reductant and a 50% aqueous acetic acid as a proton source at 60 °C over 4 h,[9] provided only 6-oxoisoindolo[2,1-*a*]benzimidazole (**8a**) in 44% yield after chromatography. The product **8a** was also obtained in 61% yield, without formation of the methoxy adduct **8′a**, from **4a** via catalytic hydrogenation at 50 psi over Pd–C 10% for 6 h in ethanol in the presence of acetic acid as a proton source. Interestingly, in this case no ethoxy adduct analogous to **8′a** could be observed (Table 1).

The ease of intramolecular α-aza-amidoalkylation by the amino-ketone cyclodehydration[9,14] or the *N*-cyclization of the supposed amino–alcohol intermediate **6a**, depending of the reduction sequence, caused us to investigate additional stabilization of these species. To this end, we considered the *para*-methyl substituted series based on the idea that an electron-donating methyl group would provide some increased stability of the nitro functions in **4b** with respect to reducing agents. Interestingly, treatment of **4b** using 3 equiv of $NaBH_4$ in methanol at 0 °C during 2 h (conditions ii outlined in Scheme 2), gave successfully the nitro-hydroxylactam **5b** as a crystalline and stable product in 65% yield. This observation was in line with the fact that the reduction of the nitro-imide functionality into the nitro-alcohol was already achieved by us on related products using sodium borohydride at lower temperature.[21] Furthermore, reaction of **5b** under conditions iii as outlined above (Scheme 2), gave directly 2-methyl-6-oxoisoindolo[2,1-*a*]benzimidaz-ole (**8b**) in comparable yields (63%) after chromatography and recrystallisation from dry ethanol.



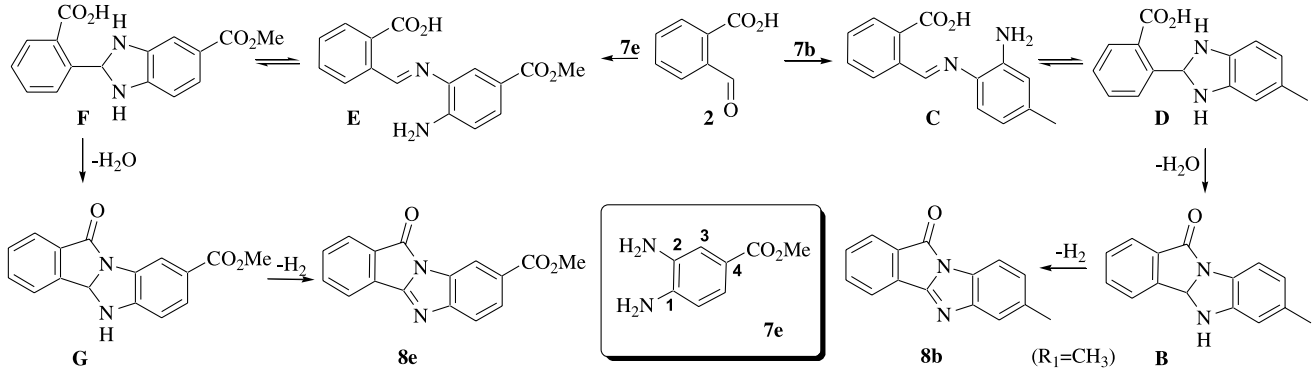
Scheme 3. Univocally 'one-pot' procedure access to 11-oxoisoindolo[2,1-*a*]-benzimidazole derivatives **8a** and **8b**.

The synthetic pathway leading to **8b** occurred through a cascade process by subsequent reduction of the nitro group of **5b** into the non isolated amino-alcohol **6b**, followed by loss of water, to form the *N*-acyliminium cation **A**, nucleophilic attack by the nitrogen atom (Scheme 2) and finally by spontaneous oxidation[22]-elimination of the resulting unstable 10*b*,11-dihydro-6-oxoisoindolo[2,1-*a*]-benzimidazole (**B**). In the case of **8a**, there was no direct evidence for the nucleophilic attack of the nitrogen atom onto the *N*-acyliminium cation since the nitro-hydroxylactam **5a** was not isolated under the set of reduction conditions.

The structure of **8a**,**b** was equally confirmed chemically, as outlined in Scheme 3, by treatment of an equimolar amount of *o*-phenylenediamine (**7a**), or 2-amino-4-methyl-aniline (**7b**) and 2-formylbenzoic acid (**2**) under azeotropic removal of water according to the classical reported procedure.[23]

It is interesting to note that this process in the case of the 4-methyl derivative **7b** proceeded in a highly regioselective manner. Scheme 4 demonstrates a plausible mechanism of the formation of the sole 2-methyl-6-oxoisoindolo[2,1-*a*] benzimidazole (**8b**). So, because the amine function at C_1 of **7b** is more nucleophilic than the one at C_2, the amino-aldehyde condensation yielded the imine **C** which then cyclized to afford the imidazoline **D**. This latter, after an intramolecular cyclodehydration into **B** followed in an ultimate step by a spontaneous oxidation/elimination reaction afforded the corresponding imidazole derivative **8b**.[24] In contrast, the opposite profile was obtained with the *o*-phenylenediamine substrate **7e**. In fact, the condensation of **2** with **7e** took another course with a more reactive amine function at C_2, giving the imine **E**. This latter intermediate, after a sequential set of reactions as outlined for **8b**, led to the product **8e** with the ester function at the C_8 position.[25]

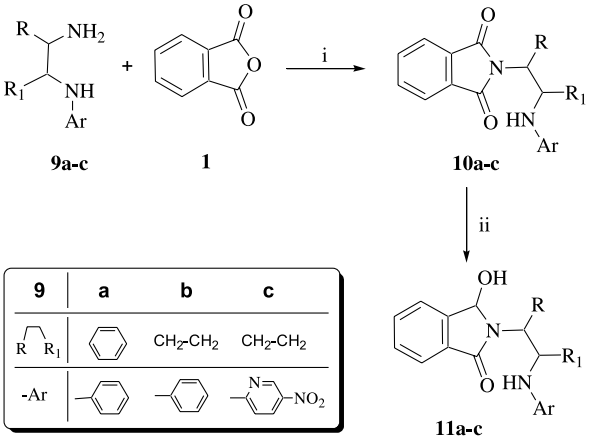
We decided next to explore another approach starting from *o*-phenylenediamine (**7a**) which was protected at one nitrogen atom with di-*t*-butyldicarbonate (Boc_2O) and acetic anhydride (Ac_2O) into carbamate **3c**[26a] and acetamide **3d**,[26b] respectively (Scheme 2). The choice of these groups was based on two considerations: first, the NHBoc and NHAc groups were rarely engaged in the intramolecular cationic cyclization, and we expected that both groups,



Scheme 4. Plausible sequential mechanism leading to 2-methyl(or 3-methoxycarbonyl)-6-oxoisoindolo[2,1-*a*]benzimidazole **8a** or **8b**.

especially the *t*-Boc, could be removed easily during[16d] or after cyclization to form the benzimidazole derivative **8a**,**b**, respectively. Second, both the *t*-butyloxy carbamate and acetyl groups are electron-withdrawing groups which could render the amino group less nucleophilic leading to the amino-alcohols **6c**,**d** as isolable intermediates. Thus, treatment of **3c**,**d** with 1 equiv of phthalic anhydride (**1**) in toluene at reflux in the presence of a catalytic amount of triethylamine over 12 h gave the imides **4c** and **4d** in 85 and 91% yields, respectively. These imides were then converted regioselectively to the *N*-acyliminium ions precursors **6c**,**d** by borohydride reduction as described above for **5b** in 85 and 89% yield.

According to our previous reports showing that trifluoroacetic acid (TFA) and acetic acid (AcOH) are good catalysts for the intramolecular α-amidoalkylation and α-heteroamidoalkylation, treatment of hydroxy-lactam **6c** with TFA in CH_2Cl_2 for 24 h or neat TFA for 4 h at room temperature afforded in both cases **8a** in about 73% yield. This product, which was identical to the one obtained from the nitro-imide **4a** (Scheme 2), resulted from an intramolecular cyclization of the *N*-acyliminium intermediate of type **A** with a nitrogen atom as nucleophile in parallel with Boc deprotection. We do have some evidence that the *t*-Boc deprotection occurs subsequently to the cyclization due to different deprotection kinetics, but this was not confirmed. Taking into account that TFA is a standard deprotecting agent for the *t*-Boc group, we decided to use a weaker acid, such as AcOH, for the cyclization process, hoping to be able to maintain the *t*.Boc protective group. Thus, α-hydroxy-lactam **6c** upon treatment with neat AcOH for 8 h or in CH_2Cl_2 for 24 h at reflux gave again **8a** in comparable yields of about 67%. In order to avoid the deprotection process, the aza-acylated α-hydroxylactam **6d** (R_2=Ac) was used as *N*-acyliminium ion precursor. In fact, the acetyl derivative **6d**, after treatment with neat TFA at rt over 4 h gave 11-acyl-6-oxoisoindolo[2,1-*a*]benzimidazo-le (**8d**) in 80% yield after recrystallization from ethanol.



Scheme 5. Sequential set leading to α-hydroxylactam precursors **11a–c**. Reagents and conditions: (i) Toluene, cat. NEt_3, reflux, Dean–Stark, 12 h; (ii) 3 equiv of $NaBH_4$, MeOH, −5 to 0 °C, aq. HCl in ethanol, 1 h.

Having established that the intramolecular α-aza-amidoalkylation route is effective for the preparation of the isoindolo[2,1-*a*]benzimidazole derivatives **8a–d**, we decided to elaborate another class of α-hydroxylactam precursors in which a nitrogen atom bear another nucleophile such as an aromatic or heteroaromatic system. Thus, as depicted in Scheme 5, the requisite α-hydroxy-lactams **11a–c** were obtained in a two-step sequence using classical procedures. Imides **10a–c** were readily prepared by amine-anhydride condensation from commercial diamines **9a–c** and phthalic anhydride (**1**) as indicated for **4c**,**d** in 76, 85 and 86%, respectively. The reaction was accelerated by adding dry triethylamine in catalytic quantity. Regioselective reduction of imides **10a–c** was accomplished with a large excess of sodium borohydride in methanol at −5 to 0 °C. In all cases, a regular addition of an ethanolic hydrogen chloride solution was necessary as already mentioned elsewhere for related structures,[17,18,21] and after 1 h of the reaction, α-hydroxylactams **11a–c** were isolated in, respectively, 80, 88 and 82% yield.

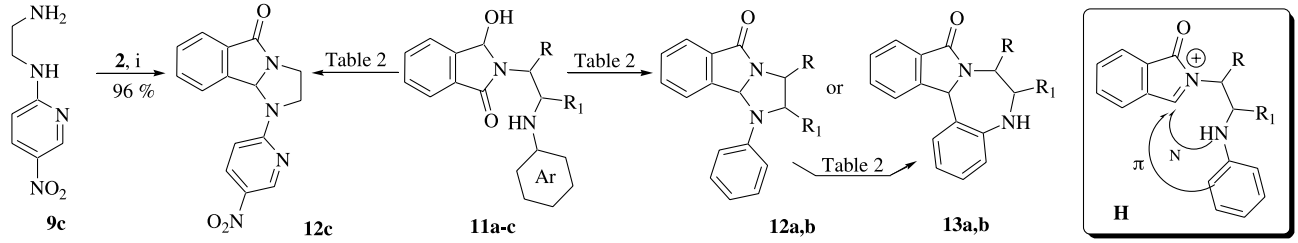
In the first set of cationic cyclizations in this series, substrate **11a** was chosen as a model for the *N*-acyl-iminium ion precursor. So, the subjection of α-hydroxy-lactam **11a** to weak AcOH (method A), weak TFA (method B) or catalytic *p*-toluenesulfonic acid (PTSA) (method C) in CH_2Cl_2 at room temperature for 12 h (Table 2, entry 1, 2 or 3) afforded only 11-phenyl-6-oxoisoindolo[2,1-*a*]benzimidazole (**12a**) in 65, 80 or 79% yield, respectively. This product resulted invariably from an intramolecular aza-cationic cyclization of the endocyclic *N*-acyliminium ion intermediate of type **H** (Scheme 6).

On the basis on our precedent work in this field and to avoid the intramolecular α-aza-amidoalkylation process to the

Table 2. Isoindolo[2,1-*a*]benzimidazole and corresponding isoindolo[1,4]dibenzodiazepine derivatives **12a**,**b** and **13a**,**b** produced via Scheme 6

	Reactant	Quantity[a] mmol	Conditions	Method	Product	Yield (%)[b]
1	**11a**	2.0	4 equiv of AcOH, CH_2Cl_2, rt, 12 h	**A**	**12a**	65
2	**11a**	2.5	4 equiv of TFA, CH_2Cl_2, rt, 12 h	**B**	**12a**	80
3	**11a**	3.0	Catalytic PTSA, CH_2Cl_2, rt, 12 h	**C**	**12a**	79
4	**11a**	4.0	Neat AcOH, rt, 12 h	**D**	**13a**	69
5	**11a**	4.0	Neat TFA, rt, 12 h	**E**	**13a**	74
6	**12a**	3.0	Neat AcOH, reflux, 24 h	**F**	**13a**	83
7	**12a**	6.0	Neat TFA, reflux, 24 h	**G**	**13a**	81
8	**12a**	5.0	Catalytic PTSA, toluene, reflux, 24 h	**H**	**13a**	90
9	**11b**	5.0	Catalytic PTSA, CH_2Cl_2, rt, 12 h	**C**	**12b**	82
10	**11b**	5.0	Neat TFA, rt, 12 h	**E**	**13b**[c]	93
11	**12b**	4.5	Neat TFA, reflux, 24 h	**G**	**13b**	89

[a] The reaction was conducted on 2–6 mmol of reactant under stirring. For entries 6–8, the isoindolo[2,1-*a*]benzimidazole **12a** was used as starting material.
[b] Isolated yield after purification by recrystallization or chromatography on silica gel column.
[c] A trace of the kinetic product **12b** were detected by ^{1}H NMR analysis and its quantity not exceed 5% of the products mixture.



Scheme 6. Reagents and conditions: (i) **2**, toluene, cat. NEt_3, reflux, Dean–Stark, 12 h; (ii) See text and Table for others procedures.

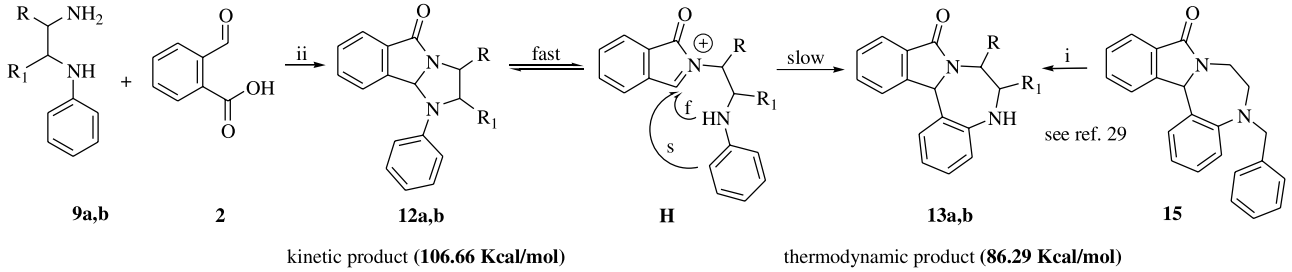
detriment of others, different reaction conditions were considered. So, the intramolecular arylation leading to isoindolo[1,4]dibenzodiazepine product **13a** as a single product occurred when neat AcOH (method D, Table 2, entry 4, 69%) or neat TFA (method E, Table 2, entry 5, 74%) was used as a proton source. Furthermore, to check the reversibility of the aza-cyclization reaction, taking into account that cyclic *N*,*N*-aminal **12a** could generate the *N*-acyliminium ion under acidic influence according to previously observations,[18c,27] we envisaged the treatment of acetal **12a** with neat AcOH (method F, Table 2, entry 6), neat TFA (method G, Table 2, entry 7) or catalytic amount of PTSA in toluene (method H, Table 2, entry 8) at reflux. Under these conditions all reactant **12a** disappeared (monitored by TLC) and the expected isoindolodibenzodiazepine product **13a** was obtained in good yield (81–90%).

The formation of these cycles **12a** and **13a** in acidic medium seems to proceed by invoking the kinetic vs thermodynamic control using the formal *N*-acyliminium ion **H** as intermediate (Schemes 6, 7). In fact, under mild conditions (methods A, B and C), the cationic intermediate **H** lead to isoindolo[2,1-*a*]benzimidazole derivative **12a** as the sole reaction product under kinetic process (fast reaction). In contrary, under stronger acidic conditions (neat acid at room temperature; methods D and E) and/or higher temperatures, the same intermediate provided in an alternate pathway isoindolo[1,4]dibenzodiazepine **13a** under thermodynamic control (slow reaction). The difference in reactivity between the two pathways can easily be contributed to the fact that the formation of **13a** requires higher activation energy due to the loss of aromaticity in the transition state. In addition, the compound **13a** proves to be about 20 kcal/mol more stable than its corresponding imidazoline **12a** according to AM1 calculations (86.29 kcal/mol vs 106.66 kcal/mol in the case of R-R_1=Ph), what clearly explains the complete conversion from **12a** to **13a** under more drastic conditions. These results confirm that the formation of the CH–N linkage of the kinetic product **12a** is reversible depending on the acidic activation. Under stronger conditions, cleavage of the CH–N bond in **12a** led back to the *N*-acyliminium ion congener **H** which in turn led to the diazepine compound **13a** as the thermodynamically more stable product.

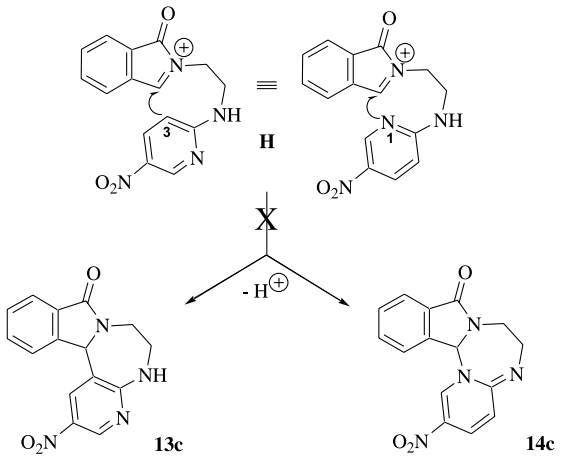
To establish the generality and versatility of this process we studied the effect of varying the nucleophilicity of the nitrogen atom which is interacts with the *N*-acyliminium ion during the cyclization process. For this purpose, two kinds of *N*-acyliminium ion precursors were considered; **11b** and **11c** in which the nitrogen atom nucleophilicity is altered with respect to the one in the reactant **11a**, and which bear a benzene or pyridine ring as a competing π-nucleophile or aza-nucleophile, respectively.

So, treatment of hydroxylactam **11b** according to method C (Table 2, entry 9), gave exclusively 1-phenyl-5-oxoisoindolo[2,1-*a*]imidazole (**12b**) under the kinetic control in 82% yield (Schemes 6 and 7). Similarly, reaction under conditions of method E, **11b** led to the cyclized thermodynamic [1,4]benzodiazepine product **13b** in excellent yield (Table 2, entry 10, 93%). During this reaction, the 1-phenyl-5-oxoisoindolo[2,1-*a*]imidazole structure **12b** was detected as a minor product but its yield did not exceed 5% in all cases.[28] As for the diazepine derivative **13a**, the product **13b** was also isolated in 89% yield starting from the kinetic product **12b** under conditions outlined in Table 2 (method G, entry 11) in a one pot procedure involving *N*-acyliminium ion intermediate **H** (Schemes 6 and 7).

In contrast, the hydroxylactam **11c**, with a reduced nucleophilicity with respect to both the N and π-aromatic nucleophilic centers due to the nitro group, afforded in all attempts with differing acidic and/or temperature conditions, the imidazoline derivative **12c** in comparable yields (85%). These results suggest that the formation of the azepine type structures **13** and **14** requires sufficiently activated aromatic systems (Scheme 8).[29]



Scheme 7. Kinetic vs thermodynamic scheme leading to imidazole and diazepine derivatives **12a**,**b** and **13a**,**b**. Reagents and conditions: (i) H_2, 10% Pd–C, AcOH–HCl, 50 °C, 6.5 h (see Ref. 30 for more details); (ii) **2**, toluene, cat. NEt_3, reflux, Dean–Stark, 12 h.



Scheme 8. Possible structures which could be resulted form a pyridine attack on the *N*-acyliminium ion intermediate **H**.

As a direct method for structural confirmation of imidazole and benzimidazole derivatives, the condensation of *o*-formylbenzoic acid (**2**) with diamines **7a**,**b** and **12a–c** under azeotropic removal of water was used successfully, thus providing isoindoloimidazoles **12b** (82%) and **12c** (96%), and isoindolobenzimidazoles **8a** (69%), **8b** (54%), and **12a** (89%) identical to the compounds obtained by the *N*-acyliminium sequence. Furthermore, the structure elucidation of these products as well as all compounds intermediates was based on their spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR including NOE Difference and DEPT experiments) as well as their microanalyses.

The NMR data of the imidazole product **8a** has been previously reported in some details.[9,14b] For related compounds **8′a**, **8b**, and **8e**, the ^{1}H NMR data have a same profile globally as for **8a** with however a side chain signal corresponding to a methoxy ($\delta=3.79$ ppm), methyl ($\delta=2.47$ ppm), and methoxycarbonyl ($\delta=3.95$ ppm) groups, respectively, with an additional NH signal at $\delta=10.48$ ppm for **8′a**. No signals for the proton in position C_{4b} of the isoindole system, appearing classically at about $\delta=6.0$ ppm, was observed in theses cases.

In the imidazoisoindolones structures **12a**, **12b** and **12c**, the angular protons appear as singlets at $\delta=7.24$, 6.12, and 6.61 ppm, respectively. These latter absorb downfield compared to the same protons of their hydroxylactams congeners **11a** ($\delta=6.22$ ppm), **11b** ($\delta=5.78$ ppm), and **11c** ($\delta=5.83$ ppm), respectively. The same fact, was also observed for the diazepinoisoindolones in comparaison to their precursors, with however a little difference on the chemical shift values which are $\Delta\delta=+0.09$ ppm and $\Delta\delta=+0.05$ ppm in favour to **13a** and **13b** to the detriment of **12a** and **12b**, respectively. These observations are in agreement with the fact that C–N and C–C bonds, formed during the cyclization process, have not the same effect on the CH angular absorbance. These results are also in agreement with previous reports on analogous compounds.[15–18]

Furthermore, the key feature in the ^{13}C NMR spectra of **8′a** and **8a–d** or **8e**, was the appearance of fourteen or fifteen signals, respectively, in the aromatic region. One of these disappears in the corresponding DEPT program spectra as the consequence of the aza-amidoalkylation cyclization process. Interestingly, if the quaternary angular carbon of the C=N bond appears at $\delta=156.4$ ppm (**8a**), $\delta=152.4$ ppm (**8b**), and $\delta=155.0$ ppm (**8e**) in comparable chemical shift values reported in the literature for related products,[14b] the one of **8′a** appeared downfield with more significant deshielding at $\delta=166.7$ ppm. This fact is due to the proximity of three heteroatoms which belong to amide, amine and etheroxide functionalities, respectively. Especially diagnostic was the differentiation between the formed five-membered ring products **8b** and **12a–c** and the cyclized seven-membered ring ones **13a**,**b**.

In fact, for the isoindolobenzimidazole **8b** the appearance of the C=N signal at $\delta=152.4$ ppm constitutes the consequence of the intramolecular cyclization of **4b**. This value is similar to those obtained for related structures.[14] Interestingly, it can be seen that the aza-cyclization process of **11a**,**b** into **12a**,**b** induces a weak variation in the carbon angular absorbance which is $\Delta\delta=+1.2$ ppm and $\Delta\delta=+7.3$ while the π-cyclization into **13a**,**b** of **11a**,**b** shifted dramatically the absorbance of the angular carbon to higher fields. In these case, an important deshielding of $\Delta\delta=+21.2$ ppm and $\Delta\delta=+20.5$ ppm was observed.

3. Conclusion

In summary, we have shown that *N*-acyliminium ion precursors **6a–d** could be generated in two pathways from nitro-hydroxylactams **5a**,**b** or corresponding amino-imides **4c**,**d** by regioselective reduction processes using iron/acetic acid or sodium borohydride/methanol, respectively. The *N*-acyliminium ion in turn furnished via an intramolecular α-aza-amidoalkylation with a nitrogen atom as nucleophile various and new 6-oxoisoindolo[2,1-*a*]benzimidazole products **8a–d** in good yields. In some cases, the amino-hydroxylactam intermediates **6** were not isolated but cyclized directly into product **8**.

Similar α-hydroxylactams **11a**,**b**, under the same process, produced efficiently under thermodynamic control the expected isoindolo[1,4]benzodiazepines **13a**,**b** in good yields and excellent regiocontrol. These latter were also obtained starting from isoindoloimidazoles **12a**,**b**, which turned out to be the kinetically formed products from cyclization of the nitrogen onto the iminium ion species produced by acid treatment of the α-hydroxylactams **11a**,**b**. The hydroxylactam **11c** only gave rise to the imidazoline derivative **12c**, clearly demonstrating the influence of electronic factors in the π-aromatic attack. Finally, the structures of the isoindoloimidazole derivatives **8a**,**b** and **12a**,**b** as well as **12c** was confirmed chemically by an alternative synthesis from *o*-formylbenzoic acid (**2**) and corresponding diamines **7a**,**b** or **9a–c** in an one pot procedure. For full exploitation of this route which provides a novel synthesis of imidazole, benzimidazole and diazepine derivatives and which is short, facile, general and more competitive, further work is currently underway to enlarge the scope of this application by accessing a wider variety of these structures.

4. Experimental

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform unless other indicated solvent and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualised using an ultraviolet lamp or iodine vapour. Mass spectral measurements were recorded on a AEI MS 902 S spectrophotometer. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt. St. Aignan, France.

4.2. General procedure for synthesis of imides (4a,b)

A mixture of powdered phthalic anhydride (**1**, 1.48 g, 10 mmol) and *o*-nitroaniline (**3a**, 1.38 g, 10 mmol) or 4-methyl-2-nitroaniline (**3b**, 1.52 g, 10 mmol) in 100 mL of glacial acetic acid was heated at reflux for 24 h. After cooling, the precipitate formed was collected by filtration, washed with cyclohexane, diethyl ether and air dried. The resulting products were purified by recrystallization from ethanol to give imides **4a** and **4b** as yellow needles.

4.2.1. *N*-(*o*-Nitrophenyl)phthalimide (4a). This product was isolated as yellow solid in 89% yield; mp = 190–195 °C (lit.,[31] mp = 202–203 °C); IR (KBr) v 3093, 1715, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1H, $1H_{benzene}$, J = 7.8 Hz), 7.61 (t, 1H, $1H_{benzene}$, J = 7.8, 7.0 Hz), 7.74–7.83 (m, 3H, $1H_{benzene}$ and $2H_{phthalimide}$), 7.93–7.98 (m, 2H, $2H_{phthalimide}$), 8.18 (d, 1H, $1H_{benzene}$, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 124 (2CH), 125.6 (Cq), 125.9 (CH), 129.8 (CH), 131.0 (CH), 131.9 (Cq), 134.3 (CH), 134.9 (2CH), 145.8 (2Cq), 166.5 (2CO); Anal. Calcd for $C_{14}H_8N_2O_4$ (268.22): C, 62.69; H, 3.01; N, 10.44. Found: C, 62.48; H, 2.95; N, 10.22.

4.2.2. *N*-(4′-Methyl-*o*-nitrophenyl)phthalimide (4b). This product was isolated as yellow needles in 91% yield; mp = 181 °C (lit.,[32] mp = 187 °C); IR (KBr) v 3082, 1716, 1534, 1383 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 2.50 (s, 3H, CH_3), 7.67 (d, 1H, $1H_{benzene}$, J = 7.6 Hz), 7.77 (d, 1H, $1H_{benzene}$, J = 7.6 Hz), 7.94–8.08 (m, 2H, $1H_{benzene}$ and $4H_{phthalimide}$); ^{13}C NMR (DMSO d_6) δ 19.8 (CH_3), 121.4 (Cq), 123.4 (2CH), 125.0 (CH), 130.3 (CH), 130.6 (Cq), 134.6 (CH), 134.8 (2CH), 140.6 (Cq), 144.6 (2Cq), 165.8 (2CO); Anal. Calcd for $C_{15}H_{10}N_2O_4$ (282.25): C, 63.83; H, 3.57; N, 9.93. Found: C, 63.66; H, 3.28; N, 9.87.

4.3. General procedure for synthesis of imides (4c,d) and (10a–c)

A mixture of α,β-diamine **4c**, **4d**, **9a**, **9b**, or **9c** (10 mmol), phthalic anhydride (**1**) (1.48 g, 10 mmol) and triethylamine (0.5 mL, 3.6 mmol) in toluene (50 mL) was refluxed with a Dean–stark apparatus for 12 h. The reaction mixture was cooled, then concentrated under reduced pressure. The residue was dissolved into dichloromethane, washed with 5% hydrochloric acid solution then with a 5% sodium hydrogenocarbonate solution. The organic layer was dried over magnesium sulfate, concentrated under vacuo, and recrystallization of the residue gave the expected imides **4c**,**d** or **10a**–**c** in good yields.

4.3.1. *N*-(*o*-*Tert*-butoxycarbonylamidophenyl)phthalimide (4c). This product was isolated as white crystals in 91% yield; mp = 269 °C (decomposition); IR (KBr) v 3417, 3034, 2990, 1731, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 9H, $3CH_3$), 7.12–7.53 (m, 4H, $4H_{benzene}$), 7.61–7.82 (m, 2H, $2H_{phthalimide}$), 7.90–7.98 (m, 2H, $2H_{phthalimide}$), 8.15 (s broad, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.9 ($3CH_3$), 80.1 (Cq), 123.4 (Cq), 124.8 (2CH), 125.6 (CH), 127.3 (CH), 129.6 (Cq), 131.1 (CH), 142.3 (CH), 134.4 (2CH), 140.6 (2Cq), 164.8 (CO), 167.2 (2CO); Anal. Calcd for $C_{19}H_{18}N_2O_4$ (338.36): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.18; H, 5.22; N, 8.31.

4.3.2. *N*-(*o*-Acetamidophenyl)phthalimide (4d). This product was isolated as white crystals in 91% yield; mp = 200 °C; IR (KBr) v 3244, 3038, 1720, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, $COCH_3$), 7.24–7.31 (m, 2H, $1H_{benzene}$ and NH, exchangeable with D_2O), 7.36–7.58 (m, 2H, $2H_{benzene}$), 7.77–7.86 (m, 3H, $1H_{benzene}$ and $2H_{phthalimide}$), 7.89–7.96 (m, 2H, $2H_{phthalimide}$); ^{13}C NMR ($CDCl_3$) δ 24.3 (CH_3), 124.0 (Cq), 124.2 (2CH), 125.9 (CH), 126.0 (CH), 128.6 (CH), 129.7 (CH), 131.8 (Cq), 133.9 (2Cq), 134.8 (2CH), 167.4 (2CO), 168.6 (CO); Anal. Calcd for $C_{16}H_{12}N_2O_3$ (280.28): C, 68.56; H, 4.32; N, 9.99. Found: C, 68.39; H, 4.25; N, 10.05.

4.3.3. *N*-(*o*-Phenylaminophenyl)phthalimide (10a). This product was isolated as a yellow solid in 76% yield; mp = 200 °C (ethanol); IR (KBr) ν 3320, 3006, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.04 (s, 1H, NH, exchangeable with D_2O), 7.08–7.27 (m, 4H, $4H_{benzene}$), 7.37–7.80 (m, 5H, $5H_{benzene}$), 8.01–8.12 (m, 2H, $2H_{phthalimide}$), 8.17–8.26 (m, 2H, $2H_{phthalimide}$); ^{13}C NMR ($CDCl_3$) δ 118.5 (2CH), 121.4 (CH), 121.7 (CH), 123.3 (Cq), 123.9 (CH), 124.2 (2CH), 129.6 (2CH), 129.7 (CH), 130.2 (CH), 132.3 (2Cq), 134.8 (2CH), 140.8 (Cq), 143.4 (Cq), 167.7 (2CO); Anal. Calcd for $C_{20}H_{14}N_2O_2$ (314.34): C, 76.42; H, 4.49; N, 8.91. Found: C, 76.09; H, 4.25; N, 8.71.

4.3.4. *N*-(*o*-Phenylaminoethyl)phthalimide (10b). This product was isolated as a white solid in 85% yield; mp = 100 °C (ethanol); IR (KBr) ν 3345, 3010, 2989, 1712; ^{1}H NMR ($CDCl_3$) δ 3.42 (t, 2H, CH_2, J = 6.3 Hz), 3.96 (t, 2H, CH_2, J = 6.3 Hz), 6.57–6.72 (m, 3H, $3H_{benzene}$), 7.08–7.19 (m, 2H, $2H_{benzene}$), 7.66–7.75 (m, 2H, $2H_{phthalimide}$), 7.77–7.87 (m, 2H, $2H_{phthalimide}$); ^{13}C NMR ($CDCl_3$) δ 37.7 (CH_2), 43.3 (CH_2), 112.9 (2CH), 117.9 (CH), 123.7 (2CH), 129.6 (2CH), 132.3 (2Cq), 134.4 (2CH), 147.9 (Cq), 169 (2CO); Anal. Calcd for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.02; H, 5.15; N, 10.41.

4.3.5. *N*-(2-(5′-Nitropyridin-2′-ylamino)ethyl)phthalimide (10c). This product was isolated as a white solid in 86% yield; mp = 191 °C (ethanol); IR (KBr) ν 3242, 3005, 2950, 1710, 1503, 1396; ^{1}H NMR (DMSO d_6) δ 3.37–3.76

(m, 4H, $2CH_2$), 6.42 (d, 1H, $H_{pyridine}$, $J=8.6$ Hz), 7.79–7.85 (m, 2H, $2H_{phthalimide}$), 8.04 (d, 1H, $H_{pyridine}$, $J=8.6$ Hz), 8.12–8.24 (m, 2H, $2H_{phthalimide}$), 8.71 (s, 1H, $H_{pyridine}$), 8.90 (t, 1H, NH, $J=2.4$ Hz, exchangeable with D_2O); ^{13}C NMR (DMSO d_6) δ 36.9 (CH_2), 38.5 (CH_2), 108.5 (CH), 122.6 (2CH), 131.4 (CH), 131.6 (Cq), 133.9 (2CH), 134.4 (2Cq), 146.1 (CH), 161.4 (Cq), 167.8 (2CO); Anal. Calcd for $C_{15}H_{12}N_4O_4$ (312.09): C, 57.69; H, 3.87; N, 17.94. Found: C, 57.51; H, 3.66; N, 17.63.

4.4. General procedure for reduction of imides (4a–d) and (10a–c)

To a mixture of 5 mmol of imide **4a** (**4b**, **4c**, **4d**, **10a**, **10b** or **10c**) in dry methanol (40 mL) at −5 to 0 °C was added sodium borohydride (283–565 mg, 7.5–15 mmol) by portions during 5 min. To this mixture was added 5 drops of ethanolic hydrochloric acid solution (prepared by addition of nine drops of concentrated hydrochloric acid into 9 mL of dry ethanol) at regular intervals of 10 min. The reaction was monitored by TLC using CH_2Cl_2 as eluent (CH_2Cl_2/MeOH (9/1) in the case of **10c**). After the end of the reaction (45 min to 1 h), the excess of sodium borohydride was decomposed by careful addition of cold water (15 mL) and 10% hydrochloric acid until pH 4. Sodium hydrogen carbonate was added and the solvent was evaporated. The resulting residue was triturated with water and dichloromethane and the organic layer was separated, washed with water, brine, dried and concentrated in vacuo. The resulting product was purified by chromatography on silica gel column or by recrystallization to give in appreciable yield **5b**, **6c**, **6d**, **8a**, **8′a**, **11a**, **11b** or **11c**, respectively.

4.4.1. 3-Hydroxy-2,3-dihydro-2-(*o*-nitrophenyl)isoindol-1-one (5a). This product was not isolated but react immediately in situ to give the cyclised product **8′a** and/or **8a**.

4.4.2. 6-Oxoisoindolo[2,1-*a*]benzimidazole (8a). This product was obtained in a range of 45–61% yield and have same characteristics to that reported in literature (lit.,[9] mp > 290 °C, 39% yield).

4.4.3. 10*b*-Methoxy-10*b*,11-dihydrobenzo[4,5]imidazo[2,1-*a*]isoindol-6-one (8′a). This product was isolated as orange crystals in 39% yield after chromatography on silica gel column using a mixture of dichloromethane/cyclohexane (7:3) as eluent; mp = 128 °C; IR (KBr) v 3246, 3023, 2958, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, OCH_3), 7.16 (t, 1H, $1H_{isoindole}$, $J=7.8$, 7.0 Hz), 7.46–7.57 (m, 3H, $3H_{benzene}$), 7.65 (t, 1H, $1H_{isoindole}$, $J=7.8$, 7.0 Hz), 7.91 (d, 1H, $1H_{benzene}$, $J=7.0$ Hz), 8.17 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz), 8.84 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz), 10.45 (s, 3H, NH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 52.8 (OCH_3), 122.6 (CH), 123.8 (CH), 125.9 (CH), 127.3 (CH), 129.2 (Cq), 130.6 (CH), 130.7 (CH), 132.6 (CH), 134.7 (Cq), 136.3 (CH), 136.8 (Cq), 137.9 (Cq), 166.8 (CO), 167.9 (Cq); Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.64; N, 11.01.

4.4.4. 3-Hydroxy-2,3-dihydro-2-(4′-methyl-*o*-nitrophen-yl)isoindol-1-one (5b). This product was isolated as a yellow solid in 65% yield; mp = 158 °C; IR (KBr) v 3351, 3082, 1690, 1532, 1383 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 3.59 (d, 1H, OH, $J=11.7$ Hz, exchangeable with D_2O), 6.17 (d, 1H, CH, $J=11.7$ Hz), 7.35–7.55 (m, 3H, $1H_{benzene}$ and $2H_{isoindole}$), 7.56–7.75 (m, 3H, $1H_{benzene}$ and $2H_{isoindole}$), 7.84 (d, 1H, $1H_{benzene}$, $J=10.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 83.9 (CH), 123.8 (CH), 124.6 (CH), 125.9 (CH), 127.5 (Cq), 130.2 (CH), 130.6 (CH), 130.8 (Cq), 134.0 (CH), 135.4 (CH), 139.7 (Cq), 145.4 (Cq), 146.7 (Cq), 166.9 (CO); Anal. Calcd for $C_{15}H_{12}N_2O_4$ (284.27): C, 63.38; H, 4.25; N, 9.85. Found: C, 63.21; H, 4.08; N, 9.71.

4.4.5. 3-Hydroxy-2,3-dihydro-2-(*o*-*tert*-butoxycarbonylamidophenyl)isoindol-1-one (6c). This product was isolated as a white solid in 85% yield; mp = 188 °C; IR (KBr) v 3446, 3280, 3010, 2970, 1736, 1663 cm^{-1}; ^1H NMR (DMSO d_6) δ 1.39 (s, 9H, $3CH_3$), 6.23 (d, 1H, OH, $J=7.1$ Hz, exchangeable with D_2O), 6.77 (d, 1H, CH, $J=7.1$ Hz), 7.14 (t, 1H, $1H_{benzene}$, $J=7.8$, 7.0 Hz), 7.34 (t, 2H, $1H_{benzene}$ and $1H_{isoindole}$, $J=7.8$, 7.8 Hz), 7.58–7.88 (m, 5H, $2H_{benzene}$ and $3H_{isoindole}$), 8.35 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO d_6) δ 28.1 ($3CH_3$), 79.5 (Cq), 83.6 (CH), 122.2 (CH), 122.9 (CH), 123.5 (CH), 123.7 (CH), 127.5 (Cq), 128.0 (CH), 129.2 (CH), 129.6 (CH), 131.4 (Cq), 132.6 (Cq), 136.6 (Cq), 145.8 (Cq), 152.9 (CO), 165.8 (CO); Anal. Calcd for $C_{19}H_{20}N_2O_4$ (340.37): C, 67.05; H, 5.92; N, 8.23. Found: C, 67.12; H, 5.81; N, 8.09.

4.4.6. 3-Hydroxy-2,3-dihydro-2-(*o*-acetamidophenyl)-isoindol-1-one (6d). This product was isolated as a white solid in 89% yield; mp = 185 °C (ethanol); IR (KBr) v 3439, 3247, 3006, 2923, 1689, 1673 cm^{-1}; ^1H NMR (DMSO d_6) δ 1.98 (s, 9H, CH_3), 6.17 (s, 1H, CH), 6.65 (s broad, 1H, OH, exchangeable with D_2O), 7.11–7.34 (m, 3H, $3H_{benzene}$), 7.46–7.56 (m, 1H, $1H_{benzene}$), 7.60–7.62 (m, 2H, $2H_{isoindole}$), 7.79 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz), 8.03 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz),$_{isoindole}$), 8.48 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO d_6) δ 24.3 (CH_3), 84.6 (CH), 123.5 (2CH), 124.1 (CH), 125.0 (CH), 127.7 (CH), 128.4 (CH), 129.7 (CH), 131.0 (Cq), 132.7 (CH), 135.8 (Cq), 141.3 (Cq), 144.9 (Cq), 170.1 (CO), 174.9 (CO); Anal. Calcd for $C_{16}H_{14}N_2O_3$ (282.29): C, 68,07; H, 5,00; N, 9,92. Found: C, 67,98; H, 4,81; N, 9,84.

4.4.7. 3-Hydroxy-2,3-dihydro-2-(*o*-phenylaminophenyl)-1*H*-isoindol-1-one (11a). This product was isolated as a yellow solid in 80% after recrystallization from ethanol; mp = 73 °C; IR (KBr) ν 3381, 3333, 3038, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.22 (s, 1H, CH), 7.17–7.36 (m, 9H, $9H_{benzene}$), 6.65–7.64 (m, 12H, $9H_{benzene}$ and $3H_{isoindole}$), 7.80–7.89 (m, 1H, $1H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 84.5 (CH), 118.5 (2CH), 120.5 (CH), 121.2 (CH), 122.5 (CH), 123.8 (CH), 124.2 (CH), 127.0 (Cq), 128.3 (CH), 129.1 (CH), 129.6 (2CH), 130.5 (CH), 131.3 (Cq), 133.1 (CH), 141.5 (Cq), 143.6 (Cq), 144.3 (Cq), 167.2 (CO); Anal. Calcd for $C_{20}H_{16}N_2O_2$ (316.35): C, 75.93; H, 5.10; N, 8.86. Found: C, 75.80; H, 5.02; N, 8.65.

4.4.8. 3-Hydroxy-2,3-dihydro-2-(*o*-phenylaminoethyl)-1*H*-isoindol-1-one (11b). This product was isolated as a white solid in 88% after recrystallization from ethanol; mp = 76 °C; IR (KBr) ν 3363, 3009, 2988, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (t, 2H, CH_2, $J=5.5$ Hz), 3.51–3.67 (m, 1H, CH_2), 3.72–3.88 (m, 1H, CH_2), 4.09 (s large, 1H,

NH, exchangeable with D_2O), 5.78 (s, 1H, CH), 6,58 (d, 2H, $J=7.8$ Hz), 6,69 (t, 1H, $J=7.1$ Hz), 7.12 (t, 2H, $J=7.8$ Hz), 7.39–7.57 (m, 3H, $3H_{isoindole}$), 7.66 (d, 1H, $1H_{isoindole}$, $J=7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 40.3 (CH_2), 43.4 (CH_2), 83 (CH), 113.5 (2CH), 118.3 (CH), 123.5 (2CH), 129.6 (2CH), 130.1 (CH), 131.5 (Cq), 132.7 (CH), 144.1 (Cq), 147.9 (Cq), 168.6 (CO); Anal. Calcd for $C_{16}H_{16}N_2O_2$ (268.31): C, 75.93; H, 5.10; N, 8.86. Found: C, 75.80; H, 5.02; N, 8.65.

4.4.9. 3-Hydroxy-2,3-dihydro-2-[2-(5′-nitropyridin-2′-ylamino)ethyl]-1*H*-isoindol-1-one (11c). This product was isolated as a yellow solid in 82% after recrystallization from dry ethanol; mp = 120 °C (decomposition); IR (KBr) ν 3467, 3307, 3093, 2935, 1704, 1504, 1337 cm^{-1}; ^1H NMR ($CDCl_3$, this product is no stable in the solution) δ 3.08 (s broad, 1H, NH, exchangeable with D_2O), 3.28–3.71 (m, 3H, CH_2–CH_2), 4.13–4.18 (m, 1H, CH_2–CH_2), 3.08 (s broad, 1H, OH, exchangeable with D_2O), 5.83 (s, 1H, CH), 6.37 (d, 1H, $1H_{pyridine}$, $J=9.4$ Hz), 7.29–7.43 (m, 1H, $1H_{benzene}$), 7.47–7.57 (m, 3H, $3H_{benzene}$), 7.99 (d, 1H, $1H_{pyridine}$, $J=9.4$ Hz), 8.58 (s, 1H, $1H_{pyridine}$); Anal. Calcd for $C_{15}H_{14}N_4O_4$ (314.30): C, 57.32; H, 4.49; N, 17.83. Found: C, 57.18; H, 4.27; N, 17.65.

4.5. Procedure for the reductive cyclization of nitro-hydroxylactam 5b

To a solution of 6 mmol of nitro-hydroxylactam **5b** in dry methanol (40 mL) at −5 to 0 °C was added sodium borohydride (679 mg, 18 mmol) by portions during 10 min. To this mixture was added 5 drops of ethanolic hydrochloric acid solution (as prepared above) at regular intervals of 5 min. The reaction was monitored by TLC using CH_2Cl_2 as eluent. After the end of the reaction (2 h), the excess of sodium borohydride was decomposed by careful addition of cold water (15 mL) and 10% hydrochloric or H_2SO_4 acid until pH 4. After sodium hydrogen carbonate was added and the solvent was evaporated. The resulting residue was triturated with water and dichloromethane and the organic layer was separated, washed with water, brine, dried and concentrated in vacuo.

4.5.1. 2-Methyl-6-oxoisoindolo[2,1-*a*]benzimidazole (8b). This product was obtained as a white powder in 63% after recrystallization from absolute ethanol; mp = 238 °C; IR (KBr) ν 3025, 2952, 1719, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H, CH_3), 7.1 (d, 1H, $1H_{benzene}$, $J=8.1$ Hz), 7.41 (s, 1H, $1H_{benzene}$), 7.49 (d, 1H, $1H_{benzene}$, $J=8.1$ Hz), 7.57–7.94 (m, 4H, $4H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 22.8 (CH_3), 115.8 (CH), 116.6 (CH), 125.4 (CH), 131.2 (Cq), 131.4 (2CH), 131.7 (CH), 132.7 (Cq), 133.3 (CH), 134.6 (Cq), 138.4 (Cq), 139.6 (Cq), 152.4 (Cq), 170.4 (CO); Anal. Calcd for $C_{15}H_{10}N_2O$ (234.26): C, 76.91; H, 4.30; N, 11.96. Found: C, 76.81; H, 4.09; N, 12.05.

4.6. General procedure for acid cyclization of hydroxy-lactams (6c,b) and (11a–c)

The procedure is general and concerns the use of neat or weak TFA, AcOH or catalytic PTSA at rt or reflux without or with a solvent as CH_2Cl_2 or toluene. For more details see Table 2. A stirred solution of 6 mmol of amino-hydroxy-lactams **6c**,**d** (or hydroxy-lactams **11a–c**) in 10 mL of appropriate acid or catalytic amount (in the case of PTSA) was left to react at room temperature or reflux in the presence or not of the solvent (For details see Table 2). After the required time, the solvent was evaporated in vacuo, and the residue was diluted with dichloromethane (10 mL) and treated with a saturated solution of hydrogenocarbonate. After separation, the organic layer was washed with water, brine, dried and concentrated in vacuo. The resulting residue was purified either by recrystallisation from ethanol or through a silica gel column.

4.6.1. 6-Oxoisoindolo[2,1-*a*]benzimidazole (8c). This product is identical to **8a** described above.

4.6.2. 11-Acetyl-10*b*,11-dihydrobenzo[4,5]imidazo[2,1-*a*]isoindol-6-one (8d). This product was isolated as a white-yellow crystals after chromatography on silica gel column using a mixture of chloroform/cyclohaxane (2:3) as eluent in 91% yield; mp = 168 °C; IR (KBr) v 3021, 2943, 1732, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, CH_3), 6.93 (s, 1H, CH), 7.05–7.19 (m, 3H, $3H_{benzene}$), 7.49–7.64 (m, 2H, $1H_{benzene}$ and $1H_{isoindole}$), 7.66–7.75 (m, 1H, $1H_{isoindole}$), 7.85 (d, 1H, $1H_{isoindole}$, $J=7.0$ Hz), 8.25 (d, 1H, $1H_{isoindole}$, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 25.3 (CH_3), 79.4 (CH), 113.1 (CH), 117.2 (CH), 124.1 (CH), 124.5 (CH), 124.9 (CH), 128.3 (CH), 130.3 (CH), 132.1 (Cq), 132.8 (Cq), 133.7 (CH), 136.0 (Cq), 145.0 (Cq), 169.3 (CO), 171.6 (CO); Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.28): C, 72.72; H, 4.58; N, 10.60. Found: C, 72.59; H, 4.32; N, 10.28.

4.6.3. 11-Phenyl-6(10*bH*)-oxoisoindolo[2,1-*a*]benzimidazole (12a). This product was obtained as white crystals in 79% after recrystallization from ethanol; mp = 208–210 °C (decomposition); IR (KBr) ν 3015, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03–7.12 (m, 1H, H benzene), 7.24 (s, 1H, CH), 7.26–7.42 (m, 2H, $2H_{benzene}$), 7.64–8.03 (m, 9H, $9H_{benzene}$), 8.28–8.37 (m, 1H, $1H_{benzene}$); ^{13}C NMR ($CDCl_3$) δ 83.3 (CH), 108.6 (CH), 116.9 (CH), 120.4 (CH), 124.2 (CH), 124.8 (2CH), 125.3 (CH), 125.6 (CH), 126.4 (CH), 130.2 (2CH), 130.4 (CH), 131.5 (Cq), 133.1 (CH), 133.9 (Cq), 141.9 (Cq), 144.1 (Cq), 146.3 (Cq), 170.7 (CO); Anal. Calcd for $C_{20}H_{14}N_2O$ (298.34): C, 80.52; H, 4.73; N, 9.39. Found: C, 80.42; H, 4.59; N, 9.19.

4.6.4. 5-Phenyl-4*b*,5,6,7-tetrahydroimidazo[2,1-*a*]isoindol-9-one (12b). This product was obtained as a white powder in 82% after recrystallization from absolute ethanol; mp = 143 °C; IR (KBr) ν 3005, 2992, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39–3.68 (m, 2H, CH_2), 3.77–3.92 (m, 1H, CH_2), 4.26–4.39 (m, 1H, CH_2), 6.12 (s, 1H, CH), 6.87–7.28 (m, 3H, $3H_{benzene}$), 7.29–7.41 (m, 2H, $2H_{benzene}$), 7.44–7.54 (m, 2H, $2H_{isoindole}$), 7.71–7.86 (m, 2H, $2H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 42.4 (CH_2), 53.3 (CH_2), 75.7 (CH), 114.7 (2CH), 119.3 (CH), 124.6 (2CH), 129.7 (2CH), 130.0 (CH), 132.9 (CH), 133.3 (Cq), 145.7 (Cq), 146.8 (Cq), 173.1 (CO); Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.84; H, 5.48; N, 11.27.

4.6.5. 2-(1-Benzyl-1*H*-benzimidazol-2-yl)-3-hydroxy-2,3-dihydroisoindol-1-one (12c). This product was obtained as a yellow orange powder in 85% after recrystallization from absolute ethanol; mp = 234 °C; IR (KBr) ν 3079, 2963, 1699, 1513, 1327 cm^{-1}; ^1H NMR (DMSO d_6) δ 3.50–3.82

(m, 2H, CH_2), 3.87–3.99 (m, 1H, CH_2), 4.33 (dd, 1H, CH_2, J=6.4, 10.7 Hz), 6.61 (s, 1H, CH), 6.78 (d, 1H, $1H_{pyridine}$, J=9.1 Hz), 7.56–7.82 (m, 3H, $3H_{isoindole}$), 8.30–8.44 (m, 2H, $2H_{isoindole}$ and $1H_{pyridine}$), 9.26 (d, 1H, $1H_{pyridine}$, J=2.7 Hz); ^{13}C NMR (DMSO d_6) δ 42.8 (CH_2), 50.4 (CH_2), 76.2 (CH), 108.6 (CH), 124.3 (CH), 128.2 (CH), 131.2 (CH), 133.2 (Cq), 134.0 (2CH), 136.6 (Cq), 145.3 (Cq), 146.8 (CH), 159.5 (Cq), 173.1 (Cq); Anal. Calcd for $C_{15}H_{12}N_4O_3$ (296.28): C, 60.81; H, 4.08; N, 18.91. Found: C, 60.70; H, 4.10; N, 18.69.

4.6.6. 5,15*b*-Dihydro-11*H*-isoindolo[2,1-*d*]dibenzo[*b*,*f*]-[1,4]diazepin-11-one (13a). This product was obtained as a yellow powder in 81–91% after recrystallization from absolute ethanol; mp=248 °C; IR (KBr) ν 3346, 3013, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.13 (s, 1H, CH), 6.61–6.83 (m, 3H, $3H_{benzene}$), 6.88–7.16 (m, 4H, $4H_{benzene}$), 7.32 (s, 1H, NH, exchangeable with D_2O), 7.42–7.68 (m, 1H, $1H_{isoindole}$), 8.2 (m, 1H, $1H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 63.3 (CH), 118.9 (CH), 119.3 (CH), 119.5 (CH), 120.1 (CH), 122.7 (CH), 124.2 (CH), 124.4 (CH), 125.3 (CH), 126.1 (Cq), 126.2 (CH), 127.2 (Cq), 128.6 (CH), 129.1 (CH), 131.1 (Cq), 133.1 (Cq), 135.2 (Cq), 142.0 (Cq), 144.1 (Cq), 166.9 (CO); Anal. Calcd for $C_{20}H_{14}N_2O$ (298.34): C, 80.52; H, 4.73; N, 9.39. Found: C, 80.41; H, 4.59; N, 9.21.

4.6.7. 5,6,7,13*b*-Tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepin-9-one (13b). This product was obtained as a white solid in 89–93% after chromatography over silica gel column using a mixture of CH_2Cl_2/hexane (9.5/0.5) as eluent and recrystallization from absolute ethanol; mp=139 °C (lit.,[29] mp=135–137 °C); IR (KBr) ν 3336, 3013, 2986, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.03–3.19 (m, 1H, CH_2), 3.49–3.68 (m, 2H, CH_2), 4.0 (s br, 1H, NH, exchangeable with D_2O), 4.25–4.39 (m, 1H, CH_2), 5.73 (s, 1H, CH), 6.77–6.92 (m, 2H, $2H_{benzene}$), 7.03 (d, 1H, $1H_{benzene}$, J=7.1 Hz), 7.16–7.25 (t, 1H, $1H_{benzene}$, J=7.1 Hz), 7.47–7.68 (m, 3H, $3H_{isoindole}$), 7.94 (d, 1H, $1H_{isoindole}$, J=7.2, Hz); ^{13}C NMR ($CDCl_3$) δ 44.3 (CH_2), 47.5 (CH_2), 62.5 (CH), 120.7 (CH), 121.8 (CH), 124.6 (CH), 125.4 (CH), 127.3 (Cq), 127.7 (CH), 128.9 (CH), 129.3 (CH), 131.2 (CH), 133.5 (Cq), 143.1 (Cq), 150.0 (Cq), 168.6 (CO); Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.59; H, 5.61; N, 11.08.

4.7. General procedure for acidic transformation of isoindoloimidazoles (12a,b) into isoindolobenzodiazepines (13a,b)

4.7.1. Products 13a and 12b. All chemicals and physicals characteristics of these products are identical to that described above in Sections 4.6.6 and 4.6.7, respectively.

4.8. General procedure for keto acids/diamines cyclodehydration into isoindoloimidazole derivatives (8a,b,e), and (12a–c)

To a solution of 2-carboxybenz-aldehyde (**2**, 1.5 g, 10 mmol) in anhydrous toluene with or without addition of PTSA (50 mg), was added 10 mmol of diamine **7a**, **7b**, **7e**, **9a**, **9b** or **9c**. The reaction mixture was refluxed for 12 h with a Dean–Stark apparatus. After cooling and removal of the solvent in vacuo, the residue was purified by recrystallization from ethanol to yield the expected isoindolobenzimidazoles **8a** (82%), **8b** (54%), **8e** (51%) or **12a** (91%), or isoindoloimidazoles **12b** (82%) or **12c** (96%), respectively, as crystals.

4.8.1. Products 8a,b and 12a–c. All chemicals and physicals characteristics of these products **8a**,**b** and **12a–c** are identical to that reported above.

4.8.2. 3-Methoxycarbonyl-6-oxoisoindolo[2,1-*a*]benzimidazole (8e). This product was isolated as white crystals in 51% yield; mp=269 °C; IR (KBr) ν 3009, 1709, 1698, 1635 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 3.95 (s, 3H, CH_3), 7.64–7.98 (m, 6H, $3H_{benzene}$ and $3H_{isoindole}$), 8.12 (s, 1H, $H_{isoindole}$); ^{13}C NMR (DMSO d_6) δ 53.0 (CH_3), 115.7 (CH), 118.0 (CH), 124.1 (CH and Cq), 130.5 (CH), 131.1 (CH and Cq), 131.4 (CH), 132.1 (CH), 134.0 (Cq), 140.1 (Cq), 143.3 (Cq), 155.1 (Cq), 167.7 (CO), 169.4 (CO); Anal. Calcd for $C_{16}H_{10}N_2O_3$ (278.27): C, 69.06; H, 3.62; N, 10.07. Found: C, 68.98; H, 3.51; N, 10.01.

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